PAC2507-0011
Leaflet_KLF0079S1_Vastinor Tablet
Size: 148(L) x 210(H)mm
Colors: Black
Current Revision: 001
Updated Revision: 002

Important information. Please read carefully.

VASTINOR™

Film-Coated Tablet 5mg/ 10mg/20mg

COMPOSITION
Vastinor Tablet 5mg: Each film-coated tablet contains 5mg Rosuvastatin (as Rosuvastatin Calcium).
Vastinor Tablet 10mg: Each film-coated tablet contains 10mg Rosuvastatin (as Rosuvastatin Calcium).
Vastinor Tablet 20mg: Each film-coated tablet contains 20mg Rosuvastatin (as Rosuvastatin Calcium).

PHARMACODYNAMICS
Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07
Rosuvastatin is a selective and competitive inhibitor of Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (or statin) where 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.

PHARMACOKINETICS
Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations are achieved about 5 hours after an oral dose.
It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. Mean volume of distribution at steady state of rosuvastatin is approximately 134 L. It is about 90% bound to plasma proteins.
The plasma elimination half-life of rosuvastatin is about 19 hours. About 90% of an oral dose of rosuvastatin appears in the faeces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.

INDICATIONS
Vastinor Tablet (rosuvastatin calcium) 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 hyperlipidemic 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, Vastinor Tablet is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization).
Vastinor Tablet is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
Combined (mixed) dyslipidemia (Type IIb).
Homozygous familial hypercholesterolaemia where Vastinor Tablet is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.
Vastinor Tablet 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.

DOSAGE AND 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 10mg 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 hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg and should only be initiated under specialist supervision (see *Warning and Precautions*). 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 / rhabdomyolysis (see *Warning and Precautions*). The dosage of Rosuvastatin should be individualised 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 Calcium 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 Calcium 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 Calcium 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 hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily (see *Special warnings and special precautions for use and Pharmacokinetic properties*).

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see *Pharmacokinetic Properties*). For patients who are known to have such specific types of polymorphisms, a lower daily dose of Vastinor is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg in patients with pre-disposing 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 Vastinor 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
Statins should not be given to patients with active liver disease, including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN). Liver function should be assessed before starting treatment and subsequently when clinically indicated. Additional assessment after 3 months and before and after dosage increases has been advised for some statins, particularly when high doses are given.
Vastinor Tablet is also contraindicated in patients with:
- hypersensitivity to rosuvastatin or to any of the excipients
- receiving concomitant cyclosporine
- severe renal impairment (creatinine clearance <30 ml/min)
- myopathy
- pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures

WARNING AND PRECAUTIONS
Systemic exposure to rosuvastatin may be higher in Asian patients and lower doses are advised in Asians and in other patients at high risk of myopathy.
Statins may cause myopathy and rhabdomyolysis, especially at higher doses, and they should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin. The statin should be stopped if creatine phosphokinase increases significantly or if myopathy is diagnosed. Statins should be used with caution in patients with renal impairment as the risk of myopathy is increased. Dose reduction may be required for statins that are excreted by the kidney and for those with a particularly high risk of myopathy.

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. 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. 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.
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 – 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 >70 years
• situations where an increase in plasma levels may occur (see *Dosage and Administration, Drug Interactions and Pharmacokinetics*)
• 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
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. 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.
There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by:
• persistent 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
Increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, 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 and Side Effects*).
Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.
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, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Renal Effects
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 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.

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.
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 the 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.

Protease Inhibitors
Increased systemic exposure to rosuvastatin has been observed in receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted.

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
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia 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/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Myasthenia Gravis/ Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Vastinor Tablet should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was re-administered have been reported.

DRUG INTERACTIONS
The most serious consequence of drug interactions with rosuvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid.
Concurrent use of fibrates may cause severe myositis and myoglobinuria.
Rosuvastatin undergoes limited metabolism, principally by the cytochrome P450 isoenzyme CYP2C9, and may not have the same interactions with enzyme inhibitors as simvastatin. However, increased plasma-rosuvastatin concentrations have been reported with cyclosporin, HIV protease inhibitors, and, to a lesser extent, with gemfibrozil, and such combinations should be avoided. If they must be given together, lower doses of rosuvastatin should be used.
Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking statins with coumarin anticoagulants.

Transporter protein inhibitors
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.
Ciclosporin:
Rosuvastatin is 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. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products
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 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe
A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

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%. 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 Cmax 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 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.

Oral contraceptive/hormone replacement therapy (HRT)
Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel. These increased plasma levels should be considered when selecting oral contraceptive doses. 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 treatment should be discontinued throughout the duration of the fusidic acid treatment.
Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be reintroduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

PREGNANCY AND LACTATION
Vastinor Tablet is contraindicated in pregnancy and lactation.
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. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

SIDE EFFECTS
The adverse reactions seen with rosuvastatin tablet are generally mild and transient.

System organ class	Common	Uncommon	Rare	Very Rare	Unknown
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 disturbance (including insomnia and nightmares) Myasthenia gravis
Respiratory, thoracic and mediastinal disorders					Cough Dysponea
Gastrointestinal 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
Musculoskeletal and connective tissue disorders	Myalagia		Myopathy (including myositis) Rhabdomyolysis	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
Eye disorders					Ocular myasthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.
The following adverse events also have been reported with some statins:
- Sexual dysfunction.
- Exceptional cases of interstitial lung disease, especially with long term therapy
- 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.
Musculoskeletal disorders: Frequency not known: Immune-mediated necrotizing myopathy.
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 non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks). Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

SYMPTOMS AND TREATMENT FOR OVERDOSAGE
There is no specific treatment in the symptom of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Haemodialysis is unlikely to be of benefit.

STORAGE CONDITION
Store below 30°C.

PRODUCT DESCRIPTION, DOSAGE FORM AND PACKAGING AVAILABLE
Vastinor Tablet 5mg: Pink, round, normal convex film-coated tablet, with 'XS' marking on one side and plain on reverse, 6mm in diameter.
Vastinor Tablet 10mg: Pink, round, normal convex film-coated tablet, with 'XS' marking on one side and plain on reverse, 7mm in diameter.
Vastinor Tablet 20mg: Pink, round, normal convex film-coated tablet, with XSP logo on one side and plain on reverse, 9mm in diameter.

Available as blister strips of 10's in packing of 30 tablets per box.

Manufacturer and Product Registration Holder
Xepa-Soul Pattinson (Malaysia) Sdn. Bhd.
1-5 Cheng Industrial Estate,
75250 Melaka, Malaysia.

KEEP OUT OF REACH OF CHILDREN/ JAUHI DARI KANAK-KANAK

For further information, please consult your pharmacist or physician.

Revision Date : 24-Jul-2025