VAPTOR
(Rosuvastatin)

5mg, 10mg & 20mg

Film-Coated Tablets

COMPOSITION

Each film-coated tablet contains:
Rosuvastatin (as Calcium) … 5mg

Each film-coated tablet contains:
Rosuvastatin (as Calcium) … 10mg

Each film-coated tablet contains:
Rosuvastatin (as Calcium) … 20mg

THERAPEUTIC 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 triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

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, non-HDL-C and ApoB in children and adolescents 7 to 17 years of age with homozygous familial hypercholesterolemia, either alone or with other lipid lowering treatments (e.g., LDL apheresis).

Hypertriglyceridemia: 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

Special population

Pediatric Use: In children and adolescents 8 to 17 years of age with heterozygous familial hypercholesterolemia & in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolemia, the safety and effectiveness of Rosuvastatin as an adjunct to diet were established. Rosuvastatin has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 8 years of age.

Geriatric Use: No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Elderly patients are at higher risk of myopathy and Rosuvastatin should be prescribed with caution in the elderly.

Renal Impairment: Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 $m^{2)}$. Exposure to Rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) who are not receiving hemodialysis and dose adjustment is required.

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.

Asian Patients: Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to Rosuvastatin in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients

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.

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. ROSUVASTATIN can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole. After initiation or upon titration of ROSUVASTATIN, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

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 and and darolutamide*:* 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 regorafenib: Concomitant use of Rosuvastatin and regorafenib, the dose of Rosuvastatin should not exceed 10 mg once daily
Patients taking atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir or combination of dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir: Initiate 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 (CLcr <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

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 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.

Dosage in patients with pre-disposing factors to myopathy: The recommended start dose is 5 mg in patients with predisposing factors to myopathy. The 40 mg dose is contraindicated in some of these patients .

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.

WARNINGS AND 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 gemfibrozil, some other lipid-lowering therapies (other fibrates or niacin), cyclosporine, darolutamide, regorafenib, atazanavir/ritonavir, lopinavir/ritonavir, simeprevir or combination of sofosbuvir/velpatasvir/voxilaprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, all combinations with ledipasvir (including ledipasvir/sofosbuvir). 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. 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 (Warfarin): 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 clinical trials, dipstick-positive proteinuria and microscopic hematuria were observed among Rosuvastatin treated patients. These findings were more frequent in patients taking Rosuvastatin 40 mg. 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.

Information about excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

DRUG INTERACTIONS

Cyclosporine
Cyclosporine increased Rosuvastatin exposure and may result in increased risk of myopathy. 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

Anti-viral Medications
Coadministration of Rosuvastatin with certain anti-viral drugs has differing effects on Rosuvastatin exposure and may increase risk of myopathy. The combination of sofosbuvir/velpatasvir/voxilaprevir which are anti-Hepatitis C virus (antiHCV) drugs, increases Rosuvastatin exposure. Similarly, the combination of ledipasvir/sofosbuvir may significantly increase Rosuvastatin exposure. For these combinations of anti-HCV drugs, concomitant use with Rosuvastatin is not recommended.

Simeprevir and combinations of dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir which are anti-HCV drugs, increase Rosuvastatin exposure. Combinations of atazanavir/ritonavir and lopinavir/ritonavir, which are anti-HIV-1 drugs, increase Rosuvastatin exposure. For these anti-viral drugs, the dose of Rosuvastatin should not exceed 10 mg once daily. The combinations of fosamprenavir/ritonavir or tipranavir/ritonavir, which are anti-HIV-1 drugs, produce little or no change in Rosuvastatin exposure. No dose adjustment is needed for concomitant use with these combinations

Darolutamide
Darolutamide increased Rosuvastatin exposure more than 5-fold. Therefore, in patients taking darolutamide, the dose of Rosuvastatin should not exceed 5 mg once daily

Regorafenib
Regorafenib increased Rosuvastatin exposure and may increase the risk of myopathy. If used together, the dose of Rosuvastatin should not exceed 10 mg once daily.

Coumarin Anticoagulants
Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs

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; caution should be used when prescribing with Rosuvastatin

Fenofibrate

When Rosuvastatin was coadministered 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

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

PREGNNACY AND LACTATION

Pregnancy (Category X): Rosuvastatin is contraindicated for use in pregnant women 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
Lactation: 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.

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.

ADVERSE DRUG REACTIONS

The adverse reactions seen with Rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin-treated patients were withdrawn due to adverse reactions.

Tabulated list of adverse reactions
Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for Rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

Table 1. Adverse reactions based on data from clinical studies and post-marketing experience

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[1]				
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 Dyspnea
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	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotizing myopathy
Renal and urinary disorders				Hematuria	
Reproductive system and breast disorders				Gynecomastia	
General disorders and administration site conditions	Asthenia				Oedema

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m^2, raised triglycerides, history of hypertension).

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. 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. Hematuria 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.
Sexual dysfunction & Exceptional cases of interstitial lung disease, especially with long term therapy have been reported with some statins.
The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.
Pediatric population: The safety profile of Rosuvastatin was similar in children and adolescents compared to adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. For ADR reporting pv@searlecompany.com

OVERDOSE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Hemodialysis is unlikely to be of benefit.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07
Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor 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.
Pharmacodynamic effects
Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I . Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Pharmacokinetic properties

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%). 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. 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 feces (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.

Summary of Clinical Studies

Clinical efficacy and safety
Crestor is effective in adults with hypercholesterolemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolemia.
From pooled phase III data, Crestor has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolemia (mean baseline LDL-C about 4.8 mmol/L) to recognized European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/L).
In a large study, 435 patients with heterozygous familial hypercholesterolemia were given Crestor from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. Thirty-three percent (33%) of patients reached EAS guidelines for LDL-C levels (<3 mmol/L).
In a force-titration, open label trial, 42 patients (including 8 pediatric patients) with homozygous familial hypercholesterolemia were evaluated for their response to Crestor 20 – 40 mg. In the overall population, the mean LDL-C reduction was 22%.
In clinical studies with a limited number of patients, Crestor has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin
In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/L (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomized to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestor 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolemia at high cardiovascular risk
In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).
Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.
LDL-cholesterol concentration was reduced by 45% (p<0.001) in the rosuvastatin group compared to the placebo group.
In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high-risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high-risk group (p=0.076).
In the JUPITER trial, there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population
In a double-blind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10 to 17 years of age (Tanner stage II-V, females at least 1-year post-menarche) with heterozygous familial hypercholesterolemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 to 13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.
LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.
At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/L.
After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. This trial (n=176) was not suited for comparison of rare adverse drug events.
Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.
After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, Month 24: 124 mg/dL) and -35% (Baseline: 241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.
Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.
No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment.
Rosuvastatin was studied in a randomized, double-blind, placebo-controlled, multi-centre, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-

over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.
A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003) and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.
During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the range of -12.1% to -21.3%.
In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolemia (see above), the percent reduction in LDL-C (21.0%), Total-C (19.2%) and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the aforementioned study in children and adolescents with homozygous familial hypercholesterolemia.
The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the pediatric population in the treatment of homozygous familial hypercholesterolemia, primary combined (mixed) dyslipidemia and in the prevention of cardiovascular events

PRECLINICAL SAFETY DATA

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.

PRESENTATION

VAPTOR (Rosuvastatin) 5mg Tablets are available in alu-alu blister pack of 10 tablets.

VAPTOR (Rosuvastatin) 10mg Tablets are available in alu-alu blister pack of 10 tablets.

VAPTOR (Rosuvastatin) 20mg Tablets are available in alu-alu blister pack of 10 tablets.

INSTRUCTIONS

-To be sold on the prescription of a registered medical practitioner only.

-Protect from sunlight, moisture and heat.

-Store below 30°C.

-Keep all medicines out of sight and reach of children.

REGISTRATION NUMBER

VAPTOR tablets 5mg: 044075

VAPTOR tablets 10mg: 044076

VAPTOR tablets 20mg: 044077

MANUFACTURING LICENSE NO. 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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