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

ROSUVAS™

(Rosuvastatin Calcium Tablets)

COMPOSITION

ROSUVAS 5 mg

Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin 5 mg

ROSUVAS 10 mg

Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin 10 mg

ROSUVAS 20 mg

Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin 20 mg

DESCRIPTION[1,2,3]

ROSUVAS (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. Chemically, it is designated as (3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl) amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1). The molecular formula of rosuvastatin is $C_{44}H_{54}CaF_2N_6O_{12}S_2$ and the molecular weight is 1001.14.

PHARMACOLOGY[1,2,3]

- **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.

- **Pharmacokinetics**

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

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

Pharmacokinetics in special populations

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

Renal impairment: In a clinical 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 (CrCl <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 impairment: 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.

CLINICAL STUDIES[1]

Rosuvastatin has been reported to reduce elevated LDL-cholesterol, total cholesterol and triglycerides and increase HDL-cholesterol. It has also been reported to lower ApoB, nonHDL-C, VLDL-C, VLDL-TG and increase ApoA-I (see Table below). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

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

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

Rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l). About 80% of patients treated with 10 mg reached the European Atherosclerosis Society (EAS) targets for LDL-C levels (<3 mmol/l).

In a clinical study, patients with heterozygous familial hypercholesterolaemia were given rosuvastatin 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 reported to reduce by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, rosuvastatin 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 (see **Warnings**).

INDICATIONS[1]

ROSUVAS (rosuvastatin) is indicated for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia resistant to dietary measures, and as an adjunct to other lipid lowering treatments in homozygous familial hypercholesterolaemia.

DOSAGE AND ADMINISTRATION[1]

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.

The recommended start dose is 10 mg orally once daily and the majority of patients are controlled at this dose. A dose adjustment to 20 mg can be made after 4 weeks, if necessary (see **CLINICAL STUDIES**). A doubling of the dose to 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 (see **PRECAUTIONS, General**).

ROSUVAS (rosuvastatin) may be given at any time of day, with or without food.

Paediatrics

Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, **ROSUVAS** (rosuvastatin) is not recommended for paediatric use at this time.

Use in the elderly

No dose adjustment is necessary.

Dosage in patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. The use of **ROSUVAS** (rosuvastatin) in patients with severe renal impairment is contraindicated (see **Contraindications** and **PHARMACOLOGY**).

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 (see **PHARMACOLOGY**). In these patients an assessment of renal function should be considered (see **Warnings**). There is no experience in subjects with Child-Pugh scores above 9. **ROSUVAS** (rosuvastatin) is contraindicated in patients with active liver disease (see **Contraindications**).

PRECAUTIONS[1,2]

- **General**

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 (see **Adverse Effects**). An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

- **Warnings**

Skeletal Muscle Effects

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. uncomplicated myalgia and myopathy, have been reported in rosuvastatin -treated patients. Rare cases of rhabdomyolysis have been reported in subjects receiving rosuvastatin 80 mg in investigational clinical trials, which were occasionally associated with impairment of renal function. All cases improved on cessation of therapy.

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 [>5 times the upper limit of normal (ULN)] a confirmatory test should be carried out within 5 - 7 days. If the repeat test confirms a baseline CK >5 times ULN, 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 rhabdomyolysis, such as, 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. 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 (>5 times ULN) 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 (>5 times ULN) or if muscular symptoms are

severe and cause daily discomfort (even if CK levels are ≤ 5 times ULN). 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.

In clinical trials, there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an 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, cyclosporin, 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 (see **Drug Interactions** and **Adverse Effects**).

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).

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

- **Contraindications**

ROSUVAS (rosuvastatin) is contraindicated:

- In patients with hypersensitivity to rosuvastatin or any other ingredient of the product.
- 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 cyclosporin.
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

- **Pregnancy**

Rosuvastatin is contraindicated in pregnancy (see **Contraindications**).

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 (see **Carcinogenicity/ Mutagenicity/ Impairment of Fertility**). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

- **Lactation**

Rosuvastatin is contraindicated during lactation. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans (see **Contraindications**).

- **Paediatrics**

Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, rosuvastatin is not recommended for paediatric use at this time (see **DOSAGE AND ADMINISTRATION**).

- **Geriatrics**

see **DOSAGE AND ADMINISTRATION**

- **Carcinogenicity/ Mutagenicity/ Impairment of Fertility**

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenicity potential. In a rat pre- and postnatal study, reproductive toxicity was evident from reduced litter sizes, litter weight and pup survival. These effects were observed at maternotoxic doses at systemic exposures several times above the therapeutic exposure level.

- **Drug Interactions**

Cyclosporin: During concomitant treatment with rosuvastatin and cyclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see **Contraindications**). Concomitant administration did not affect plasma concentrations of cyclosporin.

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) may result in an increase in International Normalized Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Gemfibrozil: As with other HMG-CoA reductase inhibitors, concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see **Warnings**).

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_{0-t} and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl oestradiol 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.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interactions with digoxin or fenofibrate are expected. Gemfibrozil, other fibrates and lipid lowering doses (≥ 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see **Warnings**).

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.

- **Adverse Effects**

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

Nervous system disorders

Common (>1/100, <1/10): headache, dizziness

Gastrointestinal disorders

Common: constipation, nausea, abdominal pain

Musculoskeletal, connective tissue and bone disorders

Common: myalgia

Rare (>1/10,000, <1/1000): myopathy

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, and has not been shown to be predictive of acute or progressive renal disease.

Skeletal muscle effects: As with other HMG-CoA reductase inhibitors, effect on skeletal muscle e.g. uncomplicated myalgia and myopathy, have been reported in rosuvastatin -treated patients. Rare cases of rhabdomyolysis have been reported in subjects receiving rosuvastatin 80 mg in investigational clinical trials, which were occasionally associated with impairment of renal function. All cases improved on cessation of therapy.

A dose-related increase in CK levels has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be temporarily discontinued (see **Warnings**).

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.

OVERDOSAGE[1]

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.

STORAGE : Store below 25°C, protected from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

SUPPLY:

ROSUVAS 5 mg : Blister strip of 10's, box of 10's, 5 x 10's.
ROSUVAS 10 mg : Blister strip of 10's, box of 10's, 5 x 10's.
ROSUVAS 20 mg : Blister strip of 10's, box of 10's, 5 x 10's.

REFERENCES

1. *ABPI Compendium of Data Sheets and Summary of Product Characteristics; CRESTOR, March 2003.*
2. *Drugs 2002; 62 (14): 2075-2085.*
3. *Drugs of Future 2001; 26 (5): 518-520.*

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