

# ROSULIP

Tablets

## Composition

### Rosulip 10 mg

Each tablet contains 10 mg Rosuvastatin (as calcium).

### Rosulip 20 mg

Each tablet contains 20 mg Rosuvastatin (as calcium).

## 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.

## Pharmacodynamics properties

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. 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.

## Pharmacokinetics and Metabolism

*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.

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

## Special populations:

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

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

*Renal insufficiency:* In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment ( $CrCl < 30$  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 insufficiency:* In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

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

## Indications

### *Treatment of hypercholesterolaemia*

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

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

### *Prevention of Cardiovascular Events*

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

## Contraindications

- 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 x 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.

A 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 & Precautions**

### Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at a 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

### Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin -treated patients with all doses and in particular with doses > 20 mg. 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 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 a 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
- 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  $\leq$  5x 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. A 40 mg dose is contraindicated with concomitant use of a fibrate.

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. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at a 40 mg dose.

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

#### Race

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

#### Protease inhibitors

The concomitant use with protease inhibitors is not recommended.

#### Lactose intolerance

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

#### Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

#### Diabetes Mellitus

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

#### Paediatric population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 10 to 17 years of age taking rosuvastatin is limited to a one-year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and

adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown.

In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

#### Pregnancy &

##### *Pregnancy Category X*

Rosuvastatin is contraindicated in pregnancy and lactation.

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

#### Lactations

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 fetus, 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.

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

### **Adverse Reactions**

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.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

#### *Immune system disorders*

*Rare:* hypersensitivity reactions including angioedema

#### *Endocrine disorders*

*Common:* diabetes mellitus

#### *Nervous system disorders*

*Common:* headache, dizziness

#### *Gastrointestinal disorders*

*Common:* constipation, nausea, abdominal pain

*Rare:* pancreatitis

#### *Skin and subcutaneous tissue disorders*

*Uncommon:* pruritus, rash and urticaria

#### *Musculoskeletal, connective tissue and bone disorders*

*Common:* myalgia

*Rare:* myopathy (including myositis) and rhabdomyolysis

#### *General disorders*

*Common:* asthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

**Renal effects:** Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Rosuvastatin and clinical trial data show that the occurrence is low.

**Skeletal muscle effects:** Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Rosuvastatin - treated patients with all doses and in particular with doses > 20 mg.

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

**Liver effects:** As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

**Post marketing experience:** In addition to the above, the following adverse events have been reported during post marketing experience for ROSUVASTATIN:

*Nervous system disorders: Very rare:* polyneuropathy, memory loss.

*Respiratory, thoracic and mediastinal disorders: Not known:* cough, dyspnoea.

*Gastrointestinal disorders: Not known:* diarrhoea.

*Hepatobiliary disorders: Very rare:* jaundice, hepatitis; *rare:* increased transaminases.

*Skin and subcutaneous tissue disorders: Not known:* Stevens-Johnson syndrome.

*Musculoskeletal disorders: Very rare:* arthralgia.

*Renal disorders: Very rare:* haematuria.

*General disorders and administration site conditions: Not known:* oedema.

The following adverse events have been reported with some statins:

- Depression.
- Sleep disturbances, including insomnia and nightmares.
- Sexual dysfunction.
- Exceptional cases of interstitial lung disease, especially with long term therapy.
- Tendon disorders, sometimes complicated by rupture.
- The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at a 40 mg dose.

**Paediatric population:** Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

## 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. 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 or another coumarin anticoagulant) 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.

*Ezetimibe:* Concomitant use of Rosuvastatin and ezetimibe resulted in no change to AUC or C<sub>max</sub> for either drug. However, a pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and ezetimibe cannot be ruled out.

*Gemfibrozil and other lipid-lowering products:* Concomitant use of Rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C<sub>max</sub> 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 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. A 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with a 5 mg dose.

*Protease inhibitors:* Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. In a pharmacokinetic study, co-administration of 20 mg rosuvastatin and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately two-fold and five-fold increase in rosuvastatin steady-state AUC<sub>(0-24)</sub> and C<sub>max</sub> respectively. Therefore, concomitant use of rosuvastatin in HIV patients receiving protease inhibitors is not recommended.

*Antacid:* The simultaneous dosing of Rosuvastatin with an antacid suspension containing aluminum 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<sub>max</sub> 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 estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

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

*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.

## **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.

Rosulip may be given at any time of day, with or without food.

#### *Treatment of hypercholesterolaemia*

The recommended start dose is 5 mg or 10 mg orally once daily in both statin naïve and patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with a 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when a 40 mg dose is initiated.

#### *Prevention of cardiovascular events*

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

#### *Paediatric population*

Paediatric use should only be carried out by specialists.

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

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

#### Children younger than 10 years

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

#### *Use in the elderly*

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

#### *Dosage in patients with renal insufficiency*

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Rosulip in patients with severe renal impairment is contraindicated for all doses.

#### *Dosage in patients with hepatic impairment*

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Rosulip is contraindicated in patients with active liver disease.

#### *Race*

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



*Dosage in patients with pre-disposing factors to myopathy*

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

**Over Dosage**

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 .

**Presentation**

**Rosulip 10 & 20**

Box of 28 tablets