

## SUMMARY OF PRODUCTS CHARACTERISTICS

### 1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

#### 1.1 Strength

Rosuvastatin Tablets 20 mg

#### 1.2 Pharmaceutical form

Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### 2.1 Qualitative declaration

International Non-Proprietary	Reason for inclusion of ingredient name
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Rosuvastatin Calcium	Active Pharmaceutical ingredient
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### 3. PHARMACEUTICAL FORM

Orange coloured, Circular biconvex film coated tablets with MICRO engraved on one side and other plain on another surface.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Treatment of hypercholesterolemia

Adults, adolescents and children aged 6 years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) 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 hypercholesterolemia 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

## **4.2 Posology and method of 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.

### **Treatment of hypercholesterolemia**

The recommended start dose is 5 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. 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 the 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 hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 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 6 to 17 years of age (Tanner Stage <II-V)

In children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5 mg daily.

- In children 6 to 9 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.

- In children 10 to 17 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

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.

Experience in children with homozygous familial hypercholesterolemia is limited to a small number of children aged between 8 and 17 years.

The 40 mg tablet is not suitable for use in paediatric patients.

### **Children younger than 6 years**

The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 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 Rosuvastatin 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. Rosuvastatin 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. The 40 mg dose is contraindicated in these patients.

## **Genetic polymorphisms**

Specific types of genetic polymorphisms are known that can lead to increased Rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.

## **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.

## **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. ciclosporin and 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 Rosuvastatin 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.

## **Method of administration**

Orally

### **4.3 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 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 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.

### **4.4 Special warnings and precautions for use**

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 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.

### **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 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
- 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. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including Rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

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, 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.

Combination with Rosuvastatin and fusidic acid is not recommended. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

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 the 40 mg dose.

In patients with secondary hypercholesterolemia 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**

Increased systemic exposure to Rosuvastatin has been observed in subjects 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/m<sup>2</sup>, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in Rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l.

### **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 6 to 17 years of age taking Rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected.

## 4.7 Interaction with other medicinal products and other forms of interaction

### Effect of co-administered medicinal products on Rosuvastatin

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: During concomitant treatment with Rosuvastatin and ciclosporin, Rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. 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. For instance, in a pharmacokinetic study, co-administration of 10 mg Rosuvastatin and a combination product of two protease inhibitors (300 mg Atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in Rosuvastatin AUC and C<sub>max</sub> respectively. 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: 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. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of Rosuvastatin in hypercholesterolemia subjects. 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%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in Cmax of Rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from in vitro and in vivo studies show that Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, Rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between Rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

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 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:**

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

Fusidic Acid: Interaction studies with Rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with Rosuvastatin and fusidic acid given concurrently.

Therefore, the combination Rosuvastatin and fusidic acid is not recommended. If possible, temporary suspension of Rosuvastatin treatment is recommended. If unavoidable, patients should be closely monitored.

Additional information on special populations

Not applicable

### **Paediatric population**

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

## **4.6 Fertility, pregnancy and lactation**

General principles

Women of childbearing potential / Contraception in males and females

Not applicable

### **Pregnancy**

Rosuvastatin 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. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

### **Breastfeeding**

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

Fertility

Not applicable

#### 4.7 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.

#### 4.8 Undesirable effects

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).

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

<b>System organ class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>	<b>Not known</b>
<i>Blood and lymphatic system disorders</i>			Thrombocytopenia		
<i>Immune system disorders</i>			Hypersensitivity reactions including angioedema		

<i>Endocrine disorders</i>	Diabetes mellitus 1				
<i>Psychiatric disorders</i>					Depression
<i>Nervous system disorders</i>	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
<i>Respiratory, thoracic and mediastinal disorders</i>					Cough Dyspnoea
<i>Gastro-intestinal disorders</i>	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
<i>Hepatobiliary disorders</i>			Increased hepatic transaminases	Jaundice Hepatitis	
<i>Skin and subcutaneous tissue disorders</i>		Pruritis Rash Urticaria			Stevens-Johnson syndrome

<i>Musculo- skeletal an d</i>	Myalgia		Myopathy (including	Arthralgia	Tendon disorders,
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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.

The following adverse events 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.

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.

#### **4.9 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In vivo studies in animals and in vitro studies in cultured animal and human cells have shown Rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In in vivo and in vitro studies, Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

#### **5.2 Pharmacokinetic properties**

##### **Absorption**

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

##### **Distribution & Plasma Protein Binding**

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.

### **Elimination**

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.

### **Special Population 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 hypercholesterolemia was similar to that of adult volunteers

### **Race:**

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C<sub>max</sub> 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 Cmax. 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 hemodialysis 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 pediatric patients with heterozygous familial hypercholesterolemia aged 10 to 17 years have not been fully characterized. A small pharmacokinetic study with Rosuvastatin (given as tablets) in 18 pediatric patients demonstrated that exposure in pediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

### **5.3 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 histopathology 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tribasic Calcium Phosphate Bp, Microcrystalline Cellulose Bp Lactose Bp, Crosspovidone Bp, Magnesium Stearate Bp, Instacoat Universal Orange.

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

Do not store above 30° C.

Keep all the medicines away from the reach of children.

### **6.5 Nature and contents of container**

10 tablets are packed in Alu/ Alu Blister. Such 3 Blisters are packed in a carton along with a pack insert.

### **6.6 Special precautions for disposal and other handling**

Not applicable

## **7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES**

Marketing Authorization Holder:

Micro Labs Limited

No.27, Race Course Road, Bangalore 5600 001, Karnataka, India

Manufacturing Site:

Micro Labs Limited 92, SIPCOT,

Hosur – 635 126, India.

**8. MARKETING AUTHORISATION NUMBER**

TAN 22 HM 0087

**9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION**

11, April 2022

**10. DATE OF REVISION OF THE TEXT**

April, 2022