



### **1.3 PRODUCT INFORMATION**

#### **1.3.1 Summary of product Characteristics (SmPC)**

The Summary of Product Characteristics has been enclosed in the following pages.

**MSN LABORATORIES PRIVATE LIMITED-FORMULATIONS DIVISION**

**ROSUVASTATIN TABLETS 10 mg**



**SMPC**

# Summary of Product Characteristics

## 1. Name of the medicinal product

LDNIL 5 (Rosuvastatin Tablets 5 mg).

LDNIL 10 (Rosuvastatin Tablets 10 mg).

LDNIL 20 (Rosuvastatin Tablets 20 mg).

LDNIL 40 (Rosuvastatin Tablets 40 mg).

## 2. Qualitative and quantitative composition

### **Rosuvastatin Tablets 5 mg/10 mg/20 mg/40 mg:**

Each film coated Tablet contains Rosuvastatin calcium equivalent to Rosuvastatin 5 mg/10 mg/20 mg/40 mg.

For a full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film coated tablet

5 mg: Yellow colored, round shaped, biconvex film coated tablets with plain surface on both sides.

10 mg: Pink colored, round shaped, biconvex film coated tablets with plain surface on both sides.

20 mg: Pink colored, round shaped, biconvex film coated tablets with plain surface on both sides.

40 mg: Pink colored, oval shaped, biconvex film coated tablets with plain surface on both sides.

## 4. Clinical particulars

### 4.1 Therapeutic indications

#### **Treatment of hypercholesterolaemia**

Adults, adolescents and children aged 6 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.

Adults, adolescents and children aged 6 years or older with 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 (see section 5.1), 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 individualised 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 hypercholesterolaemia**

The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or 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 (see section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see section 4.8), 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 (see section 4.4). 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 (see section 5.1).

#### **Paediatric population**

Paediatric use should only be carried out by specialists.

##### Children and adolescents 6 to 17 years of age (Tanner Stage <II-V)

##### Heterozygous familial hypercholesterolaemia

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

- In children 6 to 9 years of age with heterozygous familial hypercholesterolaemia, 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 hypercholesterolaemia, 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 (see section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

#### Homozygous familial hypercholesterolaemia

In children 6 to 17 years of age with homozygous familial hypercholesterolaemia, the recommended maximum dose is 20 mg once daily.

A starting dose of 5 to 10 mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20 mg once daily should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

There is limited experience with doses other than 20 mg in this population.

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 (see section 4.4). 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 <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 (see sections 4.3 and 5.2).

### **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 section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin is contraindicated in patients with active liver disease (see section 4.3).

### **Race**

Increased systemic exposure has been seen in Asian subjects (see sections 4.3, 4.4 and 5.2). 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 (see section 5.2). 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 (see section 4.4).

The 40 mg dose is contraindicated in some of these patients (see section 4.3).

### **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; see sections 4.4 and 4.5). 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 (see section 4.5).

### **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 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.

(See sections 4.4, 4.5 and 5.2)

#### **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 (see section 4.8). 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 (see section 4.5) and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin in post-marketing use is higher at the 40 mg dose.

#### *Creatine Kinase Measurement*

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline ( $>5xULN$ ) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK  $>5xULN$ , treatment should not be started.

#### *Before Treatment*

Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age  $>70$  years
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)
- 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 characterised 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 (see sections 4.5 and 4.8).

Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of Rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

### Liver Effects

As with other HMG-CoA reductase inhibitors, Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

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

### Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2, 4.3 and 5.2).

### 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. (See sections 4.2 and 4.5).

### 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 (see section 4.8). 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 (see section 5.1).

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 (see section 4.8).

## **4.5 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 (see sections 4.2, 4.4 and 4.5 Table 1).

*Ciclosporin:* During concomitant treatment with Rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). 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 (see Table 1). 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  $C_{max}$  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 (see sections 4.2, 4.4 and 4.5 Table 1).

**Gemfibrozil and other lipid-lowering products:** Concomitant use of Rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin  $C_{max}$  and AUC (see section 4.4).

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 (see sections 4.3 and 4.4). These patients should also start with the 5 mg dose.

**Ezetimibe:** Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and ezetimibe cannot be ruled out (see section 4.4).

**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  $C_{max}$  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).

**Interactions requiring rosuvastatin dose adjustments (see also Table 1):** When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastatin should be adjusted. Start with a 5 mg once daily dose of Rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of Rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of Rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of Rosuvastatin with combination ritonavir/atazanavir (3.1-fold increase).

<b>Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials</b>		
<b>Interacting drug dose regimen</b>	<b>Rosuvastatin dose regimen</b>	<b>Change in rosuvastatin AUC*</b>
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑

Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

\*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone.

Increase is indicated as “↑”, no change as “↔”, decrease as “↓”.

\*\*Several interaction studies have been performed at different Rosuvastatin dosages, the table shows the most significant ratio

OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

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

**Vitamin K antagonists:** As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of Rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

**Oral contraceptive/hormone replacement therapy (HRT):** Concomitant use of Rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel 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. The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, Rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

**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**

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 (see section 5.3). 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 (see section 4.3).

#### **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  $< 1/1000$ ); Very rare ( $< 1/10,000$ ); Not known (cannot be estimated from the available data).

**Table 2. Adverse reactions based on data from clinical studies and post-marketing experience**

<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 <sup>1</sup>				
<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</i>					Cough Dyspnoea



<i>disorders</i>					
<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>		Pruritus Rash Urticaria			Stevens-Johnson syndrome
<i>Musculo-skeletal and connective tissue disorders</i>	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy
<i>Renal and urinary disorders</i>				Haematuria	
<i>Reproductive system and breast disorders</i>				Gynaecomastia	
<i>General disorders and administration site conditions</i>	Asthenia				Oedema

<sup>1</sup>Frequency will depend on the presence or absence of risk factors (fasting blood glucose  $\geq 5.6$  mmol/L, BMI  $>30$  kg/m<sup>2</sup>, 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. 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 ( $>5$ xULN), treatment should be discontinued (see section 4.4).

**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 (see section 4.4).

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  $>10$ xULN 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 (see section 4.4). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### **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. Haemodialysis is unlikely to be of benefit.

## **5. Pharmacological properties**

### **5.1 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 (see Table 3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

**Table 3 Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)**

<b>Dose</b>	<b>N</b>	<b>LDL-C</b>	<b>Total-C</b>	<b>HDL-C</b>	<b>TG</b>	<b>nonHDL-C</b>	<b>ApoB</b>	<b>ApoA-I</b>
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Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
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.

### **Clinical efficacy and safety**

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.

From pooled phase III data, 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) to recognised 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 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 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 paediatric 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 section 4.4).

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 randomised

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 Rosuvastatin 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see section 4.2).

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 ( $\geq 50$  years) and women ( $\geq 60$  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  $\geq 5\%$  (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, randomised, 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 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia 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 10-13 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 (see section 4.4). 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 hypercholesterolaemia 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, 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 (see section 4.4).

Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multicenter, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. 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%,  $p=0.003$ ), nonHDL-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, nonHDL-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.

In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolaemia (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 hypercholesterolaemia.

The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the paediatric population in the treatment of homozygous familial

hypercholesterolaemia, primary combined (mixed) dyslipidaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

## **5.2 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%). *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 exposure in children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to or lower than that in adult patients with dyslipidaemia (see “Paediatric population” below).



**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.

**Genetic polymorphisms:** Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.

**Paediatric population:** Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

### **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 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.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

**Tablet core: Composition for 5/10/20/40 mg:** Microcrystalline cellulose, Pregelatinized starch, Crospovidone, Meglumine, Mannitol, Magnesium stearate.

**Coating material composition for 5 mg:** HPMC 2910/Hypromellose (5 cP, 15cP), Titanium Dioxide, Talc, Triacetin, Iron Oxide Yellow, Iron Oxide Red, Iron Oxide Black.

**Coating material composition for 10/20/40 mg:** HPMC 2910/Hypromellose (6 cP), Titanium Dioxide, Triacetin, Iron Oxide Red, Iron Oxide Yellow.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

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

Do not store above 30°C, Protect from light and moisture.

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

Alu - Alu blister pack of 10 tablets.

Rosuvastatin Tablets 5 mg/10 mg/20 mg/40 mg are available in pack sizes of 10 and 30 film-coated tablets.

Not all pack sizes may be marketed.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### **7. Marketing authorisation holder**

MSN Laboratories Private Limited

MSN House, Plot No.: C-24,

Industrial Estate, Sanath Nagar,

Hyderabad, Telangana,

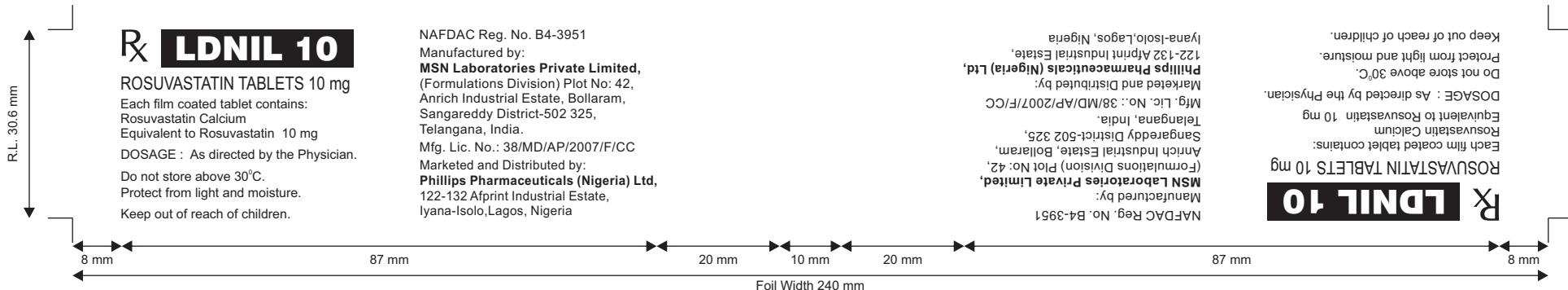
Pin code - 500018, India

#### **8. Date of revision of the text**

September 2018

### 1.3.2 Labelling (outer & inner labels)

The artworks of container label, carton & Pack Insert for LDNIL 10 (Rosuvastatin Tablets 10 mg) are enclosed in the following pages.

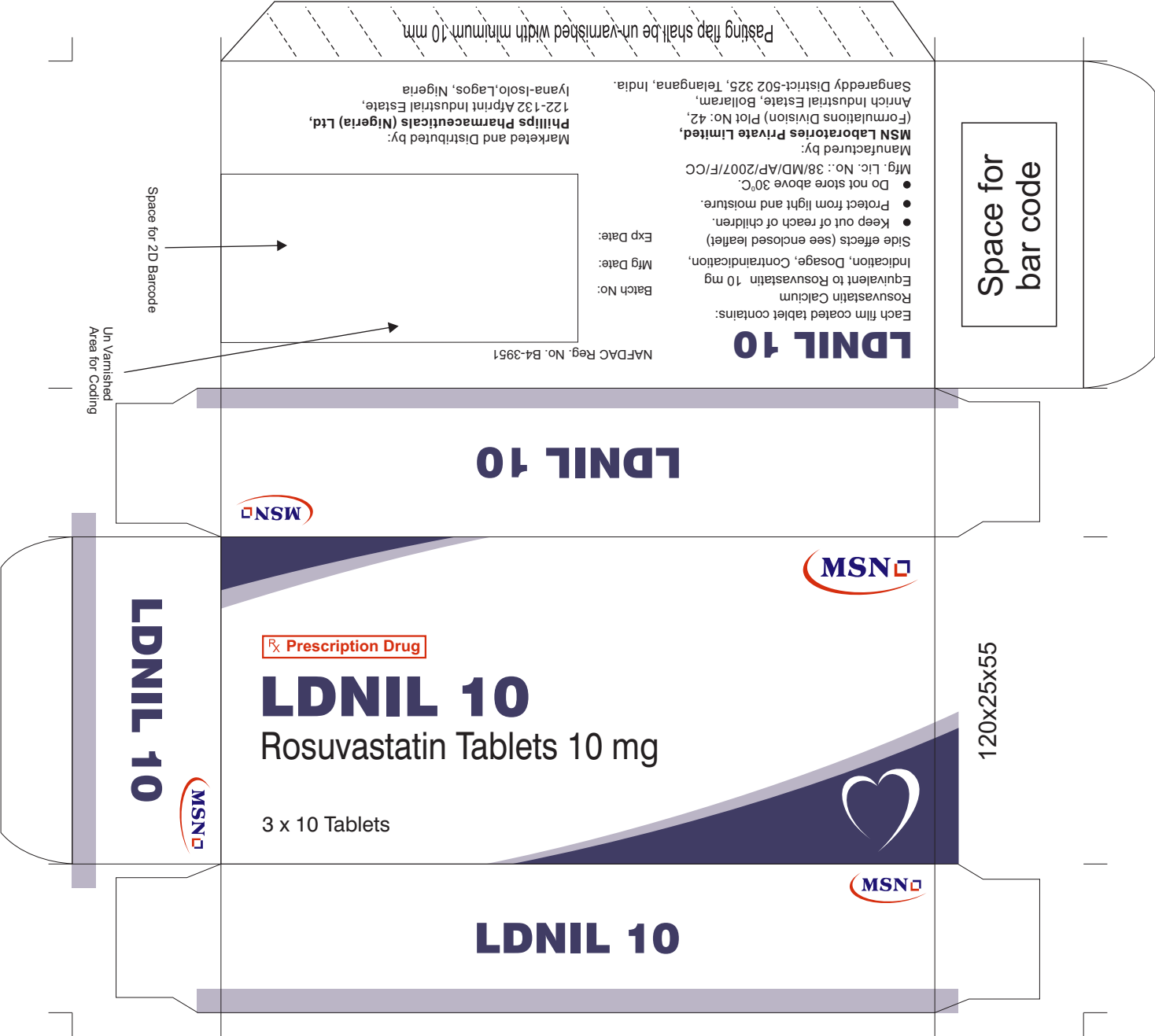


 BLACK (CMYK)

Foil Width 240 mm  
 ALUALU Blister Size 114 x 46mm (Repeat 1.5)  
 size : 8 + 87 + 20 + 10 + 20 + 87 + 8 mm

Blister Foil

Test	Specification
1. Description	Printed hard tampered aluminium foil with VMCH coating on the sealing side.
2. Thickness of Aluminium	0.023 to 0.027 mm
3. Width	240 ± 1.0 mm (239 – 241 mm)
4. Aluminium foil GSM VMCH Coating GSM	62.33 to 73.17 GSM 4 to 6 GSM
5. Pin Holes	Nil
6. Ink Adhesion Test	Nil
7. Inner Core Diameter	76 ± 1 mm



PANTONE 5265 C
  PANTONE 273 C
  PANTONE 485 C
  Black

DIMENSION : 120x25x55 mm  
 Cyber XL Board 300 gsm, Modulus 3, Page No 30  
 Wordislex.com printing area.









**1.3.3 Package Insert (also known as patient information PIL)**

Patient Information leaflet for LDNIL 10 (Rosuvastatin Tablets 10 mg) has been enclosed in the following pages.

## Package leaflet: information for the patient

**LDNIL 5 /10/20/40 (Rosuvastatin Tablets 5 mg / 10 mg/ 20 mg/ 40 mg ).**

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Rosuvastatin is and what it is used for
2. What you need to know before you take Rosuvastatin Tablets
3. How to take Rosuvastatin Tablets
4. Possible side effects
5. How to store Rosuvastatin Tablets
6. Contents of the pack and other information

#### **1. What Rosuvastatin is and what it is used for**

**Rosuvastatin** belongs to a group of medicines called statins.

#### **You have been prescribed Rosuvastatin because:**

- You have a high cholesterol level. This means you are at risk from a heart attack or stroke. Rosuvastatin is used in adults, adolescents and children 6 years or older to treat high cholesterol.

You have been advised to take a statin, because changing your diet and doing more exercise were not enough to correct your cholesterol levels. You should continue with your cholesterol-lowering diet and exercise while you are taking Rosuvastatin.

Or

- You have other factors that increase your risk of having a heart attack, stroke or related health problems.

Heart attack, stroke and other problems can be caused by a disease called atherosclerosis. Atherosclerosis is due to build up of fatty deposits in your arteries.

#### **Why it is important to keep taking Rosuvastatin**

Rosuvastatin is used to correct the levels of fatty substances in the blood called lipids, the most common of which is cholesterol.

There are different types of cholesterol found in the blood - ‘bad’ cholesterol (LDL-C) and ‘good’ cholesterol (HDL-C).

- Rosuvastatin can reduce the ‘bad’ cholesterol and increase the ‘good’ cholesterol.

- It works by helping to block your body's production of 'bad' cholesterol. It also improves your body's ability to remove it from your blood.

For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of your blood vessels causing them to narrow.

Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering your cholesterol levels, you can reduce your risk of having a heart attack, a stroke or related health problems.

You need to keep taking Rosuvastatin, even if it has got your cholesterol to the right level, because it prevents your cholesterol levels from creeping up again and causing build up of fatty deposits. However, you should stop if your doctor tells you to do so, or you have become pregnant.

## 2. What you need to know before you take Rosuvastatin Tablets

Do not take Rosuvastatin Tablets :

- If you have ever had an allergic reaction to Rosuvastatin Tablets , or to any of its ingredients.
- If you are pregnant or breast-feeding. If you become pregnant while taking Rosuvastatin Tablets stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking Rosuvastatin Tablets by using suitable contraception.
- If you have liver disease.
- If you have severe kidney problems.
- If you have repeated or unexplained muscle aches or pains.
- If you take a drug called ciclosporin (used, for example, after organ transplants).

If any of the above applies to you (or you are in doubt), please go back and see your doctor.

In addition, do not take Rosuvastatin Tablets 40 mg (the highest dose):

- If you have moderate kidney problems (if in doubt, please ask your doctor).
- If your thyroid gland is not working properly.
- If you have had any repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines.
- If you regularly drink large amounts of alcohol.
- If you are of Asian origin (Japanese, Chinese, Filipino, Vietnamese, Korean and Indian).
- If you take other medicines called fibrates to lower your cholesterol.

If any of the above applies to you (or you are in doubt), please go back and see your doctor.

### Warnings and precautions

Talk to your doctor or pharmacist before taking Rosuvastatin Tablets

- If you have problems with your kidneys.
- If you have problems with your liver.
- If you have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Also tell your doctor or pharmacist if you have a muscle weakness that is constant.
- If you regularly drink large amounts of alcohol.
- If your thyroid gland is not working properly.

- If you take other medicines called fibrates to lower your cholesterol. Please read this leaflet carefully, even if you have taken other medicines for high cholesterol before.
- If you take medicines used to treat the HIV infection e.g. ritonavir with lopinavir and/or atazanavir, please see Other medicines and Rosuvastatin Tablets .
- If you are taking or have taken in the last 7 days a medicine called fusidic acid (a medicine for bacterial infection), orally or by injection. The combination of fusidic acid and Rosuvastatin Tablets can lead to serious muscle problems (rhabdomyolysis), please see Other medicines and Rosuvastatin Tablets .
- If you are over 70 (as your doctor needs to choose the right start dose of Rosuvastatin Tablets to suit you)
- If you have severe respiratory failure.
- If you are of Asian origin - that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. Your doctor needs to choose the right start dose of Rosuvastatin Tablets to suit you.

If any of the above applies to you (or if you are not sure):

- Do not take Rosuvastatin Tablets 40 mg (the highest dose) and check with your doctor or pharmacist before you actually start taking any dose of Rosuvastatin Tablets

In a small number of people, statins can affect the liver. This is identified by a simple test which looks for increased levels of liver enzymes in the blood. For this reason, your doctor will usually carry out this blood test (liver function test) before and during treatment with Rosuvastatin Tablets .

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

#### Children and adolescents

- If the patient is under 6 years old: Rosuvastatin Tablets should not be given to children younger than 6 years.
- If the patient is below 18 years of age: The Rosuvastatin Tablets 40 mg tablet is not suitable for use in children and adolescents below 18 years of age.

#### Other medicines and Rosuvastatin Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

Tell your doctor if you are taking any of the following: ciclosporin (used for example, after organ transplants), warfarin or clopidogrel (or any other drug used for thinning the blood), fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe), indigestion remedies (used to neutralise acid in your stomach), erythromycin (an antibiotic), fusidic acid (an antibiotic - please see below and Warnings and precautions), an oral contraceptive (the pill), hormone replacement therapy or anti-viral medications such as ritonavir with lopinavir and/or atazanavir or simeprevir (used to treat infections, including HIV or hepatitis C infection - please see Warnings and precautions). The effects of these medicines could be changed by Rosuvastatin Tablets or they could change the effect of Rosuvastatin Tablets .

**If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart Rosuvastatin Tablets . Taking Rosuvastatin Tablets with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in Section 4.**

## **Pregnancy and breast-feeding**

**Do not take Rosuvastatin Tablets** if you are pregnant or breast-feeding. If you become pregnant while taking Rosuvastatin Tablets **stop taking it immediately** and tell your doctor. Women should avoid becoming pregnant while taking Rosuvastatin Tablets by using suitable contraception.

Ask your doctor or pharmacist for advice before taking any medicine.

## **Driving and using machines**

Most people can drive a car and operate machinery while using Rosuvastatin Tablets - it will not affect their ability. However, some people feel dizzy during treatment with Rosuvastatin Tablets . If you feel dizzy, consult your doctor before attempting to drive or use machines.

Rosuvastatin Tablets contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars (lactose or milk sugar), contact your doctor before taking Rosuvastatin Tablets .

For a full list of ingredients, please see **Contents of the pack and other information**.

### **3. How to take Rosuvastatin Tablets**

Always take this medicine as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

#### **Usual doses in adults**

#### **If you are taking Rosuvastatin Tablets for high cholesterol:**

##### **Starting dose**

Your treatment with Rosuvastatin Tablets must start with the **5 mg or the 10 mg dose**, even if you have taken a higher dose of a different statin before. The choice of your start dose will depend upon:

- Your cholesterol level.
- The level of risk you have of experiencing a heart attack or stroke.
- Whether you have a factor that may make you more sensitive to possible side effects.

Please check with your doctor or pharmacist which start dose of Rosuvastatin Tablets will best suit you.

Your doctor may decide to give you the lowest dose (5 mg) if:

- You are of **Asian origin** (Japanese, Chinese, Filipino, Vietnamese, Korean and Indian).
- You are **over 70 years** of age.
- You have moderate kidney problems.
- You are at risk of muscle aches and pains (myopathy).

#### **Increasing the dose and maximum daily dose**

Your doctor may decide to increase your dose. This is so that you are taking the amount of Rosuvastatin that is right for you. If you started with a 5 mg dose, your doctor may decide to

double this to 10 mg, then 20 mg and then 40 mg if necessary. If you started on 10 mg, your doctor may decide to double this to 20 mg and then 40 mg if necessary. There will be a gap of four weeks between every dose adjustment.

The maximum daily dose of Rosuvastatin Tablets is 40 mg. It is only for patients with high cholesterol levels and a high risk of heart attacks or stroke whose cholesterol levels are not lowered enough with 20 mg.

**If you are taking Rosuvastatin Tablets to reduce your risk of having a heart attack, stroke or related health problems:**

The recommended dose is 20 mg daily. However, your doctor may decide to use a lower dose if you have any of the factors mentioned above.

**Use in children and adolescents aged 6-17 years**

The dose range in children and adolescents aged 6 to 17 years is 5 to 20 mg once daily. The usual start dose is 5 mg per day, and your doctor may gradually increase your dose to find the right amount of Rosuvastatin Tablets for you. The maximum daily dose of Rosuvastatin Tablets is 10 or 20 mg for children aged 6 to 17 years depending on your underlying condition being treated. Take your dose once a day. Rosuvastatin Tablets **40 mg** tablet should **not** be used by children.

**Taking your tablets**

Swallow each tablet whole with a drink of water.

**Take Rosuvastatin Tablets once daily.** You can take it at any time of the day with or without food.

Try to take your tablet at the same time every day to help you to remember it.

**Regular cholesterol checks**

It is important to go back to your doctor for regular cholesterol checks, to make sure your cholesterol has reached and is staying at the correct level.

Your doctor may decide to increase your dose so that you are taking the amount of Rosuvastatin Tablets that is right for you.

**If you take more Rosuvastatin than you should**

Contact your doctor or nearest hospital for advice.

If you go into hospital or receive treatment for another condition, tell the medical staff that you're taking Rosuvastatin Tablets .

**If you forget to take Rosuvastatin Tablets**

Don't worry, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

### **If you stop taking Rosuvastatin Tablets.**

Talk to your doctor if you want to stop taking Rosuvastatin Tablets . Your cholesterol levels might increase again if you stop taking Rosuvastatin Tablets .

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

It is important that you are aware of what these side effects may be. They are usually mild and disappear after a short time.

**Stop taking Rosuvastatin Tablets and seek medical help immediately** if you have any of the following allergic reactions:

- Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat.
- Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing.
- Severe itching of the skin (with raised lumps).

**Also, stop taking Rosuvastatin Tablets and talk to your doctor immediately if you have any unusual aches or pains** in your muscles which go on for longer than you might expect. Muscle symptoms are more common in children and adolescents than in adults. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as *rhabdomyolysis*.

### **Common possible side effects (these may affect between 1 in 10 and 1 in 100 patients):**

- Headache
- Stomach pain
- Constipation
- Feeling sick
- Muscle pain
- Feeling weak
- Dizziness
- An increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking your Rosuvastatin tablets (only Rosuvastatin Tablets 40 mg)
- Diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

### **Uncommon possible side effects (these may affect between 1 in 100 and 1 in 1,000 patients):**

- Rash, itching or other skin reactions
- An increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking your Rosuvastatin tablets (only Rosuvastatin Tablets 5 mg, 10 mg and 20 mg).

**Rare possible side effects (these may affect between 1 in 1,000 and 1 in 10,000 patients):**

- Severe allergic reaction - signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing, a severe itching of the skin (with raised lumps). **If you think you are having an allergic reaction, then stop taking Rosuvastatin Tablets and seek medical help immediately**
- Muscle damage in adults - as a precaution, **stop taking Rosuvastatin Tablets and talk to your doctor immediately if you have any unusual aches or pains** in your muscles which go on for longer than expected
- A severe stomach pain (inflamed pancreas)
- Increase in liver enzymes in the blood

**Very rare possible side effects (these may affect less than 1 in 10,000 patients):**

- Jaundice (yellowing of the skin and eyes)
- Hepatitis (an inflamed liver)
- Traces of blood in your urine
- Damage to the nerves of your legs and arms (such as numbness)
- Joint pain
- Memory loss
- Breast enlargement in men (gynaecomastia)

**Side effects of unknown frequency may include:**

- Diarrhoea (loose stools)
- Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals)
- Cough
- Shortness of breath
- Oedema (swelling)
- Sleep disturbances, including insomnia and nightmares
- Sexual difficulties
- Depression
- Breathing problems, including persistent cough and/or shortness of breath or fever
- Tendon injury
- Muscle weakness that is constant

**Reporting of side effects:**

If you get any side effects talk to your doctor or pharmacist.



## 5. How to store Rosuvastatin Tablets

- Store below 30°C. Store in the original package in order to protect from moisture.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blisters/label after EXP. The expiry date refers to the last day of the month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information What Rosuvastatin. Calcium contains:

The active substance in Rosuvastatin Tablets is Rosuvastatin. Calcium

### Tablet core:

**Composition for 5/10/20/40 mg:** Microcrystalline cellulose, Pregelatinized starch, Crospovidone, Meglumine, Mannitol, Magnesium stearate.

**Coating material composition for 5 mg:** HPMC 2910/Hypromellose (5 cP, 15cP), Titanium Dioxide, Talc, Triacetin, Iron Oxide Yellow, Iron Oxide Red, Iron Oxide Black.

**Coating material composition for 10/20/40 mg:** HPMC 2910/Hypromellose(6 cP) ,Titanium Dioxide, Triacetin, Iron Oxide Red, Iron Oxide Yellow.

### What Rosuvastatin Tablets looks like and contents of the pack

Rosuvastatin Tablets comes in Alu - Alu blister pack of 10 tablets.

Rosuvastatin Tablets 5 mg/10 mg/20 mg/40 mg are available in pack sizes of 10 and 30 film-coated tablets.

Not all pack sizes may be marketed.

### Rosuvastatin Tablets comes in four tablet strengths:

5 mg: Yellow colored, round shaped, biconvex film coated tablets with plain surface on both sides.

10 mg: Pink colored, round shaped, biconvex film coated tablets with plain surface on both sides.

20 mg: Pink colored, round shaped, biconvex film coated tablets with plain surface on both sides.

40 mg: Pink colored, oval shaped, biconvex film coated tablets with plain surface on both sides.

### Marketing Authorisation Holder and Manufacturer

#### Marketing Authorisation Holder:

MSN Laboratories Private Limited

MSN House, Plot No.: C-24,

Industrial Estate, Sanath Nagar,

Hyderabad, Telangana,

Pin code - 500018, India

**Manufactured By:**

MSN Laboratories Private Limited - Formulations Division

Plot No.: 42, ANRICH Industrial Estate,

Bollaram, Sangareddy District, Pin Code - 502 325,

Telangana, India.