Summary Product Characteristics (SPC):

Enclosed

1. **Name of the medicinal product:** ROSHNI-5 (Rosuvastatin Tablets 5 mg)

2. **Qualitative and Quantitative composition:**

Sr. No	Ingredients	Specification	Label Claim (mg)	Overages	Qty/tab (mg)	Reason for inclusion
DRY MIXING						
1.	Rosuvastatin Calcium Eq. to rosuvastatin	BP	5.00	2%	5.30	Active
2.	Lactose	BP	--	--	30.00	Diluent
3.	Microcrystalline cellulose	BP	--	--	29.00	Diluent
4.	Polyvinyl Pyrrolidone (PVPK-30)	BP	--	--	2.70	Binder
5.	Isopropyl alcohol	BP	--	--	q.s.	Solvent
LUBRICANT						
6.	Purified Talc	BP	--	--	1.00	Glidant
7.	Magnesium Stearate	BP	--	--	0.50	Lubricant
8.	Colloidal Silicon Dioxide	BP	--	--	0.50	Glidant
9.	Croscarmellose Sodium	USPNF	--	--	1.00	Disintegrant
COATING						
10.	Instacoat yellow	IH	--	--	2.45	Coating Agent
11.	Methylene Chloride	BP	--	--	q.s.	Solvent
12.	Isopropyl alcohol	BP	--	--	q.s.	Solvent

Where, USPNF: United States Pharmacopoeia National Formulatory, BP: British Pharmacopoeia, IH: In-House, q.s.: quantity sufficient

Calculation:

- Molecular weight of Rosuvastatin Calcium is 1001.14 mg
- Molecular weight of Rosuvastatin is 481.539 mg

Here two molecules of Rosuvastatin bind with calcium ion
So, 963.078 mg of Rosuvastatin eq. to 1001.14 mg of Rosuvastatin Calcium
5 mg of Rosuvastatin eq. to 5.20 mg of Rosuvastatin Calcium

3. Pharmaceutical Form: Film coated Tablet

4. Clinical Particulars:

4.1 Therapeutic Indications
Rosuvastatin is indicated for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia resistant to dietary measures, and as an adjunct to other lipid lowering treatments in homozygous familial hypercholesterolaemia.

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.
The recommended start dose is 5 mg 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 2. 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 hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated.
Rosuvastatin Tablets 5 mg may be given at any time of day, with or without food.

Paediatric use
Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, Rosuvastatin Tablets 5 mg is not recommended for paediatric use at this time.

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 Tablets 5 mg 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 Tablets 5 mg 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.

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. Interactions requiring dose adjustments

Ciclosporin: Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant Rosuvastatin Tablets 5 mg and Ciclosporin. For the Rosuvastatin Tablets 5 mg dose range (10 – 40 mg) this combination is not recommended.

Gemfibrozil: Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant Rosuvastatin Tablets 5 mg and gemfibrozil. therefore, combination therapy with Rosuvastatin Tablets 5 mg and gemfibrozil should be avoided. If used, do not exceed Rosuvastatin Tablets 5 mg 10 mg once daily.

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 Tablets 5 mg is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins. Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosuvastatin Tablets 5 mg therapy. In situations where co-administration of these medicinal products with Rosuvastatin Tablets 5 mg is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin Tablets 5 mg dosing adjustments should be carefully considered.

4.3 Contraindications
Rosuvastatin Tablets 5 mg 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 Tablets 5 mg, in particular 40 mg, where it was transient or intermittent in most 4 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 40mg 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 Tablets 5 mg-treated patients with all doses and in particular with doses > 20mg. 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 Tablets 5 mg in post-marketing use is higher at the 40 mg dose.

There have been very rare reports of an immune-mediated necrotizing myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

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 Tablets 5 mg, 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 ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin Tablets 5 mg 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 Tablets 5 mg 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 Tablets 5 mg and gemfibrozil is not recommended If used, do not exceed ROSUVASTATIN TABLETS 5 MG 10 mg once daily. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin Tablets 5 mg 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. Rosuvastatin Tablets 5 mg 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 Tablets 5 mg 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 Tablets 5 mg 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 Tablets 5 mg.

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 Tablets 5 mg in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin Tablets 5 mg

doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin Tablets 5 mg is adjusted.

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose 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
As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin, and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes.Patients at risk (i.e. those with fasting glucose 5.6 - 6.9 mmol/L, body mass index > 30kg/m2, raised triglycerides or hypertension) should be monitored both clinically and biochemically.

Paediatric population
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 10 to 17 years of age taking rosuvastatin is limited to a one-year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown. In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations>10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

4.5 Interaction with other medicinal products and other forms of interaction
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 Tablets 5 mg 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 Tablets 5 mg and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers.
Rosuvastatin Tablets 5 mg is contraindicated in patients receiving concomitant ciclosporin.
Concomitant administration did not affect plasma concentrations of ciclosporin.
Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin Tablets 5 mg 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 Tablets 5 mg may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin Tablets 5 mg and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin Tablets 5 mg and ezetimibe cannot be ruled out.

Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin Tablets 5 mg and gemfibrozil resulted in a 2-fold increase in rosuvastatin C max 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.

Protease inhibitors:
Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure(see Table 1) . In a pharmacokinetic study, co-administration of 20 mg rosuvastatin and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately two-fold and five-fold increase in rosuvastatin steady-state AUC(0-24) and Cmax respectively. Therefore, concomitant use of rosuvastatin in HIV patients receiving protease inhibitors is not recommended.

Antacid:
The simultaneous dosing of Rosuvastatin Tablets 5 mg 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 Tablets 5 mg. The clinical relevance of this interaction has not been studied.

Erythromycin:
Concomitant use of Rosuvastatin Tablets 5 mg and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of Rosuvastatin Tablets 5 mg 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 Tablets 5 mg and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

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

Cytochrome P450 enzymes: Results from in vitro and in vivo studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4). Concomitant administration of itraconazole (an inhibitor of CYP3A4) and rosuvastatin resulted in a 28% increase in AUC of rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

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

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC
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 ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC
Eltrombopag 75 mg OD, 10 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 or 80 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	28% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	28% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

4.6 Pregnancy and Lactation

Rosuvastatin Tablets 5 mg 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.

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

4.7 Effects on the ability to drive and use machines

Studies to determine the effect of Rosuvastatin Tablets 5 mg on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamics properties, Rosuvastatin Tablets 5 mg 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 events seen with Rosuvastatin Tablets 5 mg are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin Tablets 5 mg-treated patients were withdrawn due to adverse events.
The frequencies of adverse events are ranked according to the following: Common (>1/100, 1/1000, 1/10,000, 1/10,000).
Immune system disorders
Rare: hypersensitivity reactions including angioedema
Endocrine disorders
Common: diabetes mellitus Nervous system disorders Common: headache, dizziness
Gastrointestinal disorders
Common: constipation, nausea, abdominal pain
Rare: pancreatitis
Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria
Musculoskeletal, connective tissue and bone disorders
Common: myalgia
Rare: myopathy (including myositis) and rhabdomyolysis.
General disorders
Common: asthenia
[1] Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.
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 Tablets 5 mg. 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 Tablets 5 mg 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 Tablets 5 mg-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.

Laboratory Effects: Increases in HbA1c have also been observed in patients treated with rosuvastatin. Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in a small number of patients taking ROSUVASTATIN TABLETS 5 MG and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

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 Particulars:

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.

5.2Pharmacokinetic 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 Ndesmethyl 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

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and Cmax 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 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 Tablets 5 mg is recommended.

5.3 Pre-clinical Safety:
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, 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:

Lactose	BP
Microcrystalline cellulose	BP
Polyviny Pyrrolidone (PVPK-30)	BP
Isopropyl alcohol	BP
Purified Talc	BP
Magnesium Stearate	BP
Colloidal Silicon Dioxide	BP
Croscarmellose Sodium	USPNF
Instacoat yellow	IH
Methylene Chloride	BP
Isopropyl alcohol	BP

6.2 Incompatibilities:
Not Applicable

6.3 Shelf Life:
36 months.

6.4 Special Precautions for storage:
Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container:
Alu-PVC blisters of 10 tablets, such 3 blisters are packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing Authorization Holder: VAPI CARE PHARMA PVT. LTD.

8. Marketing Authorization Number: --

9. Date of first Authorization /renewal of the authorization: --

10. Date of revision of text: April 2018