1.3.1 Summary of Product characteristics (SmPC)

1.3.1.1 Name of the medicinal product

International Non– Proprietary Name (INN)	Rosuvastatin Calcium
Trade mark name	**Ajacin-20**
Generic Name	Rosuvastatin Calcium Tablets

1.3.1.2 ATC and Forensic Classification

Name	ATC Code	Category/Name
Rosuvastatin Calcium	C10AA07	HMG CoA reductase inhibitors

1.3.1.3 Qualitative and quantitative composition

Sr. No.	Material Name	Spc.	Function	Theo. qty./ Tab. (mg)
Mixing				
1.	$Rosuvastatin Calcium (Factor: 1.040)	IH	Active	20.800
2.	Lactose DC-21	IH	Diluent	160.00
3.	MCCP (PH 102)	IH	Diluent	123.00
4.	Magnesium Hydroxide	BP	Diluent	5.000
5.	Crospovidone	USP	Disintegrant	14.200
Lubrication				
6.	Magnesium Stearate	BP	Lubricant	4.000
Film Coating				
7.	@Instacoat IC-S-6206 (Pink)	IH	Colouring Agent	6.000
8.	@Titanium Dioxide	BP	Colouring Agent	0.800
9.	@#Isopropyl Alcohol	BP	Solvent	0.060 ml
10.	@#Dichloromethane	BP	Solvent	0.1200 gm

Note: $Qty. of active materials shall be vary with assay and LOD.
(Assay considered is 100 % and LOD 0 %)
Final qty. shall be compensated with Lactose DC-21.

Quantity of these materials will not be calculated in total weight of tablet.
@ Overages of coating materials are added to compensate the loss during coating.
Average weight of coated tablet after coating should be achieved approximately 2.08 %

Note:
USP- United States Pharmacopeia
BP – British Pharmacopeia
IH- In-house Specification

1.3.1.4 Pharmaceutical Form

Solid Oral dosage form (Oral Tablet)

Description: Pink coloured, round shaped, biconvex, film coated tables having break-line on one side and other side plain.

1.3.1.5 Clinical particulars

1.3.1.5.1 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, as an adjunct to correction of other risk factors.

1.3.1.5.2 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 and patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in patients with severe 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.

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

Paediatric population

Paediatric use should only be carried out by specialists.

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

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

Race: Increased systemic exposure has been seen in Asian subjects. The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.
Genetic polymorphisms: Specific types of genetic polymorphisms are known that can lead to increased Rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.
Dosage in patients with pre-disposing factors to myopathy: The recommended start dose is 5 mg in patients with predisposing factors to myopathy.
The 40 mg dose is contraindicated in some of these patients.
Concomitant therapy: Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of Rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir and/or tipranavir). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosuvastatin therapy. In situations where co-administration of these medicinal products with Rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin dosing adjustments should be carefully considered.

1.3.1.5.3 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

1.3.1.5.4 Special warnings and precautions for use

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

Skeletal Muscle Effects: Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin in post-marketing use is higher at the 40 mg dose.

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

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

- Renal impairment
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse
- Age >70 years
- Situations where an increase in plasma levels may occur.
- Concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on Treatment: Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5xULN). 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. 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. 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.

Protease Inhibitors: Increased systemic exposure to Rosuvastatin has been observed in subjects receiving Rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of Rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased Rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin is adjusted.

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

Interstitial Lung Disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy.
Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Diabetes Mellitus: Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate.
This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m^2, 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.
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.

1.3.1.5.5 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.
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. 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 f seven-fold increase in Rosuvastatin AUC() and Cmax respectively. The concomitant use of Rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin dose adjustments based on the expected increase in Rosuvastatin exposure.

Gemfibrozil and other lipidlowering products: Concomitant use of Rosuvastatin and gemfibrozil resulted in a 2fold 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.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin 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 and ezetimibe cannot be ruled out.

Antacid: The simultaneous dosing of Rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in Rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin. The clinical relevance of this interaction has not been studied.

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

Cytochrome P_{450} enzymes: Results from in vitro and in vivo studies show that Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. Therefore, drug interactions resulting from cytochrome P450mediated metabolism are not expected. 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).

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 2fold 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).

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 ↑
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.

1.3.1.5.6 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. 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.

1.3.1.5.7 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.

1.3.1.5.8 Undesirable effects

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

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

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

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		

Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders					Cough Dyspnoea
Gastro-intestinal disorders	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Pruritis Rash Urticaria			Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated

					necrotising myopathy
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m^2, 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 (>5xULN), treatment should be discontinued.

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

The following adverse events have been reported with some statins:

Sexual dysfunction: Exceptional cases of interstitial lung disease, especially with long term therapy.

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 https://coronaremedies.com

1.3.1.5.9 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.

1.3.1.6 Pharmacological properties

1.3.1.6.1 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 Table3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios

1.3.1.6.2 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.

Biotransformation: Rosuvastatin undergoes limited metabolism (approximately 10%). In vitro metabolism studies using human hepatocytes indicate that Rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than Rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination: Approximately 90% of the Rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine.

The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%).

As with other HMG-CoA reductase inhibitors, the hepatic uptake of Rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of Rosuvastatin.

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 in children and adolescents with heterozygous familial hypercholesterolaemia 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 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 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.

1.3.1.6.3 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.

1.3.1.7 Pharmaceutical particulars

1.3.1.7.1 Incompatibilities

None reported.

1.3.1.7.2 Shelf life

36 Months

1.3.1.7.3 Special precautions for storage

Store below 30°C.
Protect from light and moisture.

1.3.1.7.4 Nature and contents of container

14 Tablets packed in Alu-Alu Blister pack and such 2 blister packs are packed in carton along with insert.

1.3.1.7.5 Special precautions for disposal

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

1.3.1.8 Registrant

Pacmai International Limited

1.3.1.9 Registration Number(s)

B4-4531

1.3.1.10 Date of initial or renewed registration

26th March 2015

1.3.1.11 Date of revision of the text

25/06/2019