1. NAME OF THE MEDICINAL PRODUCT
Rosuvastatin Sandoz film-coated tablet 10 mg
Rosuvastatin Sandoz film-coated tablet 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Rosuvastatin Sandoz film-coated tablet 10 mg
Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 52.92 mg lactose anhydrous.

Rosuvastatin Sandoz film-coated tablet 20 mg
Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 105.84 mg lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Rosuvastatin Sandoz film-coated tablet 10 mg
Brown, round, film-coated tablets with “RSV 10” debossed on one side.

Rosuvastatin Sandoz film-coated tablet 20 mg
Brown, round, film-coated tablets with “RSV 20” debossed on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of hypercholesterolaemia
Primary hypercholesterolaemia and mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and exercise is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g., LDL apheresis)**.**

Prevention of Cardiovascular Events
Indicated in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, rosuvastatin is indicated to:
- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

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

The physician who elects to use rosuvastatin at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of rosuvastatin for the individual patient. Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis (see Special warnings and precautions for use; skeletal muscle)

Use in the elderly
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 use of Rosuvastatin Sandoz in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Dosage in patients with hepatic impairment
The usual dose range applies in patients with mild hepatic impairment [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). There is no experience in subjects with severe hepatic impairment. Rosuvastatin Sandoz is contraindicated in patients with active liver disease (see section 4.3).

Use in Asian population
Increased plasma concentration of rosuvastatin has been seen in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry (see sections 4.4 and 5.2). Increased systemic exposure, which is considered a pre-disposing factor for myopathy, should be taken into consideration when making dose decisions for Asian patients. Initiation of rosuvastatin therapy with 5 mg once daily should be considered for Asian patients. This should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. Doses exceeding 20 mg are not generally recommended and should only be considered for patients with high cardiovascular risk whose hypercholesterolaemia is not controlled with doses up to 20 mg. In rare cases where rosuvastatin at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision. The physician who elects to use rosuvastatin at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of rosuvastatin for the individual patient.

Genetic polymorphisms
Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of rosuvastatin is recommended.

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 Sandoz 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). It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatin Sandoz. Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosuvastatin Sandoz therapy. In situations where co-administration of these medicinal products with Rosuvastatin Sandoz is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin Sandoz dosing adjustments should be carefully considered (see section 4.5).

4.3 Contraindications
Rosuvastatin Sandoz is contraindicated:
- in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases.

- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of child-bearing potential not using appropriate contraceptive measures.

(see sections 4.4, 4.5 and 5.2)

4.4 Special warnings and precautions for use

In rare cases where Rosuvastatin Sandoz at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision. The physician who elects to use Rosuvastatin Sandoz at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of Rosuvastatin Sandoz for the individual patient.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry compared with Caucasians (see Posology and method of administration and Pharmacokinetic properties.) A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian, Hispanic, Black and Afro-Caribbean groups.

Children and adolescents 10 to 17 years of age

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a one year period. (see section 5.1).

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. The effects were generally transient and not associated with worsening of renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered in patients with unexplained persistent proteinuria during routine urinalysis testing. An assessment of renal function is recommended during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with rosuvastatin, as with other HMG-CoA reductase inhibitors. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Rare cases of rhabdomyolysis, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin and with other marketed statins.

There have been very rare reports of an immune-mediated necrotising 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.

Before Treatment

If CK levels are significantly elevated at baseline (>10xULN) treatment should not be started.

Rosuvastatin Sandoz, 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, fibrate or niacin
- alcohol abuse
- age ≥ 65 years
- situations where an increase in plasma levels may occur
- concomitant use of fibrates and niacin

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended.

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

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 (>10xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 10xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin Sandoz 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.

The risk of myopathy during treatment with Rosuvastatin Sandoz may be increased in circumstances which increase rosuvastatin drug levels (see section 5.2).

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin Sandoz with fibrates or niacin should be carefully weighed against the potential risks of such combinations. When used in combination with fibrates or lipid lowering doses of niacin (≥ 1 g/day), the dose of Rosuvastatin Sandoz should not exceed 10 mg/day (see sections 4.5 and 4.8).

Rosuvastatin Sandoz should be temporarily withheld 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).

<u>Diabetes Mellitus</u>
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 (see Undesirable effects and Pharmacodynamic properties).

<u>Liver Effects</u>
As with other HMG-CoA reductase inhibitors, Rosuvastatin Sandoz 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 performed before and at 3 months following both the initiation of treatment and any increase of dose, and periodically (semi-annually) thereafter.

Patients with increased transaminases levels should be monitored until abnormalities resolve. Rosuvastatin Sandoz should be discontinued or the dose reduced if the level of serum transaminases is > 3 ULN.

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 Sandoz in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin Sandoz doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin Sandoz is adjusted (see sections 4.2 and 4.5).

Endocrine Effects
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin (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 Sandoz 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).

Cyclosporin
Co-administration of rosuvastatin with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state AUC (0-t) increased up to 7-fold over that seen in healthy volunteers administered the same dose. Concomitant use of Rosuvastatin Sandoz and cyclosporin is contraindicated (see Table 1 and section 4.3).

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 increase in rosuvastatin AUC. The concomitant use of Rosuvastatin Sandoz and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin Sandoz 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 (0-t). Based on data from specific interaction studies, no pharmacokinetic relevant interaction with fenofibrate is expected, however pharmacodynamic interaction may occur.

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (≥ 1g/day) of niacin (nicotinic acid) increase the risks of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, the dose of

Rosuvastatin Sandoz should not exceed 10 mg/day when given in combination with fibrates or niacin (see section 4.2 and 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 (0-t) 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 Sandoz with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastatin Sandoz should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatin Sandoz.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of rosuvastatin should not exceed 5 mg once daily.

The maximum daily dose of Rosuvastatin Sandoz should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of the recommended maximum daily dose of Rosuvastatin Sandoz taken without interacting medicinal product.

For example, where the recommended dose of Rosuvastatin Sandoz is 20 mg; the dose of Rosuvastatin Sandoz taken with a ritonavir/atazanavir combination (3.1-fold increase) should not exceed 5 mg, and the dose of Rosuvastatin Sandoz taken with gemfibrozil (1.9-fold increase) should not exceed 10 mg.

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20 mg.

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

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg single dose	7.39-fold ↑
Cyclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑

Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8-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 ↑
Velpatasvir 100 mg OD	10 mg single dose	2.69-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg/dasabuvir 400 mg BID	5 mg single dose	2.59-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10 mg single dose	2.26-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5 mg once daily	2.2-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 ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
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, 7days	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 ↑
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
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 "↑", decrease as "↓". **Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio AUC= area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily		

The following medicinal product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:
Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

Effect of rosuvastatin on co-administered medicinal products
Warfarin

As with other HMG-CoA reductase inhibitors, co-administration of Rosuvastatin Sandoz and warfarin may result in a rise in INR compared to warfarin alone. In patients taking vitamin K antagonists monitoring of INR is recommended both at initiation or cessation of therapy with Rosuvastatin Sandoz or following dose adjustment.

Oral contraceptive/hormone replacement therapy (HRT)
Concomitant use of Rosuvastatin Sandoz and an oral contraceptive resulted in an increase in ethinyl oestradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Rosuvastatin Sandoz and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

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

Endocrine function
Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol levels or impairs adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other lipid-lowering agent is administered concomitantly with drugs that may decrease levels or activity of endogenous steroid hormones (ketoconazole, spironolactone, cimetidine).

Fusidic Acid
Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Therefore, the combination rosuvastatin and fusidic acid is not recommended. If possible, temporary suspension of rosuvastatin treatment is recommended. If unavoidable, patients should be closely monitored.

4.6 Fertility, pregnancy and lactation
The safety of rosuvastatin during pregnancy and whilst breast feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures (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.

Common (≥1/100, < 1/10)	Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus[1].
Uncommon (≥1/1000, <1/100)	Pruritus, rash and urticaria
Rare (≥1/10,000, <1/1000)	Myopathy (including myositis), hypersensitivity reactions, (including angioedema), rhabdomyolysis, pancreatitis

[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.

Laboratory Effects

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, and has not been shown to be predictive of acute or progressive renal disease.

Skeletal muscle effects

Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses. 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 (> 10xULN), 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.

Other effects

In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens.

Post-Marketing Experience

In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin.

Nervous system disorders	Very Rare:	polyneuropathy, memory loss
	Frequency Unknown:	Peripheral neuropathy
Respiratory, thoracic and mediastinal disorders	Not Known:	cough, dyspnoea
Gastrointestinal disorders	Not Known:	diarrhoea
Haematological disorders	Frequency unknown:	thrombocytopenia
Hepatobiliary disorders	Very Rare:	Jaundice, hepatitis
	Rare:	increased hepatic transaminases
Skin and subcutaneous tissue disorders	Not Known:	Stevens-Johnson syndrome
Musculoskeletal disorders	Not Known:	immune-mediated necrotising myopathy
	Very Rare:	arthralgia
Renal disorders	Very Rare:	haematuria
General disorders and administration site conditions	Not Known:	oedema
Reproductive system and breast disorders:	Not Known:	gynaecomastia

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

The following adverse events have been reported with some statins

- Depression
- Sleep disturbances, including insomnia and nightmares

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Children and adolescents 10 to 17 years of age
The safety profile of rosuvastatin is similar in children or adolescent patients and adults although CK elevations > 10xULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in a clinical trial of children and adolescents. However, the same special warnings and special precautions for use in adults also apply to children and adolescents (see section 4.4).

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. 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, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it 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.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Pharmacodynamic effects
Clinical Efficacy
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 2).

Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's.

A therapeutic response to rosuvastatin is obtained within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Table 2 - Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
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

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20-40 mg titrated at a 6 week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C of less than 15%, 3 had no response or an increase in LDL-C.

In the METEOR study, the effect of rosuvastatin 40 mg on the progression of atherosclerosis was assessed by B-mode ultrasound of the carotid arteries. In this multi-center, double blind, placebo-controlled clinical trial, 984 subjects at low risk for coronary heart disease (defined as Framingham risk < 10% over ten years) and with a mean LDL-C of 154.5 mg/dL but with subclinical atherosclerosis as detected by CIMT (Carotid Intima Media Thickness) were randomized in a 5:2 ratio to treatment with either rosuvastatin 40 mg or placebo for 2 years. Rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the rate of change in the maximum CIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI -0.0196, -0.0093; p<0.0001). The change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI - 0.0041, 0.0014), but was not significantly different from zero (p=0.3224). The beneficial effects of rosuvastatin were consistent across all 4 secondary CIMT endpoints. There was significant progression in the placebo group (+0.0131 mm/year; 95% CI 0.0087, 0.0174; p<0.0001). In the rosuvastatin group, 52.1% of patients demonstrated an absence of disease progression (i.e. regressed) compared to 37.7% of patients in the placebo group (p=0.0002). Rosuvastatin 40 mg was well-tolerated and the data were consistent to the established safety profile for rosuvastatin.

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with ε2/ ε2 genotype and 4 with apo E mutation [Arg145Cys]) with dysbetalipoproteinaemia (Fredrickson type III) received rosuvastatin 10 or 20 mg daily for 6 weeks. Rosuvastatin reduced non-HDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

Table 3 Lipid-modifying effects of Rosuvastatin 10mg and 20mg in dysbetalipoproteinaemia (Fredrickson type III hyperlipoproteinaemia) after six weeks by Median Percent Change (95% CI from Baseline (N=32)

Dose	Total-C	TG	NonHDL-C	VLDL-C + LDL-C	LDL-C	HDL-C	RLP-C	Apo-E
10	-43.3 (-46.9, -37.5)	-40.1 (-44.9, -33.6)	-48.2 (-56.7, -45.6)	-46.8 (-53.7, -39.4)	-54.4 (-59.1, -47.3)	10.2 (1.9, 12.3)	-56.4 (-67.1, -49.0)	-42.9 (-46.3, -33.3)

20	-47.6 (-51.6, -42.8)	-43.0 (-52.5, -33.1)	-56.4 (-61.4, -48.5)	-56.2 (-67.7, -43.7)	-57.3 (-59.4, -52.1)	11.2 (8.3, 20.5)	-64.9 (-74.0, -56.6)	-42.5 (-47.1, -35.6)

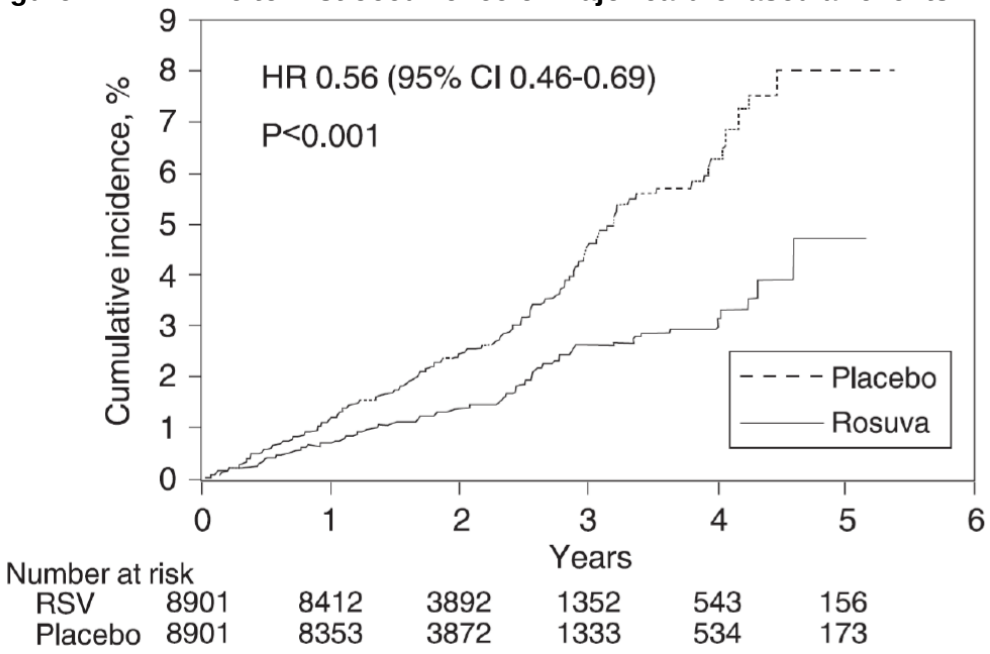
Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥ 50 years) and women (≥ 60 years) who had no clinically evident cardiovascular disease, LDL-C levels < 130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥ 2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. 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. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary endpoint was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 1). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C or hsCRP levels.

Figure 1 Time to first occurrence of major cardiovascular events in JUPITER



The individual components of the primary end point are presented in Figure 2. Rosuvastatin

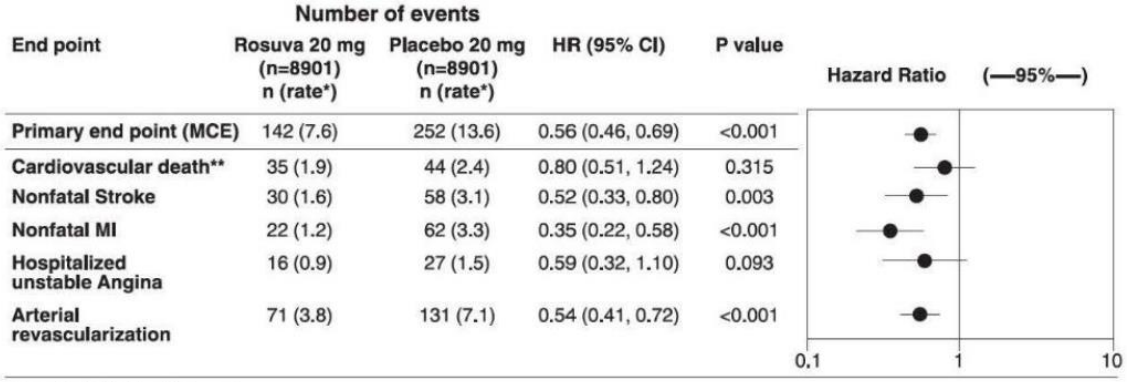
significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58 nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

In JUPITER, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2.8% of patients in the rosuvastatin group and 2.3% of patients in the placebo group (HR: 1.27, 95% CI: 1.05-1.53, p=0.015). The difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c change from baseline was approximately 0.1%. The cardiovascular and mortality benefits of rosuvastatin therapy exceeded the diabetes hazard in the trial population as a whole (see Special warnings and precautions for use and Undesirable effects).

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin=725, placebo=680) with a hsCRP ≥ 2 mg/L and no other traditional risk factors (smoking, BP ≥ 140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

Figure 2 Major CV events by treatment group in JUPITER



* event rate/1000-patient years
** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

5.2 Pharmacokinetic properties

Rosuvastatin is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Exposure increases linearly over the dose range. The half-life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance.

Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound, accounts for greater than 90% of the circulating active HMG CoA reductase inhibitor activity.

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethylform,

and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Special populations

Age and sex

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults.

Renal insufficiency

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma 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 in 12 subjects with mild to moderate hepatic impairment there was evidence of increased exposure to rosuvastatin in the 2 subjects with the higher Child-Pugh scores (8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Race

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups

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 an approximate 1.6-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Anhydrous Lactose
Silica, Colloidal Anhydrous
Silicified Microcrystalline Cellulose
Maize Starch
Talc
Sodium Stearyl Fumarate

Tablet coat

Hypromellose
Mannitol
Macrogol 6000
Talc
Titanium dioxide E171

Ferric oxide, yellow E172
Ferric oxide, red E172

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to expiry date on outer carton.

6.4 Special precautions for storage
Store below 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container
Rosuvastatin Sandoz Film Coated Tablets are packaged in blisters placed into cardboard boxes containing 30 film-coated tablets.

Not all presentations may be available locally.

7. PRODUCT REGISTRANT
Novartis (Singapore) Pte Ltd
20 Pasir Panjang Road,
#10-25/28, Mapletree Business City,
Singapore 117439

8. DATE OF REVISION OF THE TEXT
Mar 2022