PACKAGE INSERT

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

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

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

3. PHARMACEUTICAL FORM
Film-coated tablet.

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

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

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
As an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, ApoB, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C, in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including: Prevention of Cardiovascular Events: In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers e.g., an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease. Rosuvastatin Sandoz is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, myocardial infarction (MI), unstable angina, or arterial revascularization).

As an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (type III hyperlipoproteinemia).

Primary hypercholesterolaemia.

Combined (mixed) dyslipidemia (type IIb).

Homozygous familial hypercholesterolaemia where Rosuvastatin Sandoz is used either alone or as an adjunct to diet, and other lipid-lowering treatment e.g., apheresis.

As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower total-C and LDL-C to target levels.

4.2 Posology and method of administration
Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the ATP III TLC diet) before receiving Rosuvastatin Sandoz, and should continue on this diet during treatment with it.

If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Rosuvastatin Sandoz, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed. After initiation or upon titration of Rosuvastatin Sandoz, lipid levels should be analyzed within 2-4 weeks and the dosage adjusted accordingly.

Usual Recommended Starting Dose: 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for special patient populations or patients requiring less aggressive LDL-C reductions. The choice of starting dose should take into account the individual patients' cholesterol level and future cardiovascular risk, as well as the potential risk for adverse reactions.

Majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustments to the next dose level can be made after 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy. The physician who elects to use Rosuvastatin Sandoz at a dose >20 mg should periodically reevaluate the long-term risk/benefit of Rosuvastatin Sandoz for the individual patient.

Rosuvastatin Sandoz should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis (see Precautions).

The dosage of Rosuvastatin Sandoz should be individualised according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels, the recommended target lipid values and the patient response.

Lipid levels should be monitored periodically, and if necessary, the dose of Rosuvastatin Sandoz should be adjusted based on target lipid levels recommended by guidelines.

Renal Insufficiency: The usual dose range applies in patients with mild to moderate renal impairment. The use of Rosuvastatin Sandoz in patients with severe renal impairment is contraindicated.

Hepatic Insufficiency: There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of ≤7. 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 >9. Rosuvastatin Sandoz is contraindicated in patients with active liver disease.

Elderly: The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years.
The efficacy of rosuvastatin in the geriatric population (≥65 years) was comparable to the efficacy observed in the non-elderly.

Dosage on Asian Patients: Initiation of Rosuvastatin Sandoz therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily.

Concomitant Therapy: The effect of Rosuvastatin Sandoz on LDL-C and total-C may be enhanced when used in combination with a bile acid-binding resin.
If Rosuvastatin Sandoz is used in combination with gemfibrozil, the dose of Rosuvastatin Sandoz should be limited to 10 mg once daily.

<u>Dosage in patients with pre-disposing factors to myopathy</u>
The recommended start dose is 5 mg in patients with pre-disposing factors to myopathy.

<u>Concomitant Therapy</u>
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. 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 Sandoz 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.

<u>Method of administration</u>
For oral use.

4.3 Contraindications

Rosuvastatin Sandoz 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 3x 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 special precautions for use

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see Section 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see Section 4.5) and caution should be exercised with their combined use.

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

Creatine Kinase Measurement

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

Before Treatment

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 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 (> 5x ULN) 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 (> 5x ULN) 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 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.
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:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

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. The patient 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).

<u>Liver Effects</u>
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.

<u>Race</u>

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 protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted.

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 patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus.

Special warnings regarding excipients
Rosuvastatin Sandoz contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of co-administered medicinal products on rosuvastatin
Transporter protein inhibitors
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Ciclosporin
During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin (see Section 4.3).
Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors
Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. Co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin steady-state AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products
Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC.

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.

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

Ezetimibe
Concomitant use of 10mg rosuvastatin and 10mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. However, a pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

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

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

Cytochrome P450 enzymes
Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, medicinal product 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
When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products.

<u>Effect of rosuvastatin on co-administered medicinal products</u>
Vitamin K antagonists
As with other HMG-CoA reductase inhibitors, the initiation of treatment or dose up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

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

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

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or

pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

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

4.6 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.

4.7 Effects on ability to drive and use machines
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 Sandoz are generally mild and transient.

List of adverse reactions
Adverse reactions listed below are classified according to frequency and system organ class (SOC).

Blood and lymphatic system disorders
Rare: Thrombocytopenia

Immune system disorders
Rare: Hypersensitivity reactions including angioedema

Endocrine disorders
Common: Diabetes mellitus[1]

Psychiatric disorders
Not known: Depression

Nervous system disorders
Common: Headache, dizziness
Very rare: Polyneuropathy, memory loss
Not known: Peripheral neuropathy, sleep disturbances (including insomnia and nightmares)

Respiratory, thoracic and mediastinal disorders
Not known: Cough, dyspnoea

Gastrointestinal disorders
Common: Constipation, nausea, abdominal pain
Rare: Pancreatitis
Not known: Diarrhoea

Hepatobiliary disorders
Rare: Increased hepatic transaminases
Very rare: Jaundice, hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, rash, urticaria

Not known: Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders
Common: Myalgia
Rare: Myopathy (including myositis), rhabdomyolysis
Very rare: Arthralgia
Not known: Immune-mediated necrotising myopathy, Tendon disorders, sometimes complicated by rupture

Renal and urinary disorders
Very rare: Haematuria

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Common: Asthenia
Not known: 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 (> 5x ULN), 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.

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 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

4.9 Overdose
There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Lipid modifying agent, plain, HMG-CoA reductase inhibitors
ATC code: C10A A07

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate- limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects
Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 1: 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

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy
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.

5.2 Pharmacokinetic properties
Absorption
Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution

Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation
Rosuvastatin undergoes limited metabolism (approximately 10%). 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Tablet coating
Hypromellose
Mannitol
Macrogol 6000
Titanium dioxide
Ferric Oxide, Yellow
Ferric Oxide, Red
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Storage Condition
Store in the original package in order to protect from moisture.
Store below 30ºC.

6.5 Nature and contents of container
28, 30 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precaution for disposal and other handling
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS 21/58, Damansara Uptown,
47400 Petaling Jaya, Selangor, Malaysia

8. DATE OF REVISION OF THE TEXT

Jul 2024