PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ROSUVASTATIN UNICORN 5 (film-coated tablets)

ROSUVASTATIN UNICORN 10 (film-coated tablets)

ROSUVASTATIN UNICORN 20 (film-coated tablets)

ROSUVASTATIN UNICORN 40 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROSUVASTATIN UNICORN 5: Each film-coated tablet contains 5,198 mg of rosuvastatin calcium equivalent to 5 mg of rosuvastatin.

ROSUVASTATIN UNICORN 10: Each film-coated tablet contains 10,396 mg rosuvastatin calcium equivalent to 10 mg of rosuvastatin.

ROSUVASTATIN UNICORN 20: Each film-coated tablet contains 20,791 mg rosuvastatin calcium equivalent to 20 mg of rosuvastatin.

ROSUVASTATIN UNICORN 40: Each film-coated tablet contains 41,583 mg rosuvastatin calcium equivalent to 40 mg of rosuvastatin.

Each ROSUVASTATIN UNICORN 5 mg tablet contains sugar (anhydrous lactose 57,920 mg) and mannitol (0,150 mg).

Each ROSUVASTATIN UNICORN 10 mg tablet contains sugar (anhydrous lactose 52,920 mg) and mannitol (0,150 mg).

Each ROSUVASTATIN UNICORN 20 mg tablet contains sugar (anhydrous lactose 105,840 mg) and mannitol (0,300 mg).

Each ROSUVASTATIN UNICORN 40 mg tablet contains sugar (anhydrous lactose 211,680 mg) and mannitol (0,600 mg).

3. PHARMACEUTICAL FORM

ROSUVASTATIN UNICORN 5: Light brown, round, film-coated tablets with “RSV 5” debossed on one side.

ROSUVASTATIN UNICORN 10: Brown, round, film-coated tablets with “RSV 10” debossed on one side.

ROSUVASTATIN UNICORN 20: Brown, round, film-coated tablets with “RSV 20” debossed on one side.

ROSUVASTATIN UNICORN 40: Brown, round, film-coated tablets with “RSV 40” debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk of cardiovascular events:

In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated high-sensitivity C-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, ROSUVASTATIN UNICORN is indicated to reduce the risk of non-fatal stroke, non-fatal MI and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

- ROSUVASTATIN UNICORN is indicated for patients with primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial and non-familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.

- ROSUVASTATIN UNICORN is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia).
- ROSUVASTATIN UNICORN is also indicated to reduce Total Cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

ROSUVASTATIN UNICORN 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of ROSUVASTATIN UNICORN or alternative therapy.
Specialist supervision is recommended when the 40 mg dose is initiated (see section 4.4).

Children and adolescents 10 to 17 years of age:

ROSUVASTATIN UNICORN is indicated to reduce the Total Cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

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 range for ROSUVASTATIN UNICORN is 5 to 40 mg orally once a day. The recommended start dose is 5 mg once a day. The dosage of ROSUVASTATIN UNICORN should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 2 to 4 week intervals (see section 5.1).
ROSUVASTATIN UNICORN may be given at any time of the day, with or without food.

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia) and isolated hypertriglyceridaemia:

The recommended start dose is 5 mg once a day.

A 5 mg starting dose is recommended for patients of Asian ancestry, and for patients requiring a smaller reduction in LDL-C to achieve treatment target.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia:

For patients with homozygous familial hypercholesterolaemia a start dose of 20 mg once a day is recommended.

Children and adolescents 10 to 17 years of age:

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5 to 20 mg orally once daily. The dose should be appropriately titrated to achieve treatment goal. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

Special populations:

Use in the elderly:

The usual dose range applies.

Dosage in patients with renal insufficiency:

The starting dose applies in patients with mild to moderate renal impairment. For patients with severe renal impairment the dose of ROSUVASTATIN UNICORN should not exceed 10 mg once daily.

Dosage in patients with hepatic insufficiency:

The usual starting dose applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with ROSUVASTATIN UNICORN 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above ROSUVASTATIN UNICORN 10 mg should be carefully considered (see section 5.2).

Race:

A 5 mg starting dose of ROSUVASTATIN UNICORN should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see sections 4.4 and 5.2). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolaemia is not adequately controlled at doses up to 20 mg daily.

Concomitant therapy:

ROSUVASTATIN UNICORN has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

ROSUVASTATIN UNICORN can also be used in combination with ezetimibe or bile acid sequestrants (see section 4.4).

Interactions requiring dose adjustments:

Ciclosporin:

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant ROSUVASTATIN UNICORN and Ciclosporin. For the ROSUVASTATIN UNICORN dose range (10 to 40 mg) this combination is not recommended (see section 4.3).

Gemfibrozil:

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant ROSUVASTATIN UNICORN and gemfibrozil. Patients taking this combination should start therapy with ROSUVASTATIN UNICORN 5 mg once daily and should not exceed a dose of ROSUVASTATIN UNICORN 20 mg once daily (see section 4.5).

4.3 Contraindications

ROSUVASTATIN UNICORN is contraindicated in:

- Patients with hypersensitivity to rosuvastatin or to any of the excipients of ROSUVASTATIN UNICORN
- Patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN)
- Patients with severe renal impairment (creatinine clearance <30 ml/min)
- Patients with myopathy
- Patients receiving concomitant ciclosporin
- Patients receiving concomitant combination of sofosbuvir / velpatasvir / voxilaprevir (see section 4.5)
- Pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures

The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy / rhabdomyolysis. Such factors include:

- Moderate renal impairment (creatinine clearance < 60 ml/min)
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse

- Situations where an increase in plasma levels may occur
- Asian patients
- Concomitant use of fibrates

(See sections 4.4, 4.5 and 5.2)

Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

Renal Effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of ROSUVASTATIN UNICORN 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 patients treated with rosuvastatin at 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.

Patients who develop any signs or symptoms suggestive of myopathy should have their creatine kinase (CK) levels measured. ROSUVASTATIN UNICORN therapy should be discontinued if myopathy is diagnosed or suspected.

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 to 7 days. If the repeat test confirms a baseline CK > 5xULN, treatment should not be started.

Before Treatment:

ROSUVASTATIN UNICORN should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

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

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

Whilst on Treatment:

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (> 5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing ROSUVASTATIN UNICORN 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 UNICORN and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving HMG-CoA reductase inhibitors such as ROSUVASTATIN UNICORN together with ciclosporin, fibric acid derivatives, including gemfibrozil, 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 UNICORN and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of ROSUVASTATIN UNICORN with fibrates or niacin should be carefully

weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3, 4.5 and 4.8).

ROSUVASTATIN UNICORN 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 this combination (see section 4.5).

Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of ROSUVASTATIN UNICORN and fusidic acid should only be considered on a case by case basis and under close medical supervision.

ROSUVASTATIN UNICORN 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).

Severe Cutaneous Adverse Reactions:

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appear, ROSUVASTATIN

UNICORN should be discontinued immediately, and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of ROSUVASTATIN UNICORN, treatment with ROSUVASTATIN UNICORN must not be restarted in this patient at any time.

Liver Effects:

ROSUVASTATIN UNICORN 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 UNICORN 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 UNICORN.

Race:

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

Protease inhibitors:

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir.

Consideration should be given both to the benefit of lipid lowering by use of ROSUVASTATIN UNICORN in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating ROSUVASTATIN UNICORN doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of ROSUVASTATIN UNICORN is adjusted (see sections 4.2 and 4.5).

Interstitial lung disease:

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus:

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/l, BMI > 30 kg/m^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.

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 10 to 17 years

taking rosuvastatin is limited to a 1 year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see section 5.2).

In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults (see section 4.8).

Lactose intolerance:

ROSUVASTATIN UNICORN contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ROSUVASTATIN UNICORN.

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines 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 UNICORN with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5 Table 1).

Ciclosporin:

Co-administration of rosuvastatin with ciclosporin resulted in no significant changes in ciclosporin plasma concentration. However during concomitant treatment with ROSUVASTATIN UNICORN and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). ROSUVASTATIN UNICORN is contraindicated in patients receiving concomitant ciclosporin (see sections 4.2 and 4.3).

Protease inhibitors:

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving rosuvastatin with various protease inhibitors in combination with ritonavir (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively. Adverse events attributed to rosuvastatin in these studies were consistent with the known safety profile of rosuvastatin.

The concomitant use of ROSUVASTATIN UNICORN and some protease inhibitor combinations may be considered after careful consideration of ROSUVASTATIN UNICORN dose adjustments based on the expected increase in rosuvastatin exposure.

The lowest dose of ROSUVASTATIN UNICORN that provides therapeutic benefit to the patient should be used, and close monitoring of adverse events is indicated. In HIV-infected patients receiving protease inhibitors the potential risks of this increased rosuvastatin plasma concentrations when initiating and up-titrating ROSUVASTATIN UNICORN doses in patients treated with protease inhibitors, as the combination, may lead to an increased incidence of adverse events (see sections 4.2, 4.4 and 4.5 Table 1).

Gemfibrozil and other lipid-lowering products:

Concomitant use of rosuvastatin calcium and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and $AUC_{(0-t)}$ (see section 4.4).

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose

is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4). These patients should also start with the 5mg dose.

Ezetimibe:

Concomitant use of rosuvastatin 10 mg and ezetimibe 10 mg 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 UNICORN and ezetimibe cannot be ruled out (see section 4.4).

Antacids:

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 UNICORN and erythromycin resulted in a 20 % decrease in AUC and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes:

In vitro and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer).

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 andCYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Ticagrelor:

Ticagrelor can cause renal insufficiency and may affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. In some cases, co-administered ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis. Renal function and CPK control is recommended while using ticagrelor and rosuvastatin concomitantly.

Interactions requiring rosuvastatin dose adjustments (see also Table 1):

When it is necessary to co-administer ROSUVASTATIN UNICORN with other medicines known to increase exposure to rosuvastatin, doses of ROSUVASTATIN UNICORN should be adjusted. Start with a 5 mg once daily dose of ROSUVASTATIN UNICORN if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of ROSUVASTATIN UNICORN should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of ROSUVASTATIN UNICORN taken without interacting medicines, for example a 20 mg dose of ROSUVASTATIN UNICORN with gemfibrozil (1,9-fold increase), and a 10 mg dose of ROSUVASTATIN UNICORN with combination ritonavir/atazanavir (3,1-fold increase).

If the medicine 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 UNICORN dose above 20 mg.

Table 1 Effect of co-administered medicines on rosuvastatin exposure (AUC; in order of decreasing magnitude)

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	10mg single dose	7,4-fold ↑

Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7,1-fold ↑
Darolutamide 600 mg BID, 5 days	5mg, 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 ↑
Velpatasvir 100 mg OD	10 mg, single dose	2,7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2,6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2,3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	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 ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1,9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
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 ↑
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 medical product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at co-administration:

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 medicines:

Vitamin K antagonists:

The pharmacokinetics of warfarin are not significantly affected following co-administration with ROSUVASTATIN UNICORN. However, as with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of ROSUVASTATIN UNICORN 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 UNICORN may result in a decrease in INR.
In such situations, monitoring of INR is recommended both at initiation or cessation of therapy with ROSUVASTATIN UNICORN or following dose adjustment.

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 medicines:

In clinical studies rosuvastatin was co-administered with antihypertensive and anti-diabetic medicines. These studies did not produce any evidence of clinically significant adverse interactions.

Digoxin:

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

Fusidic acid:

Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, 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.

Therefore, the combination ROSUVASTATIN UNICORN and fusidic acid is not recommended. If treatment with systemic fusidic acid is necessary, ROSUVASTATIN UNICORN treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Paediatric population:

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

4.6 Fertility, pregnancy and lactation

ROSUVASTATIN UNICORN is contraindicated in pregnancy and lactation (see section 4.3).

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. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

The safety of ROSUVASTATIN UNICORN during pregnancy and whilst breastfeeding has not been established.

Women of child-bearing potential should use appropriate contraceptive measures.

4.7 Effects on ability to drive and use machines

Pharmacology testing revealed no evidence of a sedative effect of ROSUVASTATIN UNICORN. From the safety profile, ROSUVASTATIN UNICORN is not expected to adversely affect the ability to drive or 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 reactions seen with ROSUVASTATIN UNICORN are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.

Tabulated list of adverse reactions:

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin.

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Blood and the 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).
Cardiac disorders		Angina pectoris, chest pain, hypertension	

Vascular disorders		Peripheral oedema	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, rhinitis, sinusitis, cough.	
Gastrointestinal disorders	Diarrhoea, abdominal pain, constipation, vomiting, nausea	Pancreatitis, gastritis, dyspepsia	
Hepato-biliary disorders		Jaundice, hepatitis, increased hepatic transaminases	
Skin and subcutaneous tissue disorders		Pruritus, rash, urticaria	Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders	Myalgia	Myopathy (including myositis), rhabdomyolysis, which may occasionally be associated with impairment of renal function, has been	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy

		reported with rosuvastatin lupus-like syndrome, muscle rupture, arthralgia	
Renal and urinary disorders		Haematuria	Proteinuria (see “Investigations”)
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions	Asthenia	Flu syndrome	Oedema
Investigations			A dose-related increase in liver transaminases and creatine kinase (CK). Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria). The protein detected was mostly tubular in origin.
[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 UNICORN. 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 UNICORN 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 UNICORN-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 (see section 4.4).

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

The following adverse events have been reported with some statins:
Sexual dysfunction.

Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

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

Children and adolescents 10 to 17 years of age:

The safety profile of ROSUVASTATIN UNICORN is similar in children or adolescent patients and adults although CK elevations > 10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trials 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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via Patientsafety.sacg@novartis.com.

4.9 Overdose

Symptoms of overdosage:

See section 4.8.

Treatment of overdosage:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

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.

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). Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol, triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.

A therapeutic response to rosuvastatin is evident 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.

5.2 Pharmacokinetic properties

Absorption:

After oral administration peak plasma levels occur 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.

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 children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to or lower than that in adult patients with dyslipidaemia.

Race:

Pharmacokinetic studies show a 1,26 to 2,31 fold elevation in geometric mean $AUC_{(0-t)}$ in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians (see section 4.2).

A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malaysian, 27 (8 %) Japanese, 27 (8 %) Philipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analyses in these studies.

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

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 or the N-desmethyl metabolite. However, 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. Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

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.421CCgenotypes. 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.

Children and adolescents 10 to 17 years of age:

One pharmacokinetic study with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 years of age (total of 176 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 1-year period.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Anhydrous lactose

Maize starch

Silica colloidal anhydrous

Silicified microcrystalline cellulose (prosolv SMCC90)

Sodium stearyl fumarate

Talc

Tablet coat:

Ethanol 96 %

Ferric oxide red E172

Ferric oxide yellow E172

Hypromellose (2910)

Macrogol 6000

Mannitol

Purified water

Talc

Titanium dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C in a cool, dry place. Protect from light.

6.5 Nature and contents of container

ROSUVASTATIN UNICORN 5: 5 mg film-coated tablets packed into Al/Al blister packaging. Pack size: 30 tablets.

ROSUVASTATIN UNICORN 10: 10 mg film-coated tablets packed into Al/Al blister packaging. Pack size: 30 tablets.

ROSUVASTATIN UNICORN 20: 20 mg film-coated tablets packed into Al/Al blister packaging. Pack size: 30 tablets.

ROSUVASTATIN UNICORN 40: 40 mg film-coated tablets packed into Al/Al blister packaging. Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. Marketing authorisation number(s)

ROSUVASTATIN UNICORN 5: 46/7.5/0307

ROSUVASTATIN UNICORN 10: 46/7.5/0308

ROSUVASTATIN UNICORN 20: 46/7.5/0309

ROSUVASTATIN UNICORN 40: 46/7.5/0310

9. Date of first authorisation/renewal of the authorisation

23 November 2017

10. Date of revision of the text

TBA

[1]Company Reg. No.: 1990/001979/07