SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE:

VUSOR 5 film-coated tablets

VUSOR 10 film-coated tablets

VUSOR 20 film-coated tablets

VUSOR 40 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

VUSOR 5: each tablet contains rosuvastatin 5 mg as rosuvastatin calcium

VUSOR 10: each tablet contains rosuvastatin 10 mg as rosuvastatin calcium

VUSOR 20: each tablet contains rosuvastatin 20 mg as rosuvastatin calcium

VUSOR 40: each tablet contains rosuvastatin 40 mg as rosuvastatin calcium

Contains sugar.

VUSOR 5 contains 42,55 mg lactose monohydrate.

VUSOR 10 contains 37,35 mg lactose monohydrate.

VUSOR 20 contains 74,70 mg lactose monohydrate.

VUSOR 40 contains 149,40 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM:

Film-coated tablets.

VUSOR 5: Yellow, round convex shaped coated tablet with ‘RU5’ on one side and blank on the other side.

VUSOR 10: Pink, round convex shaped coated tablet with ‘RU10’ on one side and blank on the other side.

VUSOR 20: Pink, round convex shaped coated tablet with 'RU20' on one side and blank on the other side.

VUSOR 40: Pink, oval shaped coated tablet with 'RU40' on one side and blank on the other 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, VUSOR is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

- VUSOR 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.
- VUSOR is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia).
- VUSOR 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).

VUSOR 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 VUSOR 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:

VUSOR 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:

Posology:

Before treatment initiation, the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose range for VUSOR is 5 mg to 40 mg orally once a day. The recommended starting dose is 5 mg once a day.

The dosage of VUSOR 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).

VUSOR 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 starting 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 starting dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia:

For patients with homozygous familial hypercholesterolaemia a starting 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 mg 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 VUSOR should not exceed 10 mg once daily.

Dosage in patients with hepatic insufficiency:

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

Race:

A 5 mg starting dose of VUSOR should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see section 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:

VUSOR 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.

VUSOR can also be used in combination with bile acid sequestrants or ezetimibe. When used concomitantly with protease inhibitors, the maximum dose should be 10 mg per day (see section 4.4).

Interactions requiring dose adjustments:

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when VUSOR is administered concomitantly with certain medicines 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 section 4.4 and 4.5). Whenever possible, alternative medicines should be considered, and, if necessary, consider temporarily discontinuing VUSOR therapy. In situations where co-administration of these medicines with VUSOR is unavoidable, VUSOR dosing adjustments should be carefully considered (see section 4.5).

Ciclosporin:

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant VUSOR and ciclosporin. For the VUSOR dose range (10 mg 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 VUSOR and gemfibrozil. Patients taking this combination should start therapy with VUSOR 5 mg once daily and should not exceed a dose of VUSOR 20 mg once daily (see section 4.5: Effect of co-administered medicines on rosuvastatin as contained in VUSOR).

4.3 Contraindications:

VUSOR 40 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 with fibrates (see section 4.5).

VUSOR (all of the strengths) is contraindicated in:

- patients with hypersensitivity to rosuvastatin or other HMG-CoA reductase inhibitors or any component of VUSOR
- 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)
- concomitant use with ciclosporin (see section 4.5).
- patients with myopathy
- safety in pregnancy and lactation has not been established (see section 4.6)
- patients with severe renal impairment (CrCl < 30 ml/min).
- patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5)

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 as contained in VUSOR, 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. uncomplicated myalgia, myopathy and rhabdomyolysis, have been reported in patients treated with rosuvastatin contained in VUSOR. The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose of VUSOR.

Cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors such as rosuvastatin contained in VUSOR. A pharmacodynamic interaction cannot be excluded (see section 4.5) and caution should be exercised with combined use.

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 (> 5 x ULN) a confirmatory test should be carried out within 5 to 7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment should not be started.

Before treatment:

VUSOR should be prescribed with caution to patients with predisposing factors for myopathy and rhabdomyolysis such as renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate,

alcohol abuse, age > 70 years, concomitant use of fibrates and situations where an increase in rosuvastatin plasma levels may occur (see section 4.5)

If CK levels are significantly elevated at baseline (> 5 x 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. VUSOR therapy should be discontinued if CK levels are markedly elevated (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN).

If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing VUSOR 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 reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin as contained in VUSOR. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

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 VUSOR and gemfibrozil is not recommended. The 40 mg dose is contraindicated with concomitant use of a fibrate (see section 4.3, 4.5 and 4.8).

VUSOR 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).

Fusidic acid

VUSOR 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, such as VUSOR, in 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 VUSOR and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Liver effects:

VUSOR 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 should be performed in patients before initiating VUSOR therapy, and 3 months thereafter. VUSOR should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal (see section 4.3). 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 VUSOR.

If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, VUSOR should not be restarted.

Cognitive impairment:

There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia,

memory impairment and confusion) associated with statin use such as VUSOR**.** These reported symptoms were generally not serious and reversible upon discontinuation with variable times to symptom onset (between a day, to years) and symptom resolution with a median of 3 weeks.

Race:

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

Protease inhibitors:

VUSOR should be used with caution in patients taking various protease inhibitors in combination with ritonavir as pharmacokinetic studies have shown an increase in the AUC and C_{max} of rosuvastatin.

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

Interstitial lung disease:

Exceptional cases of interstitial lung disease have been reported with some statins such as rosuvastatin contained in VUSOR, 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, VUSOR should be discontinued.

Diabetes mellitus:

Increased glycosylated haemoglobin (HbA1c), fasting serum glucose levels and worsening of glycaemic control have been reported in the use of statins, such as VUSOR.

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. VUSOR should be used with care in patients with Type 2 diabetes, and 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.

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 VUSOR. 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 appears, VUSOR 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 VUSOR, treatment with rosuvastatin must not be restarted in this patient at any time.

Paediatric population:

It has been reported that after a two year study period there was no effect on growth (height), weight, BMI (body mass index) or secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking rosuvastatin as contained in VUSOR.

There have been reports in children and adolescents receiving rosuvastatin as contained in VUSOR for 52 weeks, that CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity were observed more frequently than compared to that reported in adults (see section 4.8).

Risk of myasthenia gravis and ocular myasthenia:

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis

or ocular myasthenia (see section 4.8). Rosuvastatin tablets should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Information on excipients of VUSOR:

VUSOR contains lactose. Patients who are lactose intolerant or who have rare heredity problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take VUSOR.

4.5 Interactions with other medicines and other forms of interaction:

Effect of co-administered medicines on VUSOR:

Transporter protein inhibitors:

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of VUSOR with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see section 4.4 and Table 1 below).

Ciclosporin:

Co-administration of VUSOR with ciclosporin resulted in no significant changes in ciclosporin plasma concentrations. However, after co-administration with ciclosporin, rosuvastatin plasma concentration increased up to 7-fold over that seen in healthy volunteers administered the same dose of rosuvastatin (see Table 1 below). VUSOR is contraindicated in patients receiving concomitant ciclosporin (see section 4.3).

Protease inhibitors: (see section 4.4)

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving VUSOR with various protease inhibitors in combination with ritonavir (see Table 1 below). This increase in systemic exposure to VUSOR may lead to an increased incidence of adverse events.

The concomitant use of VUSOR and some protease inhibitor combinations may be considered after careful consideration of VUSOR dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4 and Table 1 below).

Gemfibrozil and other lipid-lowering medicines:

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

No pharmacokinetic relevant interaction with fenofibrate has been reported, 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 such as rosuvastatin contained in VUSOR, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate (see section 4.3 and 4.4). These patients should also start with the 5 mg dose (see section 4.2).

Ezetimibe:

Concomitant use of VUSOR 10 mg and ezetimibe 10 mg may result in a 1,2-fold increase in the AUC of rosuvastatin in hypercholesterolaemic subjects (see Table 1). A pharmacodynamic interaction, cannot be ruled out as cases of rhabdomyolysis have been reported when ezetimibe is used in combination with rosuvastatin (see section 4.4).

Antacids:

The simultaneous dosing of VUSOR 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 VUSOR. The clinical relevance of this interaction has not been studied.

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, medicine 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).

Erythromycin:

Concomitant use of VUSOR and erythromycin can result in a 20 % decrease in the $AUC_{(0-t)}$ and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gastrointestinal motility caused by erythromycin.

Ticagrelor

Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and 4 rhabdomyolysis.

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

When it is necessary to co-administer VUSOR with other medicines known to increase exposure to rosuvastatin, doses of VUSOR should be adjusted.

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

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

Interacting medicine 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	7.4 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7,1-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	2,7-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 ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1,6-fold ↑
Darunavir 600 mg/ ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1,5-fold ↑
Tipranavir 500 mg/ ritonavir 200 mg BID, 11 days	10 mg, single dose	1,4-fold ↑
Dronedarone 400 mg BID	Not available	1,4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	** 1,4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	** 1,2-fold ↑
Fosamprenavir 700 mg/ ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0,3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔

Erythromycin 500 mg QID, 7 days	80 mg, single dose	28 % ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47 % ↓

* Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone.

Data given as % change represent % difference relative to rosuvastatin alone.

Increase is indicated as "↑", no change as "↔", decrease as "↓".

** Several interaction studies have been performed at different **VUSOR** dosages; the table shows the most significant ratio.

OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Effect of VUSOR on co-administered medicines:

Vitamin K antagonists:

The initiation of treatment or dosage up-titration of VUSOR 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 VUSOR 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 VUSOR and an oral contraceptive can result in an increase in ethyl oestradiol and norgestrel AUC of 26 % and 34 %, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. Although there are no pharmacokinetic data available in women taking concomitant HRT, a similar effect cannot be excluded. It has, however, been reported that the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicines:

In clinical studies VUSOR was co-administered with antihypertensive agents and antidiabetic agents. 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. The risk of myopathy, including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins such as rosuvastatin as contained in VUSOR. 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, VUSOR treatment should be discontinued throughout the duration of the fusidic acid treatment. Also 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:

Women of childbearing potential:

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

Pregnancy:

VUSOR is contraindicated in pregnancy (see section 4.3). The safety of VUSOR during pregnancy has not been established.

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 therapy with VUSOR, treatment should be discontinued immediately.

Breastfeeding:

VUSOR is contraindicated during breastfeeding (see section 4.3). The safety of VUSOR whilst breastfeeding has not been established.

4.7 Effects on ability to drive and use machines:

VUSOR may cause dizziness, therefore patients taking VUSOR should not drive or use machines until their individual susceptibility to dizziness is known.

4.8 Undesirable effects:

VUSOR has the following side effects:

In controlled clinical trials less than 4 % of VUSOR treated patients were withdrawn due to adverse events.

Blood and the lymphatic system disorders:

Less frequent: thrombocytopenia

Immune system disorders:

Less frequent: hypersensitivity reactions including anaphylaxis, angioedema

Endocrine disorders:

Frequent: increased serum glucose levels, diabetes mellitus *

* 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).

Psychiatric disorders:

Less frequent: depression, cognitive impairment such as memory loss, forgetfulness, amnesia, memory

impairment and confusion

Nervous system disorders:

Frequent: headache, dizziness

Less frequent: polyneuropathy, peripheral neuropathy, sleep disturbances including insomnia and nightmares, fever

Frequency unknown: Myasthenia gravis

Eye disorders:

Frequency unknown: Ocular myasthenia

Respiratory, thoracic and mediastinal disorders:

Less frequent: cough, dyspnoea, hypersensitivity pneumonitis

Gastro-intestinal disorders:

Frequent: constipation, nausea, abdominal pain

Less frequent: pancreatitis, diarrhoea

Hepato-biliary disorders:

Less frequent: increased hepatic transaminases, hepatitis, jaundice, cholestasis

Skin and subcutaneous tissue disorders:

Frequent: pruritus, rash and urticaria

Less frequent: photosensitivity, flushing, alopecia

Frequency unknown: Stevens-Johnson syndrome, medicine reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal, connective tissue and bone disorders:

Frequent: myalgia

Less frequent: myopathy (including myositis), rhabdomyolysis, lupus-like syndrome, muscle rupture, arthralgia

Frequency unknown: tendon disorders sometimes complicated by rupture, immune-mediated necrotising myopathy

Renal and urinary effects:

Less frequent: proteinuria (see *Renal effects* below*)*, nephritis, haematuria

Reproductive system and breast disorders:

Less frequent: sexual dysfunction, gynaecomastia

General disorders and administrative site conditions:

Frequent: asthenia, oedema

The incidence of adverse medicine reactions tends to increase with increasing dose.

Renal effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with VUSOR. Shifts in urine protein from none or trace to ++ or more were seen in < 1 % of patients at some time during treatment with 10 mg 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. A causal association between proteinuria and acute or progressive renal disease has not been identified.

Haematuria with low occurrence has been reported in patients treated with VUSOR.

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 VUSOR-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 reported cases were mild, asymptomatic and transient. If CK levels are elevated (> 5 x ULN), 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.

Paediatric population:

Creatine kinase elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity were reported more frequently in a 52-week study of children and adolescents compared to adults (see section 4.4). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after 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.

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 and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 7.5 Serum cholesterol reducers

ATC code: C10A A07 – Pharmacotherapeutic group: HMG-CoA reductase inhibitors

Rosuvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol.

Rosuvastatin produces its lipid-modifying effects in 2 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 liver (reverse cholesterol transport).

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

5.2 Pharmacokinetic properties:

Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20 %. Peak plasma concentrations occur about 5 hours after oral dosing.

The absorption is not affected by food. The AUC of rosuvastatin does not differ following evening or morning administration.

Absorption increases linearly over the dose range.

The half-life is 19 hours and does not increase with increasing dose. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver.

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

Rosuvastatin undergoes limited metabolism in humans (approximately 10 %), mainly to the N-desmethyl form, and 90 % is eliminated as unchanged rosuvastatin in the faeces with the remainder being excreted unchanged in the urine.

Special populations:

Race:

Pharmacokinetic studies show a 1,26 to 2,31 fold elevation in geometric mean $AUC_{(0-t)}$ in Asian subjects compared with Caucasians. A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) Filipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analysis in these studies. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups (see section 4.2 :*Race)*.

Renal insufficiency:

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentration of rosuvastatin. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.

Haemodialysis is unlikely to be of benefit for medicine removal.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet Core:

Lactose monohydrate

Microcrystalline cellulose (Type 101 & 102)

Crospovidone (type A)

Sodium carbonate monohydrate

Sodium laurylsulphate

Magnesium stearate

Film-coating:

Opadry II 85F62533 Yellow (for 5 mg tablets) consisting of polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), polyethylene glycol, talc, iron oxide yellow (E172).

Opadry II 85F64743 Pink (for 10 mg, 20 mg and 40 mg tablets) consisting of polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), polyethylene glycol, talc, iron oxide red (E172), iron oxide yellow (E172), allura red AC (E129), indigo carmine (E132).

6.2 Incompatibilities:

None.

6.3 Shelf life:

3 years.

6.4 Special precautions for storage:

Blister packs:

Store at or below 25 °C in the original container and protect from light. Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container:

VUSOR 5, 10 and 20 mg tablets are packed into:

Opaque, silver coloured foil, dull on one side with a clear PVC film and opaque, silver coloured, shiny foil of 10 tablets per strip. 30 tablets are packed in a carton i.e. 3 blister strips per carton.

VUSOR 40 mg tablets are packed into:

Opaque, silver coloured foil, dull on one side with a clear PVC film and opaque, silver coloured, shiny foil of 5 or 10 tablets per strip. 30 tablets are packed in a carton. ~~OR~~

7 HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park, Magwa Crescent West

Waterfall City, Midrand

2090

8 REGISTRATION NUMBER~~:~~

VUSOR 5: 45/7.5/0310

VUSOR 10: 45/7.5/0311

VUSOR 20: 45/7.5/0312

VUSOR 40: 45/7.5/0313

9 DATE OF FIRST AUTHORISATION:

30 June 2013

10 DATE OF REVISION OF THE TEXT

23 May 2023