PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ZUVAMOR® 5; 5 mg film-coated tablets

ZUVAMOR® 10; 10 mg film-coated tablets

ZUVAMOR® 20; 20 mg film-coated tablets

ZUVAMOR® 40; 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZUVAMOR 5: Each tablet contains 5 mg rosuvastatin as rosuvastatin calcium

ZUVAMOR 10: Each tablet contains 10 mg rosuvastatin as rosuvastatin calcium

ZUVAMOR 20: Each tablet contains 20 mg rosuvastatin as rosuvastatin calcium

ZUVAMOR 40: Each tablet contains 40 mg rosuvastatin as rosuvastatin calcium

Contains sugar: lactose monohydrate.

ZUVAMOR 5: Each tablet contains 94,88 mg lactose monohydrate

ZUVAMOR 10: Each tablet contains 91,30 mg lactose monohydrate

ZUVAMOR 20: Each tablet contains 182,60 mg lactose monohydrate

ZUVAMOR 40: Each tablet contains 168,32 mg lactose monohydrate

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

ZUVAMOR 5: Yellow, film-coated, round, biconvex, approximately 7 mm (diameter) intagliated tablet; obverse side “ZD4522 5”, reverse side none.

ZUVAMOR 10: Pink, film-coated, round, biconvex, approximately 7 mm (diameter) intagliated tablet; obverse side “ZD4522 10”, reverse side none.

ZUVAMOR 20: Pink, film-coated, round, biconvex, approximately 9,1 mm (diameter) intagliated tablet; obverse side “ZD4522 20”, reverse side none.

ZUVAMOR 40: Pink, film-coated, oval, biconvex, approximately 11,5 x 7,1 mm (length x width) intagliated tablet; obverse side “ZD4522”, reverse side “40”.

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, ZUVAMOR is indicated to reduce the risk of non- fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

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

ZUVAMOR 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 ZUVAMOR or alternative therapy and in whom routine follow-up will be performed (see section 4.4).

Specialist supervision is recommended when the 40 mg dose is initiated (see section 4.4).

Children and adolescents 10-17 years of age:

ZUVAMOR 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.

Treatment of hypercholesterolaemia:

The recommended start dose is 5 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see section 4.8), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

The dosage of ZUVAMOR 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 4 week intervals (see section 5.1).

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.

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.

Special populations

Use in the elderly:

The usual dose range applies.

Dosage in patients with renal insufficiency:

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of ZUVAMOR in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Dosage in patients with hepatic insufficiency:

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. The usual starting dose applies in patients with mild to moderate hepatic impairment. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Patients with severe hepatic impairment should start therapy with ZUVAMOR 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above ZUVAMOR 10 mg should be carefully considered (see section 5.2). ZUVAMOR is contraindicated in patients with active liver disease (see section 4.3).

Race:

A 5 mg starting dose of ZUVAMOR 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. The 40 mg dose is contraindicated in these patients.

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of ZUVAMOR should not be exceeded (see section 4.4, 4.5 and 5.2).

Concomitant therapy:

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when ZUVAMOR is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir (see section 4.4 & 4.5).

It is recommended that prescribers consult the relevant product information when considering administration of such products together with ZUVAMOR. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing ZUVAMOR therapy. In situations where co-administration of these medicinal products with ZUVAMOR is unavoidable, the benefit and the risk of concurrent treatment and ZUVAMOR dosing adjustments should be carefully considered (see section 4.4).

Paediatric population

Children and adolescents 10-17 years of age

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5-20 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).

Method of administration

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

4.3 Contraindications

ZUVAMOR is contraindicated in:

- patients with hypersensitivity to the active substance or to any of the excipients of ZUVAMOR.
- patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- patients with severe renal impairment (creatinine clearance <30 ml/min).
- patients with myopathy
- concomitant use with ciclosporin (see section 4.5)
- 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/rhabdomyolisis. 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)

4.4 Special warnings and precautions for use

Liver Effects:

ZUVAMOR 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 enzyme tests be performed before the initiation of ZUVAMOR, 3 months following, the initiation of treatment and if signs or symptoms of liver injury occur. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including ZUVAMOR. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with ZUVAMOR, promptly interrupt therapy. If an alternate aetiology is not found, do not restart ZUVAMOR.

Renal effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of ZUVAMOR, 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 on skeletal muscles e.g. myalgia, myopathy and rhabdomyolysis, have been reported in patients treated with ZUVAMOR. The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their Creatine kinase (CK) levels measured. ZUVAMOR 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 (> 5 x ULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment should not be started.

Before Treatment

ZUVAMOR 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 (> 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. 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 ZUVAMOR 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 necrotizing myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including ZUVAMOR. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

An increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

ZUVAMOR 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 (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 coadministration of ZUVAMOR and fusidic acid should only be considered on a case by case basis and under close medical supervision.

ZUVAMOR should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism or situations where an increase in plasma levels may occur (see section 4.5 and section 5.2).

ZUVAMOR 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).

Diabetes Mellitus:

Increases in HbA1c and serum glucose levels have been observed in patients treated with ZUVAMOR and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus. This was observed primarily in patients already at high risk for developing diabetes (see section 4.8). Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m2, 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 (100-124 md/dL).

Race:

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see section 4.2 and section 5.3).

Children and adolescents 10-17 years of age:

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a 1 year period (see section 5.1)

Protease inhibitors:

ZUVAMOR 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 Cmax of rosuvastatin (see section 4.2 and section 4.4).

Lactose:

ZUVAMOR contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take ZUVAMOR.

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.

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 ZUVAMOR 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: During concomitant treatment with ZUVAMOR and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). ZUVAMOR 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 (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and sevenfold increase in rosuvastatin AUC and Cmax, respectively. The concomitant use of ZUVAMOR and some protease inhibitor combinations may be considered after careful consideration of ZUVAMOR dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4 and 4.5 Table 1).

Gemfibrozil and other lipid-lowering products: Concomitant use of ZUVAMOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (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 HMGCoA 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 5 mg dose.

Ezetimibe: Concomitant use of 10 mg ZUVAMOR and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between ZUVAMOR and ezetimibe cannot be ruled out (see section 4.4).

Antacids: The simultaneous dosing of ZUVAMOR 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 ZUVAMOR. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of ZUVAMOR 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, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

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

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

If 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 ZUVAMOR dose above 20 mg.

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

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting 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 ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5,2-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3,8 -fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3,1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2,8-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2,7 -fold ↑

Ombitasvir 25 mg/ paritaprevir 150 mg/ ritonavir 100 mg/dasabuvir 400 mg BID	5 mg single dose	2,6-fold ↑
Grazoprevir 200 mg/ elbasvir 50 mg OD	10 mg single dose	2,3-fold ↑
Glecaprevir 400 mg/ pibrentasvir 120 mg OD for 7 days	5 mg once daily	2,2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2,1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1,9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting medicine 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 or 80 mg, single dose	**1,4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1,2-fold ↑
Decrease in AUC of rosuvastatin		
Interacting medicine 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 ZUVAMOR 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 coadministration:

Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole

200mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

Effect of rosuvastatin on co-administered medicines:

Warfarin:

The pharmacokinetics of warfarin are not significantly affected following co-administration with ZUVAMOR. However, as with other HMG-CoA reductase inhibitors, co-administration of ZUVAMOR and warfarin may result in a rise in INR compared to warfarin alone. In patients taking warfarin monitoring of INR is recommended both at initiation or cessation of therapy with ZUVAMOR or following dose adjustment.

Niacin:

The risk of skeletal muscle effects may be enhanced when ZUVAMOR is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; caution should be used when prescribing with ZUVAMOR (see section 4.4).

Consideration should be given both to the benefit of lipid lowering by the use of ZUVAMOR in HIV-infected patients receiving protease inhibitors and the potential risks of this increased rosuvastatin plasma concentrations when initiating and up-titrating ZUVAMOR doses in patients treated with protease inhibitors, as the combination may lead to an increased incidence of adverse events (see section 4.2 and 4.4).

The lowest dose of ZUVAMOR that provides therapeutic benefit to the patient should be used and close monitoring of adverse events is indicated (see section 4.2).

Other medicines:

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. 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, ZUVAMOR 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.

There were no clinically significant interactions with an oral contraceptive.

In clinical studies ZUVAMOR was co-administered with antihypertensive agents, antidiabetic agents and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

ZUVAMOR is contraindicated in pregnancy and lactation.

The safety of ZUVAMOR during pregnancy and whilst breast feeding has not been established. 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 (see section 5.3). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

4.7 Effects on ability to drive and use machines

Studies to determine the effect of ZUVAMOR on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, ZUVAMOR is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

a. **Summary of the safety profile**

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

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

b. Tabulated summary of adverse reactions

The frequencies of adverse events are ranked according to the following: common (≥ 1/100, < 1/10); uncommon (≥1/1 000, < 1/100); rare (≥1/10 000, < 1/1 000); very rare (<1/10 000) not known (cannot be estimated from the available data).

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

System organ class	Frequency	Adverse Event
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Endocrine disorders	Common	Diabetes mellitus[1]
Psychiatric disorder	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

Hepatobiliary disorders	Rare	Increased hepatic transaminases
	Very rare	Jaundice Hepatitis
	Not known	Fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash, urticaria
	Rare	Hypersensitivity reactions including angio-oedema
	Not known	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Rare	Myopathy including (myositis), rhabdomyolysis Lupus-like syndrome Muscle rupture Arthralgia
	Not known	Tendon disorders, sometimes complicated by rupture Immune- mediated necrotising myopathy
Renal and urinary disorders	Very Rare	Haematuria
Reproductive system and breast disorders	Not known	Gynaecomastia
General disorders and administration site conditions	Common	Asthenia
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m2, raised triglycerides, history of hypertension).		

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

c. Description of selected adverse reactions

Skeletal muscle effects:

Rhabdomyolysis, which may occasionally be associated with impairment of renal function, has been reported with ZUVAMOR.

Renal effects:

Proteinuria (see “Laboratory effects”).

Laboratory effects:

A dose-related increase in liver transaminases and Creatine kinase (CK) has been observed in patients taking ZUVAMOR. Increases in HbA1c have also been observed in

patients treated with ZUVAMOR (see section 4.4). Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen in patients taking ZUVAMOR. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappeares spontaneously on continued therapy and is not predictive of acute or progressive renal disease.

Other effects:

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

In ZUVAMOR treated patients, there was no impairment of adrenocortical function.

The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

d. Paediatric population

Children and adolescents 10-17 years of age:

The safety profile of ZUVAMOR is similar in children or adolescent patients and adults although CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in clinical trials of children and adolescents. However, the same 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8**.**

Acino Pharma (Pty) Ltd: E-mail: drugsafety_za@acino.swiss Tel: 060 998 7896

By reporting side effects, you can help provide more information on the safety of ZUVAMOR.

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: HMG-CoA reductase inhibitors

ATC code: C10A A07

Mechanism of action

Rosuvastatin is a lipid lowering agent that acts by selective and competitive inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, leading to reduced hepatic synthesis of cholesterol and VLDL.

This is followed by increased number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL.

Pharmacodynamic effects

Overall, rosuvastatin reduces elevated LDL cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I.

ZUVAMOR also lowers LDL-C/HDL-C, total C/HDL-C, non-HDL-C/HDL and ApoB/ApoA-I ratio's.

A therapeutic response to ZUVAMOR 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:

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, mostly albumin.

Metabolism:

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.

Excretion:

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 pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to or lower than that of adult patients with dyslipidaemia (see “Paediatric population” below).

Race:

Pharmacokinetic studies show a 1,26-2,31-fold elevation in geometric mean AUC(0-t) in Asian subjects compared with Caucasians.

Renal insufficiency:

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

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2,8 % of patients in the rosuvastatin group and 2,3 % of patients in the placebo group (HR: 1,27, 95 % CI: 1,05-1,53, p=0.015).

In the JUPITER study, the difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c from baseline was approximately 0,1 %.

A post hoc analysis of this study suggests that the risk of development of diabetes on rosuvastatin therapy is limited to patients already at high risk of developing diabetes. The cardiovascular and mortality benefits of rosuvastatin therapy exceeded the diabetes hazard in the trial population as a whole as well as in participants at increased risk of developing diabetes (see section 4.4 and section 4.8).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Calcium phosphate
Crospovidone
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Tablet coat:
Glycerol triacetate
Hypromellose
Iron oxide yellow (E172) (5 mg tablet)
Iron oxide red (E172) (10 mg, 20 mg and 40 mg tablets)
Lactose monohydrate
Titanium dioxide (E171)

6.2 Incompatibilities

Not appliable

6.3 Shelf life

ZUVAMOR 5: 36 months
ZUVAMOR 10: 24 months
ZUVAMOR 20: 24 months
ZUVAMOR 40: 24 months

6.4 Special precautions for storage

Blister packs: Store at or below 30 °C. Keep the blister in the carton until required for use.
HDPE bottles: Store at or below 30 °C. Keep container tightly closed.

6.5 Nature and contents of container

ZUVAMOR 5 mg, 10 mg, 20 mg and 40 mg tablets:
Aluminium laminate/aluminium foil blister packs of 28 or 30 tablets.
ZUVAMOR 5 mg, 10 mg, 20 mg and 40 mg tablets:
HDPE bottles: bottles containing 30, 90 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd.
106, 16th Road
Midrand, 1686

8 REGISTRATION NUMBERS

ZUVAMOR 5: 43/7.5/138
ZUVAMOR 10: 36/7.5/0353
ZUVAMOR 20: 36/7.5/0354

ZUVAMOR 40: 36/7.5/0355

9 DATE OF FIRST AUTHORISATION

ZUVAMOR 5: 27 July 2017

ZUVAMOR 10: 07 April 2006

ZUVAMOR 20: 07 April 2006

ZUVAMOR 40: 07 April 2006

10 DATE OF REVISION OF THE TEXT

23 October 2024