PROFESSIONAL INFORMATION FOR VASROV TABLETS

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VASROV 5 (5 mg film-coated tablets)

VASROV 10 (10 mg film-coated tablets)

VASROV 20 (20 mg film-coated tablets)

VASROV 40 (40 mg film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VASROV 5: Each film-coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium)

VASROV 10: Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium)

VASROV 20: Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium)

VASROV 40: Each film-coated tablet contains 40 mg rosuvastatin (as rosuvastatin calcium)

Excipients with known effect

Each 5 mg film-coated tablet contains 29,750 mg lactose monohydrate.

Each 10 mg film-coated tablet contains 59,500 mg lactose monohydrate.

Each 20 mg film-coated tablet contains 119,00 mg lactose monohydrate.

Each 40 mg film-coated tablet contains 238 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

VASROV 5 mg:

Yellow, round, biconvex, film coated tablets debossed with “CL” on one side and “86” on other side.

VASROV 10 mg:

Pink, round, biconvex, film coated tablets debossed with 'CL 87' on one side and plain on other side.

VASROV 20 mg:

Pink, round, biconvex, film coated tablets debossed with 'CL 88' on one side and plain on other side.

VASROV 40 mg:

Pink, oval, biconvex, film coated tablets debossed with 'CL 89' on one side and plain on 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, **VASROV** is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

VASROV 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.

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

VASROV 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).

VASROV 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 **VASROV** 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:

VASROV 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.

Posology

The dosage range for **VASROV** is 5 - 40 mg orally once a day. The recommended start dose is 5 mg once a day.

The dose 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 – 4 week intervals.

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Frederickson 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.

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 **VASROV** 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 **VASROV** 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above **VASROV** 10 mg should be carefully considered (see section 5.2).

Race:

A 5 mg starting dose of **VASROV** should be considered for Asian patients. Increased plasma concentration of rosuvastatin is 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:

VASROV has 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.

VASROV 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 commitment **VASROV** and ciclosporin. For the **VASROV** dose range (10 - 40 mg) this combination is not recommended (see section 4.3).

Gemfibrozil:

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

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 approximately 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

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

4.3 Contraindications

VASROV is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients of **VASROV**.
- in 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).
- in patients with severe renal impairment (creatinine clearance < 30 ml/min).
- in patients receiving concomitant ciclosporin (see section 4.5).
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- in patients with myopathy
- 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 rosuvastatin-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

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of **VASROV**, in particular 40 mg, it was transient or intermittent in most cases. Proteinuria has not been shown to be a precursor to 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 must 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 at all doses, particularly at doses higher than 20 mg.

As with other HMG-CoA reductase inhibitors, 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. **VASROV** therapy should be discontinued if myopathy is diagnosed or suspected.

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.

VASROV 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 5.2).

Creatine Kinase Measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of alternative causes of CK increase which may influence the 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 must not be started.

Before treatment

HMG-CoA reductase inhibitors, such as **VASROV**, 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
- above 70 years of age
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)
- concomitant use of fibrates.

In this patient-group, the risk of treatment should be considered in relation to possible benefit. Clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x ULN) treatment must not be initiated.

During treatment

Patients must be advised 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 must 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 **VASROV** 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. 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

Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors, such as **VASROV**. Therefore, the combination of **VASROV** and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of **VASROV** 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 4.5 and 4.8).

Fusidic acid

VASROV 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 are to 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 concomitant administration of **VASROV** and fusidic acid should only be considered on a case by case basis and under close medical supervision.

VASROV must not be used in patients with acute, serious conditions 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).

Liver effects

HMG-CoA reductase inhibitors, such as **VASROV**, must 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. **VASROV** must 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 **VASROV**.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasian subjects (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 **VASROV** in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating **VASROV** doses in patients treated with protease inhibitors.

The concomitant use with certain protease inhibitors is not recommended unless the dose of **VASROV** is adjusted (see sections 4.2 and 4.5).

Interstitial Lung Disease

Cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). Presenting features may 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 must be discontinued.

Diabetes Mellitus

Satins as a class of medicine may raise blood glucose. 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.

VASROV should be used with care in patients with Type 2 diabetes and in patients at risk, being patients with a fasting glucose of 5.6 to 6.9 mmol/l, BMI > 30 kg/m2, raised triglycerides or hypertension. Patients at risk must be clinically and biochemically monitored.

Children and adolescents 10 – 17 years of age

The safety profile of **VASROV** 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 children and adolescents. However, the same special warnings and special precautions for use in adults also apply to children and adolescents.

Lactose Intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

*Effect of co-administered medicines on **VASROV***

Transporter protein inhibitors:

Rosuvastatin, as contained in **VASROV**, is a substrate for certain transporter proteins including the hepatic uptake transporter organic-anion-transporting polypeptide 1B1 (OATP1B1) and efflux transporter breast-cancer-resistance protein (BCRP). Concomitant administration of **VASROV** 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 **VASROV** and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). **VASROV** is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors:

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving **VASROV** with various protease inhibitors in combination with ritonavir (see Table 1 below). This increase in systemic exposure to **VASROV** may lead to an increased incidence of adverse events. The concomitant use of **VASROV** and some protease inhibitor combinations may be considered after careful consideration of **VASROV** dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4, 4.5 and Table 1 below).

Gemfibrozil and other lipid-lowering medicines:

Concomitant use of **VASROV** and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (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 **VASROV**, 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 start with the 5 mg dose.

Ezetimibe:

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

Antacid:

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

Erythromycin:

Concomitant use of **VASROV** 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:

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).

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

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

Start with a 5 mg once daily dose of **VASROV** if the expected increase in exposure (AUC) is approximately 2-fold or higher.

The maximum daily dose of **VASROV** should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of **VASROV** taken without interacting medicines, for example a 20 mg dose of **VASROV** with gemfibrozil (1.9-fold increase), and a 10 mg dose of **VASROV** 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*
Ciclosporin 75 mg twice daily to 200 mg twice daily, 6 months	10 mg once daily, 10 days	7.1-fold ↑
Regorafenib 160 mg, once daily, 14 days	5 mg, single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg once daily, 8 days	10 mg, single dose	3.1-fold ↑
Velpatasvir 100 mg once daily	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg once daily / dasabuvir 400 mg twice daily, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg once daily, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg once daily, 7 days	5 mg once daily, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg twice daily, 17 days	20 mg once daily, 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 twice daily, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg once daily, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg twice daily, 7 days	10 mg once daily, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg twice daily, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg twice daily	Not available	1.4-fold ↑
Itraconazole 200 mg once daily, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg once daily, 14 days	10 mg, once daily, 14 days	**1.2-fold ↑

Fosamprenavir 700 mg/ritonavir 100 mg twice daily, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg three times daily, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg three times daily, 7 days	10 mg, 7 days	↔
Rifampicin 450 mg once daily, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg twice daily, 7 days	80 mg, single dose	↔
Fluconazole 200 mg once daily, 11 days	80 mg, single dose	↔
Erythromycin 500 mg four times daily, 7 days	80 mg, single dose	20 % ↓
Baicalin 50 mg three times daily, 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 dosages, the table shows the most significant ratio.

Effect of rosuvastatin on co-administered medicines:

Warfarin:

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

Oral contraceptive/hormone replacement therapy (HRT):

Concomitant use of **VASROV** 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 **VASROV** and hormone replacement therapy, therefore, a similar effect cannot be excluded.

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, **VASROV** 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

Women of childbearing potential / Contraception in males and females

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

Pregnancy

VASROV is contraindicated in pregnancy (see section 4.3).

Lactation

VASROV is contraindicated in lactation. Rosuvastatin is excreted in the milk of rats. There is no data available with respect to excretion of rosuvastatin in milk in humans (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions seen with **VASROV** are generally mild and transient.

Table 2: Tabulated list of adverse reactions

System Organ Class	**Frequency**	
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions including angioedema
Endocrine disorders	Frequent	Diabetes mellitus[1]
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache Dizziness
	Less frequent	Polyneuropathy Memory loss
	Frequency unknown	Peripheral neuropathy
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough Dyspnoea
Gastro-intestinal disorders	Frequent	Constipation Nausea Abdominal pain
	Less frequent	Pancreatitis
	Frequency unknown	Diarrhoea
Hepatobiliary disorders	Less frequent	Increased hepatic transaminases Jaundice Hepatitis
Skin and subcutaneous tissue	Less frequent	Pruritus

disorders		Rash Urticaria
	Frequency unknown	Stevens- Johnson syndrome
Musculoskeletal and connective tissue 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 disorders	Less frequent	Haematuria
	Frequency unknown	Proteinuria
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Asthenia
	Less frequent	Oedema

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).

As with other HMG-CoA reductase inhibitors, such as **VASROV**, the incidence of adverse 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 **VASROV**. Shifts in urine protein from none or trace to 100 mg/dL 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 30 mg/dL 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 **VASROV** 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 **VASROV**-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 (> 5 x ULN), treatment should be discontinued (see section 4.4).

Liver effects:

A dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin as in **VASROV**; 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 – 17 years of age

Creatine kinase elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial 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 Reaction 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 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

A 7.5 Serum-cholesterol reducers

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-CoA (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 produces its lipid-modifying effects in 2 ways; it increases the number of hepatic low density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very low density lipoprotein (VLDL**)**, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains apolipoprotein A-I (ApoA-I) is involved, amongst other

things, in transport of cholesterol from tissues back to liver (reverse cholesterol transport).

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

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

Metabolism:

Rosuvastatin undergoes limited metabolism in humans (approximately 10 %) mainly to the N-desmethyl form.

Elimination:

Approximately 90 % of the rosuvastatin dose is excreted unchanged in the faeces and the remaining part is excreted in the urine.

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. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race:

Pharmacokinetic studies show a 1,26 - 2,31 fold elevation in geometric mean AUC ($_{0\text{-}t}$) 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 %) 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. (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 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.421CC genotypes. 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 **VASROV** is recommended.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose,

lactose monohydrate,

anhydrous dibasic, calcium phosphate,

hypromellose,

crospovidone,

magnesium stearate

Tablet coat

Ready to use coating material I (For 10 mg, 20 mg & 40 mg Tablets):

HPMC 2910/hypromellose (e464),

titanium dioxide (e171),

triacetin

iron oxide red (e172)

Ready to use coating material II (For 5 mg Tablets):

HPMC 2910/hypromellose (e464),

titanium dioxide (e171),

triacetin,

iron oxide yellow (e172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

HDPE container pack: 36 months from the manufacturing date.

Blister pack: 48 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed

Keep out of reach of children

6.5 Nature and contents of container

Blister Pack: **VASROV** 5/10/20/40 mg

Silver coloured cold form foil, OPA/AI/PVC 25/45/60 micron as the forming material and plain, silver coloured, 30 micron aluminium foil/6-8 gsm HSL as the lidding material, packed in a pre-printed unit carton.

Pack size include 10's, 14's, 28's, 30's and 100's tablets.

HDPE container pack**:**

VASROV 5/10/20 mg

60 cc round, white, HDPE container with 33 mm neck finish, containing 28 or 30 or 90 tablets and 2 silica gel sachets, closed with a white closure, 33 mm with white printed pulp and heat seal liner and packed in a pre-printed unit carton.

VASROV 40 mg

60 cc / 75 cc round, white, HDPE container with 33 mm / 38 mm neck finish respectively, containing 28 or 30 or 90 tablets and 2 silica gel sachets, closed with a white closure, 33 mm / 38 mm with white printed pulp and heat seal liner and packed in a pre-printed unit carton.

Pack size include 28's, 30's & 90's tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8 REGISTRATION NUMBER(S)

VASROV 5 mg: 50/7.5/0014
VASROV 10 mg: 50/7.5/0015
VASROV 20 mg: 50/7.5/0016
VASROV 40 mg: 50/7.5/0017

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

21 SEPTEMBER 2021

10 DATE OF REVISION OF THE TEXT

26 SEPTEMBER 2023

PM0097-01

05/09/2024