SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

LYPOVAS 5

LYPOVAS 10

LYPOVAS 20

LYPOVAS 40

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

COMPOSITION:

LYPOVAS 5 film-coated tablets

Each film-coated tablet contains 5.20 mg of rosuvastatin calcium equivalent to 5 mg rosuvastatin.

Contains sugar: lactose monohydrate 21.125 mg

LYPOVAS 10 film-coated tablets

Each film-coated tablet contains 10.40 mg of rosuvastatin calcium equivalent to 10 mg rosuvastatin.

Contains sugar: lactose monohydrate 42.25 mg

LYPOVAS 20 film-coated tablets

Each film-coated tablet contains 20.80 mg of rosuvastatin calcium equivalent to 20 mg rosuvastatin.

Contains sugar: lactose monohydrate 84.50 mg

LYPOVAS 40 film-coated tablets

Each film-coated tablet contains 41.60 mg of rosuvastatin calcium equivalent to 40 mg rosuvastatin.

Contains sugar: lactose monohydrate 169.00 mg

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM:

Film-coated tablets

LYPOVAS 5

Pink, 4.50 mm, round, biconvex, bevelled edge, film-coated tablet, debossed with ‘R5’ on one side and plain on other side

LYPOVAS 10

Pink, 5.50 mm, round, biconvex, bevelled edge, film-coated tablet, debossed with ‘R10’ on one side and plain on other side.

LYPOVAS 20

Pink, 7.00 mm, round, biconvex, film-coated tablet, debossed with ‘R20’ on one side and plain on other side.

LYPOVAS 40

Pink, 11.50 mm X 6.90 mm, oval, biconvex, film-coated tablet, debossed with ‘R40’ 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, **LYPOVAS** is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolemia:

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

LYPOVAS is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinemia).

LYPOVAS is also indicated to reduce Total Cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

LYPOVAS 40 mg should only be considered in patients with severe hypercholesterolemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of **LYPOVAS** or alternative therapy.

Specialist supervision is recommended when the 40 mg dose is initiated.

Children and adolescents 10-17 years of age:

LYPOVAS 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.

Posology

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

The dosage of **LYPOVAS** 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. (See section 5.1).

Adults

Primary hypercholesterolemia (including heterozygous familial hypercholesterolemia), mixed dyslipidemia, dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinemia), 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.

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

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).

Special populations:

Elderly

The usual dose range applies.

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 of <60 mL/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of **LYPOVAS** tablets in patients with severe renal impairment is contraindicated for all doses (see section 4.3 and section 5.2).

Hepatic impairment

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

Race

A 5 mg starting dose of **LYPOVAS** should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian patients. (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

LYPOVAS 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.

LYPOVAS can also be used in combination with ezetimibe or bile acid sequestrants.

Ciclosporin:

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant **LYPOVAS** and ciclosporin. For the **LYPOVAS** dose range (10-40 mg) this combination is not recommended. (See section 4.3) *Gemfibrozil:*

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant **LYPOVAS** and gemfibrozil. Patients taking this combination should start therapy with **LYPOVAS** 5 mg once daily and should not exceed a dose of **LYPOVAS** 20 mg once daily.

Paediatric population

Paediatric use should only be carried out by specialists

Method of administration

For oral use.

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

4.3 Contraindications

LYPOVAS tablets is contraindicated:

-in patients with hypersensitivity to rosuvastatin or to any of the excipients listed in section 6.1.

-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 with myopathy.

- in patients receiving concomitant ciclosporin.

- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

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

− moderate renal impairment (creatinine clearance < 60 mL/min)

− hypothyroidism

− personal or family history of hereditary muscular disorders

− previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate

− alcohol abuse

− situations where an increase in plasma levels may occur

− Asian patients

− concomitant use of fibrates.

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

Skeletal Muscle Effects

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

The reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

Creatine Kinase Measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (> 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

LYPOVAS, 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 **LYPOVAS** tablets 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 **LYPOVAS**. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

There was no evidence of increased skeletal muscle effects in the small number of patients dosed with ~~**LYPOVAS**~~ rosuvastatin tablets and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA

reductase inhibitors. Therefore, the combination of **LYPOVAS** tablets and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of **LYPOVAS** tablets 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).

LYPOVAS 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. 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 co-administration of **LYPOVAS** and fusidic acid should only be considered on a case by case basis and under close medical supervision.

LYPOVAS tablets should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

<u>Liver Effects</u>

LYPOVAS tablets should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. **LYPOVAS** tablets should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with **LYPOVAS** tablets.

Race

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

Protease inhibitors

Increased systemic exposure to rosuvastatin has been observed in patients receiving **LYPOVAS** concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of **LYPOVAS** in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating **LYPOVAS** doses in patients treated

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

Interstitial lung disease

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

Diabetes Mellitus

Some evidence suggests that statins, as a class, raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically.

Paediatric population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking **LYPOVAS** is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see section 5.1).

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

LYPOVAS film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose -galactose malabsorption should not take **LYPOVAS**.

4.5 Interaction with other medicines and other forms of interaction

Transporter protein inhibitors:

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of **LYPOVAS** tablets 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)

Ciclosporin:

During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin plasma concentration levels were on average 7 times higher than those observed in healthy patients. **LYPOVAS** tablets 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. The concomitant use of **LYPOVAS** and some protease inhibitor combinations may be considered after careful consideration of **LYPOVAS** tablets dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products:

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin-plasma concentration levels. (see section 4.4). Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate (see section 4.3 and section 4.4). These patients should also start with the 5 mg dose.

Ezetimibe

Concomitant use of 10 mg of rosuvastatin tablets and 10 mg ezetimibe resulted in a 1.2-fold increase in plasma concentration levels of rosuvastatin in hypercholesterolaemic patients. A pharmacodynamic interaction, in terms of adverse effects, between **LYPOVAS** tablets and ezetimibe cannot be ruled out (see section 4.4).

Antacid:

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

Erythromycin:

Concomitant use of rosuvastatin and erythromycin resulted in a 20 % decrease in AUC(0-t) and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Vitamin K antagonists:

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of **LYPOVAS** tablets 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 **LYPOVAS** tablets may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT):

Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in plasma concentration levels of ethinyl estradiol and norgestrel. These increased plasma levels

should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in patients taking concomitant **LYPOVAS** and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

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, **LYPOVAS** treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

LYPOVAS tablet is contraindicated during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Breastfeeding

LYPOVAS tablet is contraindicated during lactation. (see section 4.3)

4.7 Effects on the ability to drive and use machines

LYPOVAS may cause dizziness and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery, or engage in other potentially hazardous activities until it is known whether **LYPOVAS** affects their ability to perform these activities

4.8 Undesirable effects

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Blood and lymphatic system disorders		Thrombocytopenia	

Immune system disorders		Hypersensitivity reactions including angioedema	
Endocrine disorders	Diabetes mellitus		
Psychiatric disorders			Depression
Nervous system disorders	Headache, dizziness	Polyneuropathy, memory loss	Peripheral neuropathy, sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders			Cough, dyspnoea
Gastrointestinal disorders	Constipation, Nausea, abdominal pain	Pancreatitis,	Diarrhoea

Hepatobiliary disorders		increased hepatic transaminases jaundice, hepatitis	
Skin and subcutaneous tissue disorders		Pruritis, rash, urticaria	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Myalgia	Myopathy (including myositis), rhabdomyolysis, arthralgia	Tendon disorders sometimes complicated by rupture, immune-mediated necrotising myopathy
Renal and urinary disorders		Haematuria	
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions	Asthenia		Oedema

Description of selected adverse reactions

Renal Effects:

Proteinuria- A dose-related increase in liver transaminases and Creatine kinase (CK) has been observed in

patients taking rosuvastatin. Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen in patients taking **LYPOVAS**. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy,

and is not predictive of acute or progressive renal disease.

Skeletal muscle effects:

Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin -treated patients with all doses and in particular with doses > 20 mg.

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; most 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.

Reporting suspected adverse

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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 Reactions Reporting Form",** found online under SAHPRA's publications: hppts://www.sahpra.or.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

Pharmacological Classification: A7.5 Serum-cholesterol reducers.

Mechanism of action:

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 of 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 the liver (reverse cholesterol transport).

Summary of clinical studies:

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

rosuvastatin also lowers the LDL -C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's. A therapeutic response to rosuvastatin is evident within 1 week of commencing therapy and 90 % of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

5.2 Pharmacokinetic properties

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

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

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 were no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial

hypercholesterolemia appears to be similar to or lower than to that of adult patients with dyslipidemia (see “Paediatric population” below).

Race:

Pharmacokinetic studies show a 1,26 - 2- 31fold elevation in median plasma concentrations in Asian patients (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency:

In a study in patients with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Patients 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 patients undergoing haemodialysis were approximately 50 % greater compared to healthy volunteers.

Hepatic insufficiency:

In a study with patients with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in patients with Child-Pugh scores of 7 or below. However, two patients with Child-Pugh scores of 8 and 9 showed an increase in systemic

exposure of at least 2-fold compared to patients with lower Child-Pugh scores. There is no experience in patients 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 Rosuvastatin tablets is recommended.

Paediatric population:

Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolemia 10-17 or 6-17 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

- Cellulose microcrystalline,
- crospovidone,
- lactose monohydrate,
- magnesium stearate,
- sodium hydrogen carbonate,
- Opadry II pink contains:
    - Hypromellose,
    - iron oxide red,
    - lactose monohydrate
    - titanium dioxide,
    - triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in original container. Protect from light and moisture.

6.5 Nature and contents of container

LYPOVAS 5, 10, 20 & 40

Blister packs of 10's, 28's, 30's, 56's, 84's: tablets are packed in one blister of cold forming base foil and aluminium lid foil

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 Holder of certificate of registration

Innovata Pharmaceuticals (Pty) LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8 Registration numbers

LYPOVAS 5: 55/7.5/0563

LYPOVAS 10: 55/7.5/0564

LYPOVAS 20: 55/7.5/0565

LYPOVAS 40: 55/7.5/0566

9 Date of first authorization/Renewal of the authorization

16 August 2022

10 Date of revision of the text

TBI