1.3.1

Summary Of Product Characteristics (SPC)

1. NAME OF THE DRUG PRODUCT

Invented Name of the Medicinal Product

ROSUTOR 10

Rosuvastatin Calcium Tablets 10 mg

Strength

Rosuvastatin Calcium Tablets 10 mg

Dosage Form

Solid Dosage form.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Rosuvastatin Calcium

Equivalent to Rosuvastatin……. 10 mg

Excipients: …….Q.S

3. PHARMACEUTICAL FORM

Film Coated Tablet

Brown coloured round shaped biconvex film coated tablet plain on both side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypercholesterolaemia

Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type II a including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type II b) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Adults, adolescents and children over 6 years or older with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of cardiovascular events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology:

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

Treatment of hypercholesterolaemia

The recommended start dose is 5 mg or 10 mg orally once daily in both statin naïve or patients switched from another HMG-CoA reductase inhibitor. Administration of a 5 mg dose can be achieved by halving a 10 mg tablet with the breakline.

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. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, 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. Specialist supervision is recommended when the 40 mg dose is initiated.

Administration: Rosuvastatin may be given at any time of day, with or without food.

4.3 CONTRAINDICATIONS

Rosuvastatin is contraindicated:

- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any
  serum transaminase elevation exceeding 3× 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.

4.4 WARNING AND PRECAUTIONS

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. The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal muscle effects

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

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin. 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. 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 seven-fold increase in rosuvastatin AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin 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 C_{max} and AUC. Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg

dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

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 rosuvastatin. The clinical relevance of this interaction has not been studied.

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

Cytochrome P450 enzymes: 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).

Other medicinal products:

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, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Paediatric population

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

4.6 PREGNANCY AND LACTATION

Rosuvastatin is contraindicated in pregnancy and lactation.

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. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, rosuvastatin 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

The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.

Tabulated list of adverse reactions

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

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

system organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Endocrine disorders	Common	Diabetes mellitus[1]
Psychiatric disorders	Not known	Depression
Nervous system disorders	Common	Headache, Dizziness
	Very rare	Polyneuropathy, Memory loss
Respiratory, thoracic and mediastinal disorders	Not known	Cough, Dyspnoea
Gastrointestinal disorders	Common	Constipation, Nausea Abdominal pain
	Rare	Pancreatitis
	Not known	Diarrhoea
Hepatobiliary disorders	Rare	Increased hepatic transaminases
	Very rare	Jaundice, Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, Rash, Urticaria
	Not known	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Rare	Myopathy (including myositis) Rhabdomyolysis
	Very rare	Arthralgia
	Not known	Immune-mediated necrotising myopathy Tendon disorders, sometimes complicated by rupture
General disorders and administration site conditions	Common	Asthenia
	Not known	Oedema

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in < 1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-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× ULN), treatment should be discontinued.

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

Paediatric population

Creatine kinase elevations > 10× 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. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

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

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects

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 (see Table 3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 3. Dose response in patients with primary hypercholesterolaemia (type II a and II b) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	Non HDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is 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.

Biotransformation

Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination

Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity

Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Povidone
Magnesium Stearate
Purified Talc
Croscarmellose Sodium
Hydroxy propyl methyl Cellulose
Purified Talc
Titanium Dioxide
Red Oxide of Iron
Polyethylene Glycol - 4000
Methylene Chloride
Isopropyl Alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store below 30°C. Protected from light.

6.5 Nature and contents of container

Alu/Alu 10 Tablets in one blister such 03 blister pack in a and along with insert.

6.6 Special precautions for disposal and other Special handling

None

7. Marketed by:

REALS PHARMACEUTICALS LIMITED.,
Plot 1, Alhaji Junaid Dosunmu, CBD
Alausa, Ikeja, Lagos, Nigeria.,

8. Manufactured By

SWISS PHARMA PVT. LTD.
3709, G.I.D.C., Phase-IV, Vatva,
Ahmedabad-382 445

9. NAFDAC REGISTRATION NUMBER(S)