1. Name of the medicinal product

ROSUVASTATIN TABLETS BP 10 MG

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABEL CLAIM	OVERAGES %	QTY./ TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Rosuvastatin Calcium Eq. to Rosuvastatin*	BP	(10.395 mg) 10 mg	6.00%	11.019 mg	API
INACTIVE INGREDIENTS						
2.	Maize starch	BP	-	0.00%	65.231 mg	Diluent
3.	Microcrystalline cellulose	BP	-	0.00%	65.250 mg	Diluent
4.	Colloidal silicon Dioxide	USP	-	0.00%	1.000 mg	Glidant
5.	Purified talc	BP	-	0.00%	1.500 mg	Glidant
6.	Magnesium stearate	BP	-	0.00%	1.500 mg	Lubricant
7.	Croscarmellose sodium	BP	-	0.00%	4.500 mg	Disintegrant

*6.00 % overages are added on label claim due to water content of API.

3. Pharmaceutical form

Oral Tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypercholesterolemia: Adults, adolescents and children aged 6 years or older with primary hypercholesterolemia (type IIA including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIB) 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 aged 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. Rosuvastatin may be given at any time of day, with or without food.

Treatment of hypercholesterolemia: The recommended start dose is 5 or 10 mg orally once daily in both statin-naïve and 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. 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 dose, a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), 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.

Paediatric population: Paediatric use should only be carried out by specialists.

Children and adolescents 6 to 17 years of age (Tanner Stage <II-V):

Heterozygous familial hypercholesterolemia: In children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5 mg daily.

- In children 6 to 9 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.
- In children 10 to 17 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Initiation; this diet should be continued during rosuvastatin treatment.

Homozygous familial hypercholesterolaemia: In children 6 to 17 years of age with homozygous familial hypercholesterolaemia, the recommended maximum dose is 20 mg once daily. A starting dose of 5 to 10 mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20 mg once daily should be conducted according to the individual response and tolerability in Paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. There is limited experience with doses other than 20 mg in this population. The 40 mg tablet is not suitable for use in paediatric patients

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Children younger than 6 years: The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 years.

Use in the elderly: A start dose of 5 mg is recommended in patients >70. No other dose adjustment is necessary in relation to age.

4.3 Contraindications

Rosuvastatin is contraindicated:

- In patients with hypersensitivity to the active substance or to any of the excipients in the formulation.
- 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 combination of sofosbuvir/velpatasvir/voxilaprevir
- 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 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. 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 land 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 (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK>5xULN, treatment should not be started.

Liver Effects: As with other HMG-CoA reductase inhibitors, rosuvastatin 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. Rosuvastatin 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 rosuvastatin.

4.5 Interaction with other medicinal products 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 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 five to 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 subjects. 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.

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.

Ticagrelor: Ticagrelor can cause renal insufficiency and may affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. In some cases, co-administered ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis. Renal function and CPK control is recommended while using ticagrelor and rosuvastatin concomitantly.

4.6 Fertility, 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

Blood and lymphatic system disorders: Rare: Thrombocytopenia
Immune system disorders: Rare: Hypersensitivity reactions including angioedema
Endocrine disorders: Common: Diabetes mellitus
Respiratory, thoracic and mediastinal disorders: Very rare: Cough, Dyspnoea
Nervous system disorders: Common: Headache, Dizziness; **Very Rare:** Polyneuropathy, Memory loss; **Not known:** Peripheral neuropathy, Sleep disturbances (including insomnia and nightmares)
Musculo-skeletal and connective tissue disorders: Common: Myalgia; **Rare:** Myopathy (including myositis), Rhabdomyolysis, Lupus-like syndrome, Muscle rupture; **Very rare:** Arthralgia; **Not known:** Tendon disorders, sometimes complicated by rupture, Immune-mediated necrotising myopathy

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 Pharmacodynamics properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors;
ATC code: C10AA07

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.

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 is not extensively metabolized, as demonstrated by the small amount of radiolabeled dose that is recovered as a metabolite (~10%). Cytochrome P450 (CYP) 2C9 is primarily responsible for the formation of rosuvastatin's major metabolite, N-desmethylrosuvastatin, which has approximately 20-50% of the pharmacological activity of its parent compound in vitro. However, this metabolic pathway isn't deemed to be clinically significant as there were no observable effects found on rosuvastatin pharmacokinetics when rosuvastatin was coadministered with fluconazole, a potent CYP2C9 inhibitor.

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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at

maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

6. Pharmaceutical particulars

6.1 List of excipients

- Maize starch
- Microcrystalline cellulose
- Colloidal silicon Dioxide
- Purified talc
- Magnesium stearate
- Croscarmellose sodium

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in dry place below 30^0C. Protect from light.

6.5 Nature and contents of container

3 X 10 Tablets Alu-PVC Blister pack, packed in printed and laminated carton.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing authorization holder

West Coast Pharmaceutical Works LTD, Ahmedabad

8. Marketing authorization number(s)

Not Applicable

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text

August, 2022