1. Name of the medicinal product

ROSUVASTATIN TABLETS 10 MG

2. Qualitative and Quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Rosuvastatin Calcium Eq. Rosuvastatin*	BP	10 mg (10.83mg)	0.00%	11.000 mg	API
INACTIVE INGREDIENTS						
2.	Maize Starch	BP	-	0.00%	65.250 mg	Diluent
3.	Microcrystalline cellulose	BP	-	0.00%	65.250 mg	Diluent
4.	Magnesium stearate	BP	-	0.00%	1.500 mg	Lubricant
5.	Purified talc	BP	-	0.00%	1.500 mg	Glidant
6.	Croscarmellose sodium	BP	-	0.00%	4.500 mg	Disintegrant
7.	Colloidal silicon Dioxide	USP	-	0.00%	1.000 mg	Glidant

*Round up figure.

3. Pharmaceutical form

Oral Tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Hypercholesterolaemia: Adults, Adolescents and Children aged 10 years or older with primary Hypercholesterolaemia (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.
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 Hypercholesterolemia: The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions.

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

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

In children and adolescents with heterozygous familial hypercholesterolaemia 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.

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.

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 years. No other dose adjustment is necessary in relation to age.

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

4.3 Contraindications

- In patients with hypersensitivity to Rosuvastatin or to any of the excipients.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x 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.

- Moderate Renal Impairment (CreatinineClearance < 60 ml/min)
- Hypothyroidism
- Personal or family history of Hereditary Muscular Disorders
- Previous history of muscular toxicity with another HMG-coaReductase 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

Rosuvastatin, as with other HMG-CoA reductase inhibitors, 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
- Concomitant use of fibrates.

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.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin and Gemfibrozil resulted in a 2fold increase in Rosuvastatin C_{max} and AUC.

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.

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. Therefore, drug interactions resulting from Cytochrome P450 mediated metabolism are not expected.

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: 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
Gastro-intestinal 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, Muscle rupture, Arthralgia, Immune-mediated necrotising myopathy
Renal and urinary disorders: Haematuria
Reproductive system and breast disorders: Gynaecomastia

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07.
Mechanism of Action: Rosuvastatin is a 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.

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 50litres/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
- Magnesium stearate
- Purified talc
- Croscarmellose Sodium
- Colloidal silicon Dioxide

6.2 Incompatibilities

Not known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

3 x10 Tablets Alu- Alu 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, 2019