ZOBITOR 20 (Rosuvastatin Tablets BP 20 mg)

Module 1- Administrative information and prescribing information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

ZOBITOR 20 (Rosuvastatin Tablets BP 20 mg)

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ZOBITOR 20 (Rosuvastatin Tablets BP 20 mg)

Strength

Each film coated tablet contains:
Rosuvastatin calcium BP
Eq. to Rosuvastatin 20 mg
Excipients q.s.
Color: Approved Color Used

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No	Ingredients	Spec	Qty/tab (mg)	(%) Over-ages	Input Quantity per tablet (mg)	Category
Dry Mixing						
1.	Rosuvastatin calcium eq. to Rosuvastatin	BP	20.800	-	20.800	API
2.	Lactose	BP	110.240	-	110.240	Binder
3.	Tri basic calcium phosphate	BP	15.000	-	15.000	Diluent
4.	Micro crystalline cellulose	BP	100.630	-	100.630	Diluent
5.	Cross povidone	BP	12.000	-	12.000	Disintegrant
Wet granulation						
6.	Maize Starch	BP	10.000	-	10.000	Disintegrant
7.	Purified water	BP	Q.S.	-	Q.S.	Solvent
8.	P.V.P.K-30 (Povidone)	BP	3.000	-	3.000	Diluent.
9.	Sodium methyl paraben	BP	0.300	-	0.300	Preservativ
10.	Sodium propyl paraben	BP	0.030	-	0.030	Preservativ.
Blending						
11.	Cross povidone	BP	13.000	-	13.000	Disintegrant
12.	Colloidal Anhydrous	BP	6.000	-	6.000	Viscosity

ZOBITOR 20 (Rosuvastatin Tablets BP 20 mg)

Sr. No	Ingredients	Spec	Qty/tab (mg)	(%) Over-ages	Input Quantity per tablet (mg)	Category
	Silica (Aerosil)					Agent
13.	Purified Talc	BP	6.000	-	6.000	lubricant
Lubrication						
14.	Magnesium Stearate	BP	3.000	-	3.000	lubricant
Total Weight of Uncoated Tablets					**300.0 mg**	
Coating						
15.	Colour Red Oxide of Iron and Titanium dioxide film coat	In-House	10.000	-	10.000	Film Forming agent
16.	Isopropyl alcohol#	BP	Q.S.	-	Q.S.	solvent
17.	Dichloromethane#	BP	Q.S.	-	Q.S.	Coating agent
Total Weight of coated Tablets					**310.0 mg**	

BP: British Pharmacopeia
* Qty. to be calculated on basis of assay and LOD.
** Qty. to be compensate.
# Quantity is not calculated in total weight of tablet due to evaporated during process.

3. PHARMACEUTICAL FORM

Brown colour, round shape, 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 hypercho- lesterolaemia (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 hypercholest-erolaemia 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 individualized according to the goal of therapy and patient response, using current consensus guidelines. Rosuvastatin Tablets may be given at any time of day, with or without food.

Treatment of hypercholesterolaemia

The recommended start dose is 5 or 10 mg orally once daily in both statin naive 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 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.

Prevention of cardiovascular events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily. Paediatric population

Paediatric use should only be carried out by specialists.

Method of Administration

Oral use

4.3 Contraindications

Rosuvastatin Tablets is contraindicated:

- 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 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.

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 Tablets, 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 Tablets -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 Tablets in post-marketing use is higher at the 40 mg dose.

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 Rosuvastatin Tablets in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin Tablets doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin Tablets is adjusted.

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 6 to 17 years of age taking rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
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 Tablets with medicinal products that are

inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy 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 Cmax respectively. The concomitant use of Rosuvastatin Tablets and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin Tablets dose adjustments based on the expected increase in rosuvastatin exposure.
Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin Tablets and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC.

Effect of rosuvastatin on co-administered medicinal products
Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin 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 Rosuvastatin 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 Tablets 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 Rosuvastatin Tablets and HRT, therefore, a similar effect cannot be excluded.

4.6 Fertility, pregnancy and lactation

Rosuvastatin Tablets 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

Rosuvastatin Tablets on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, Rosuvastatin Tablets 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

Adverse reactions are as below:

Blood and lymphatic system disorders: Thrombocytopenia Immune system disorders: Hypersensitivity reactions Endocrine disorders: Diabetes mellitus
Psychiatric disorders: Depression

Nervous system disorders: Headache, Dizziness, Peripheral neuropathy Respiratory, thoracic and mediastinal disorders: Cough, Dyspnoea Gastro-intestinal disorders: Constipation, Nausea, Abdominal pain

Hepatobiliary disorders: Increased hepatic transaminases

Skin and subcutaneous tissue disorders: Pruritus, Rash, Urticaria

Musculo-skeletal and connective tissue disorders: Myopathy Rhabdomyolysis, Lupus-like syndrome, Muscle rupture

Renal and urinary disorders: Haematuria

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

Mode 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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose	BP
Calcium phosphate	BP
Microcrystalline Cellulose	BP
Crospovidone	BP
Maize starch	BP
Purified Water	BP
Povidone	BP
Sodium Methyl Paraben	BP
Sodium Propyl Paraben	BP
Colloidal Anhydrous Silica	BP
Purified Talc	BP
Magnesium Stearate	BP
Colour Red oxide of Iron and titanium dioxide film coat	In-House
Isopropyl Alcohol	BP
Dichloromethane	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, Protect from light and Preserve in air tight container.

6.5 Nature and contents of container

3 X 10 Alu- Alu Blister Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

NAME AND ADDRESS OF APPLICANT

ZOBIF PHARMACEUTICALS LTD

1, ONAFOWOKAN STREET,

ISHERI-OSUN, ALIMOSHO, LAGOS

NAME AND ADDRESS OF MANUFACTURER

SHUKRA PHARMACEUTICALS LTD

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