SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

Afrab Rosuvastatin 10mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 10mg of Rosuvastatin as Rosuvastatin calcium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

A peach colour coated tablet with AFRAB inscribed on one side and a marked line on the other.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Prevention of Major Cardiovascular events

In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease.

Rosuvastatin is indicated to:

• Reduce the risk of nonfatal myocardial infarction

• Reduce the risk of nonfatal stroke

• Reduce the risk of coronary artery revascularisation

Hypercholesterolaemia

Rosuvastatin is indicated to:

• Reduce elevated LDL-C, total cholesterol, triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolaemia (heterozygous familial and non familial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb). Rosuvastatin also lowers ApoB, nonHDL-C, VLDLC, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I in these populations.

• Treat isolated hypertriglyceridaemia.

• Reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or alone if such treatments are unavailable. Prior to initiating therapy with rosuvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteina

4.2 Posology and method of administration

Prevention of Major Cardiovascular events

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events.

Hypercholesterolaemia

The usual dose range is 10 - 40 mg orally once a day.

The dosage of Rosuvastatin should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the start dose. However, if necessary, dose adjustment can be made at 2 to 4 week intervals. (See section 5.1 Pharmacodynamic Properties).

A dose of 40 mg once a day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once a day is assessed. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg must not be exceeded in any patient taking rosuvastatin.

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia and isolated hypertriglyceridaemia

The usual start dose is 10 mg once a day.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia

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

Use in children

In children and adolesccents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

Use in the elderly

The usual dose range applies.

Dosage in patients with renal insufficiency

The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment the dose of Rosuvastatin should not exceed 10 mg once daily. (See sections 5.2 Pharmacokinetic Properties and 4.3 Contraindications).

Dosage in patients with hepatic insufficiency

The usual dose range applies in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with Rosuvastatin 10 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above Rosuvastatin 10 mg should be carefully considered. (See section 5.2 Pharmacokinetic Properties).

Race

A 5 mg starting dose of Rosuvastatin should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties). 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.

Genetic polymorphisms

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of Rosuvastatin is recommended (see sections 4.4 Special Warnings and Precautions for Use, 4.5 Interactions and 5.2 Pharmacokinetic Properties).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin, ticagrelor and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see sections 4.4 Special Warnings and Precautions for Use and 4.5 Interactions). It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatin. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing Rosuvastatin therapy. In situations where coadministration of these medicinal products with Rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin dosing adjustments should be carefully considered (see 4.5 Interactions).

Method of administration

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

4.3 Contraindications

Rosuvastatin is contraindicated in patients with hypersensitivity to any component of this product.

Rosuvastatin is contraindicated in patients with active liver disease or persistent, unexplained elevations in transaminases.

Rosuvastatin is contraindicated during pregnancy, while breastfeeding and in women of child-bearing potential not using appropriate contraceptive measures.

Rosuvastatin is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

• 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 rosuvastatin plasma levels may occur

• severe renal impairment (CrCl < 30 mL/min)

• Asian patients

• concomitant use of fibrates.

4.4 Special warnings and precautions for use

Liver

Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. 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.

Skeletal muscle

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMGCoA reductase inhibitors, the reported rate for rhabdomyolysis in post-marketing use is higher at

the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. Rosuvastatin therapy should be discontinued if CK levels are markedly elevated (>10xULN) or if myopathy is diagnosed or suspected. There have been very rare reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. HMG-CoA reductase inhibitors may in rare instances induce or aggravate myasthenia gravis or ocular myasthenia (see section 4.8 Undesirable Effects) including reports of recurrence when the same or a different HMG-CoA reductase inhibitor was administered.

Rosuvastatin should be used with caution in patients with these conditions, and should be discontinued if these conditions are induced or aggravated.

In Rosuvastatin trials there was no evidence of increased skeletal muscle effects when R osuvastatin was dosed with any 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 ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur (see sections 4.5 Interactions and 5.2 Pharmacokinetic Properties). Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Rosuvastatin should be temporarily withheld 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). Diabetes Mellitus There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at increased risk of developing type 2 diabetes. Risk factors for the development of type 2 diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass index. Patients at risk should be monitored both clinically and biochemically according to national guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro and in vivo data indicate that rosuvastatin has no clinically significant cytochrome P450 Rosuvastain interactions (as a substrate, inhibitor or inducer). 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 (see Table 1, and sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use). Ticagrelor: Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations. Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastain should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatain. If medicinal product is observed to increase rosuvastatin AUC approximately 2 fold or higher, the starting dose of Rosuvatatin should not exceed 5 mg once daily. The maximum daily dose of Rosuvatatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Rosuvaqstaqtin taken without interacting medicinal products, for example a 5 mg dose of R with ciclosporin (7.1 fold increase in exposure), a 10 mg dose of Rosuvastatin with ritonavir/atazanavir combination (3.1 fold increase) and a 20 mg dose of Rosuvaqstatin with gemfibrozil.

Protease Inhibitors: Co-administration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (see Table1). Dose adjustment are needed depending on the level of effect on rosuvastatin exposure.

Antacid: The simultaneous dosing of Rosuvaswtatin 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.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in postmarketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Rosuvastatin during pregnancy and whilst breastfeeding has not been established. However, due to Rosuvastatin'S mechanism of action, there is a potential risk for adverse reactions in the foetus. Women of child-bearing potential should use appropriate contraceptive measures. If a pregnant woman is exposed to Rosuvastain she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist. It is recommended that Rosuvastatin is discontinued as soon as pregnancy is recognised.

Breast-feeding

Breastfeeding is not recommended during treatment with Rosuvastaqtin. Limited data from published reports indicate that Rosuvastatin is present in human milk. Due to Rosuvastatin'S mechanism of action, there is a potential risk for adverse reactions in the infant

4.7 Effects on ability to drive and use machines

Pharmacology testing revealed no evidence of a sedative effect of Rosuvastatin. From the safety profile, Rosuvastatin is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable effects

Rosuvastatin is generally well tolerated. The adverse events seen with Rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin treated patients were withdrawn due to adverse events. This withdrawal rate was comparable to that reported in patients receiving placebo.

Common (>1/100, 1/1000, 1/10,000,) Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus*.

Uncommon (>1/1000, 1/10,000,) Pruritus, rash and urticaria.

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. 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, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver. Rosuvastatin produces its lipid-modifying effects in two 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). The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C,

TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio. Clinical Efficacy and Safety Rosuvastain reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDLcholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (See Table 2 and Table 3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-Iratio's.

The clinical trial program showed that Rosuvastatin is effective in a wide variety of patient populations, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia. 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

Rosuvastain is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Exposure increases linearly over the dose range.

The half life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing. Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound accounts for greater than 90% of the circulating active HMG-CoA reductase inhibitor activity. Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Special populations

Age and sex

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and Cmax in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Renal insufficiency

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin.

Hepatic insufficiency
In a study in subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in the 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child Pugh scores.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose 112, Di-Calcium Phosphate DC, Crospovidone, Magnesium stearate, Lactose Monohydrate DC grade, Red Iron Oxide, HPMC Premix (Spraycel).

6.2 Incompatibilities
None.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Afrab Rosuvastatin tablet should be Store below 30°C.

6.5 Nature and contents of container
Blister pack of 3 x 10 tablets

6.6 Special precautions for disposal and other handling
None stated.

7 MARKETING AUTHORISATION HOLDER
Afrab Chem Limited
22 Abimbola Street,Isolo Ind.Estate,Isolo-Lagos