1.5.5.2 FINAL PACKAGE INSERT

SCHEDULING STATUS: S 4

PROPRIETARY NAME (and Dosage Form):

Crestor® 5; Crestor® 10; Crestor® 20; Crestor® 40 (Tablet)

COMPOSITION:

Each tablet contains 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin as rosuvastatin calcium.

Contains sugar (lactose monohydrate).

List of excipients:

Tablet core:

Calcium phosphate, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Tablet coat:

Glycerol triacetate, hypromellose, iron oxide red (E172), iron oxide yellow (E172), lactose monohydrate, titanium dioxide (E171).

PHARMACOLOGICAL CLASSIFICATION:

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

Rosuvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

Rosuvastatin produces its lipid-modifying effects in 2 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).

Summary of clinical studies:

CRESTOR 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.

CRESTOR also lowers the LDL -C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's.

A therapeutic response to CRESTOR 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.

Pharmacokinetic properties:

After oral administration peak plasma levels occur 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.

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 in humans (approximately 10 %), mainly to the N-desmethyl form, and 90 % is eliminated as unchanged compound 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.

The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race:

Pharmacokinetic studies show a 1,26-2,31 fold elevation in geometric mean AUC $_{(0\text{-}t)}$ in Asian subjects compared with Caucasians.

A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) Philipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analyses in these studies.

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. (See: "**Dosage and directions for use:** Race").

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. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.

Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

INDICATIONS:

To reduce the risk of cardiovascular events:

In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated high-sensitivity C-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

- CRESTOR is indicated for patients with primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial and non-familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.

- CRESTOR is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia).

- CRESTOR is also indicated to reduce Total Cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

CRESTOR 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of CRESTOR or alternative therapy.

Specialist supervision is recommended when the 40 mg dose is initiated. (See: **"*Special Precautions*"**).

Children and adolescents 10-17 years of age:

CRESTOR is indicated to reduce the Total Cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

CONTRAINDICATIONS:

CRESTOR is contraindicated in:

- patients with hypersensitivity to any component of this product
- patients with active liver disease
- concomitant use with ciclosporin (see "**INTERACTIONS**")
- patients with myopathy

Safety in pregnancy and lactation has not been established.

INTERACTIONS:

Interaction with other medicinal products and other forms of interaction:

Warfarin:

The pharmacokinetics of warfarin are not significantly affected following co-administration with CRESTOR. However, as with other HMG-CoA reductase inhibitors, co-administration of CRESTOR and warfarin may result in a rise in INR compared to warfarin alone. In patients taking warfarin monitoring of INR is recommended both at initiation or cessation of therapy with CRESTOR or following dose adjustment.

Ciclosporin:

Co-administration of CRESTOR with ciclosporin resulted in no significant changes in ciclosporin plasma concentration. However, rosuvastatin steady state AUC $_{(0\text{-}t)}$ increased up to 7-fold over that seen in healthy volunteers administered the same dose. (See "**Dosage and directions for use AND contraindications**").

Gemfibrozil:

Concomitant use of CRESTOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC $_{(0\text{-}t)}$. (See "**Dosage and directions for use**").

Protease inhibitors:

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving CRESTOR with various protease inhibitors in combination with ritonavir. Adverse events attributed to CRESTOR in these studies were consistent with the known safety profile of rosuvastatin.

The lowest dose of CRESTOR that provides therapeutic benefit to the patient should be used, and close monitoring of adverse events is indicated.

Consideration should be given both to the benefit of lipid lowering by the use of CRESTOR in HIV-infected patients receiving protease inhibitors and the potential risks of this increased rosuvastatin plasma concentrations when initiating and up-titrating CRESTOR doses in patients treated with protease inhibitors, as the combination may lead to an increased incidence of adverse events. (See: "***Special Precautions***").

Antacids:

The simultaneous dosing of CRESTOR 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 CRESTOR. The clinical relevance of this interaction has not been studied.

Cytochrome P450 enzymes:

In vitro and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer).

Other medications:

There were no clinically significant interactions with an oral contraceptive, digoxin, ezetimibe or fenofibrate.

In clinical studies CRESTOR was co-administered with antihypertensive agents, antidiabetic agents and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

PREGNANCY AND LACTATION:

The safety of CRESTOR during pregnancy and whilst breastfeeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures.

DOSAGE AND DIRECTIONS FOR USE:

Before treatment initiation, the patient should be placed on a standard cholesterol-lowering diet

that should continue during treatment.

The dose range for CRESTOR is 5-40 mg orally once a day. The recommended start dose is 5 mg once a day.

The dosage of CRESTOR should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 2-4 week intervals. (See: **"Pharmacological action: *Pharmacodynamic properties*"**).

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

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia), and isolated hypertriglyceridaemia:

The recommended start dose is 5 mg once a day.

A 5 mg starting dose is recommended for patients of Asian ancestry, and for patients requiring a smaller reduction in LDL-C to achieve treatment target.

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.

Children and adolescents 10-17 years of age:

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5-20 mg orally once daily. The dose should be appropriately titrated to achieve treatment goal. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

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

Special populations:

Use in the elderly:

The usual dose range applies.

Dosage in patients with renal insufficiency:

The starting dose applies in patients with mild to moderate renal impairment. For patients with severe renal impairment the dose of CRESTOR should not exceed 10 mg once daily.

Dosage in patients with hepatic insufficiency:

The usual starting dose applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with CRESTOR 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above

CRESTOR 10 mg should be carefully considered. (See: **"Pharmacological action: *Pharmacokinetic properties*"**).

Race:

A 5 mg starting dose of CRESTOR should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects. (See: **"*Special Precautions*"** and **"*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.

Concomitant therapy:

CRESTOR has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

CRESTOR can also be used in combination with ezetimibe or bile acid sequestrants. (See: **"*Special Precautions*"**).

Interactions requiring dose adjustments:

Ciclosporin:

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant CRESTOR and Ciclosporin. For the CRESTOR dose range (10-40 mg) this combination is not recommended. (See "**CONTRAINDICATIONS**")

Gemfibrozil:

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant CRESTOR and gemfibrozil. Patients taking this combination should start therapy with CRESTOR 5 mg once daily and should not exceed a dose of CRESTOR 20 mg once daily. (See: **"Interactions:** *Interactions with other medicinal products and other forms of interaction*").

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

In controlled clinical trials less than 4 % of CRESTOR treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following:

Common (≥1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100);

Rare (≥ 1/10 000, < 1/1 000); Very rare (<1/10 000).

Clinical trials:

Nervous system disorders:

Common: headache, dizziness

Gastrointestinal disorders:

Common: constipation, nausea, abdominal pain

Rare: pancreatitis

Musculoskeletal, connective tissue and bone disorders:

Common: myalgia

Rare: myopathy (including myositis), rhabdomyolysis

General disorders:

Common: asthenia

Skin disorders:

Uncommon: pruritus, rash, urticaria

Rare: hypersensitivity reactions including angio-oedema

Post marketing experience:

In addition to the above, the following adverse events have been reported during post marketing experience for CRESTOR:

Hepatobiliary disorders:

Jaundice, hepatitis, increased hepatic transaminases.

Musculoskeletal disorders:

Arthralgia.

The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

The incidence of adverse drug reactions tends to increase with increasing dose.

Skeletal muscle effects:

Rhabdomyolysis, which may occasionally be associated with impairment of renal function, has been reported with rosuvastatin.

Renal effects:

Proteinuria (see: "*Laboratory effects*").

Nervous system disorders:

Memory loss.

Laboratory effects:

A dose-related increase in liver transaminases and Creatine kinase (CK) has been observed in patients taking rosuvastatin. Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen in patients taking CRESTOR. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

Other effects:

In a long-term controlled clinical trial CRESTOR was shown to have no harmful effects on the ocular lens.

In CRESTOR treated patients, there was no impairment of adrenocortical function.

Children and adolescents 10-17 years of age:

The safety profile of CRESTOR is similar in children or adolescent patients and adults although CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in clinical trials of children and adolescents. However, the same special warnings and special precautions for use in adults also apply to children and adolescents (see: "***Special Precautions***").

Special Precautions:

Liver:

CRESTOR should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

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 with subjects with lower Child-Pugh scores.

Renal effects:

An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal muscle:

Effects on skeletal muscle e.g. uncomplicated myalgia, myopathy and rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reporting 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 Creatine kinase (CK) levels measured. CRESTOR therapy should be discontinued if myopathy is diagnosed or suspected.

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.

CRESTOR 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: **"Pharmacological action: *Pharmacokinetic properties*"**).

CRESTOR 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).

Race:

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians. (See: **"Dosage and directions for use"** and **"*Pharmacokinetic properties*"**).

Children and adolescents 10-17 years of age:

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a 1 year period. (See: "***Pharmacodynamic properties***").

CRESTOR should be used with caution in patients taking various protease inhibitors in combination with ritonavir as pharmacokinetic studies have shown an increase in the AUC and C_{max} of rosuvastatin. (See "**INTERACTIONS"***).*

Lactose:

CRESTOR contains lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take CRESTOR.

Effects on ability to drive and use machines:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

5 mg: Yellow, film-coated, round, biconvex, approximately 7 mm (diameter) intagliated tablet; obverse side “ZD4522 5”, reverse side none.

10 mg: Pink, film-coated, round, biconvex, approximately 7 mm (diameter) intagliated tablet; obverse side “ZD4522 10”, reverse side none.

20 mg: Pink, film-coated, round, biconvex, approximately 9,1 mm (diameter) intagliated tablet; obverse side “ZD4522 20”, reverse side none.

40 mg: Pink, film-coated, oval, biconvex, approximately 11,5 x 7,1 mm (length x width) intagliated tablet; obverse side “ZD4522”, reverse side “40”.

PRESENTATION:

CRESTOR 5-40 mg tablets:

Aluminium laminate/aluminium foil blister strips containing multiples of 7,10, 14 tablets.

CRESTOR 10-40 mg tablets:

HDPE bottles: bottles containing 30, 90 or 100 tablets.

STORAGE INSTRUCTIONS:

Blister packs: Store below at or 30 °C. Keep the blister in the carton until required for use.

HDPE bottles: Store below at or 30 °C. Keep container tightly closed.

Keep out of reach of children.

REGISTRATION NUMBERS:

CRESTOR 5: 41/7.5/0298

CRESTOR 10: 36/7.5/0349

CRESTOR 20: 36/7.5/0350

CRESTOR 40: 36/7.5/0351

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park,

17 Georgian Crescent West,

Bryanston, Johannesburg, 2191,

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

26 October 2012.

Ref: Crestor 5-10-20-40 mg Tablets - EPI (08-02-2012)

CDS: 29 Nov 2006, 11 Sept 2007, 17 Dec 2007, Jan 2009, March 2009

Inclusion of Namibia + Botswana registration details (28-10-2010)

Crestor 5 mg NAMIBIA: NS2 Reg. No.: 10/7.5/0268	Crestor 10 mg NAMIBIA: NS2 Reg. No.: 05/7.1/0477	Crestor 20 mg NAMIBIA: NS2 Reg. No.: 05/7.1/0478	Crestor 40 mg NAMIBIA: NS2 Reg. No.: 05/7.1/0479

Crestor 5 mg BOTSWANA: S2 Reg. No.: BOT 1001768	Crestor 10 mg BOTSWANA: S2 Reg. No.: BOT 0700970	Crestor 20 mg BOTSWANA: S2 Reg. No.: BOT 0700971	Crestor 40 mg BOTSWANA: S2 Reg. No.: BOT 0700972