SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Rovista Tablets 20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Rosuvastatin……20mg
(as calcium salt)

Excipient with known effect
Each 20mg tablet contains 37 mg lactose monohydrate
For the full list of excipients, please refer to Section 6.1

3. PHARMACEUTICAL FORM

Green colored oval shaped biconvex film coated tablet engraved "GETZ" on one side and engraved "20" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Hypercholesterolemia:
Adults, adolescents and children aged 10 years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (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 hypercholesterolemia as an adjunct to diet and other lipid lowering treatments 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

Treatment of Hypercholesterolemia:
The initial recommended dose is 5mg or 10mg orally once daily. The dose can be increased, if necessary at intervals of at least 4 weeks to next dose level once daily. When initiating therapy with Rovista Tablets or switching from another HMG-CoA reductase inhibitor therapy, the appropriate starting dose should first be utilized and only then titrated according to the patients response and individualized goal of therapy. After initiation or upon titration of Rovista

Tablets, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

Prevention of Cardiovascular Events:
The recommended dose used is 20mg once daily.

Homozygous Familial Hypercholesterolemia:
The recommended starting dose of Rovista Tablets is 20mg once daily.
Response to therapy should be estimated from preapheresis LDL-C levels.

Pediatric Population:
Pediatric use should only be carried out by specialists.

Children and Adolescents 10 to 17 years of age:
In children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5mg daily. The usual dose range is 5-20mg orally once daily. Titration should be conducted according to the individual response and tolerability in pediatric patients. Children and adolescents should be placed on standard cholesterol-lowering diet before Rosuvastatin treatment initiation; this diet should be continued during Rosuvastatin treatment.

Asian Origin:
Initially 5mg once daily increased if necessary to maximum 20mg daily.
Note: Initially 5mg once daily with concomitant fibrate increased if necessary to maximum of 20mg daily.

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 10mg once daily.

Hepatic Insufficiency:
The usual dose range applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with 10mg. Increased systemic exposure to Rosuvastatin has been observed in these patients, therefore the use of doses above 10mg should be carefully considered.

Elderly:
A start dose of 5mg is recommended in patients >70 years.

4.3 Contraindications

Rosuvastatin is contraindicated in:
- patients with hypersensitivity to Rosuvastatin or to any of the excipients.
- 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).
- patients with severe renal impairment (creatinine clearance <30ml/min).
- patients with myopathy.

- patients receiving concomitant cyclosporin.
- pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and special precautions for use

- Hypothyroidism should be managed adequately before starting treatment with statin.
- Statins should be used with caution in patients with predisposing risk factors for myopathy or rhabdomyolysis. The patients should be advised to report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.
- It should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease. It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically thereafter.
- Caution should be exercised if Rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone and cimetidine.
- Rosuvastatin therapy should be withheld temporarily in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure, secondary to rabdomyolysis.
- Dose reduction should be considered for patients on Rosuvastatin therapy with unexplained persistent proteinuria and/or hematuri during routine urinalysis testing.
- Caution should be exercised when Rosuvastatin is co-administered with protease inhibitors given in combination with ritonavir.
- Long term use of Rosuvastatin therapy may report Interstitial Lung Disease, presenting features can include Dyspnoea, non-productive cough and detoriation in general health (fatigue, weight loss and fever). It is advisable that the therapy should be discontinued.
- Patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with Rosuvastatin has been associated with an increased risk of diabetes mellitus.
- Rovista (Rosuvastatin) Tablet 5mg contains lactose. Patients with galactose intolerance should not take this medicine.

4.5 Interaction with other medicaments

Rosuvastatin may result in increase risk of myopathy when co-administered with the following:
- Antibacterials (e.g. Daptomycin)
- Antivirals (e.g. Darunavir, Fosamprenavir, Indinavir, Ritonavir, Saquinavir, Nelfinavir)
- Colchicine
- Fibrates.
- Nicotinic acid.
- Concomitant administration of Rosuvastatin and Erythromycin may reduce the plasma concentration of Rosuvastatin.
- Concomitant use of Rosuvastatin with Tipranavir and Eltrombopag may increase the plasma concentration of Rosuvastatin.

- Concomitant use of Rosuvastatin with Oestrogen and Progestron increases the plasma level of Ethinylestradiol and Norgestrel respectively.
- Concomitant use of Rosuvastatin with cyclosporin significantly increases Rosuvastatin exposure. Therefore, in such patients therapy should be limited to 5mg once daily.
- Gemfibrozil significantly increases Rosuvastatin exposure. Therefore, combination therapy with Rosuvastatin and gemfibrozil should be avoided.

If used, do not exceed Rosuvastatin 10 mg once daily.

- In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.
- 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%. The antacid should be taken at least 2 hours after Rosuvastatin administration.
- The risk of skeletal muscle effects may be enhanced when Rosuvastatin is used in combination with niacin, a reduction in Rosuvastatin dosage should be considered.

4.6 Pregnancy and Lactation

Pregnancy

Rosuvastatin is contraindicated in pregnancy and lactation. Women of child bearing potential should use appropriate contraceptive measures.

Nursing Mothers

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the fetus, 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 machine

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

Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient.

Common:

Diabetes mellitus, Headache, dizziness, constipation, nausea, abdominal pain, myalgia, asthenia.

Uncommon:

Pruritus, rash and urticaria.

Rare:
Pancreatitis, Hypersensitivity reactions including angioedema, myopathy, rhabdomyolysis, arthralgia, increased hepatic transaminases.

Laboratory Abnormalities:
Proteinuria has been observed in patients treated with Rosuvastatin. This finding was more frequent in patients taking Rosuvastatin 40mg, when compared to lower doses of Rosuvastatin.

Other abnormal laboratory values reported were elevated creatinine phosphokinase, dose related increase in transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin and thyroid function abnormalities.

4.9 OVERDOSAGE

Symptoms and Treatment of Overdosage:
There is no specific treatment in the event of Rosuvastatin overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.
In *in vivo* and *in vitro* studies, Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

5.2 Pharmacokinetic properties

Absorption
Maximum Rosuvastatin plasma concentrations achieved approximately in 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. Mean volume of distribution at steady state of Rosuvastatin is

approximately 134 litres. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism
Rosuvastatin is not extensively metabolized, (approximately 10%). The major metabolite is N-desmethyl (50% less active than parent), which is formed principally by cytochrome P450 2C9, and lactone metabolites (clinically inactive). Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion
Following oral administration, Rosuvastatin and its metabolites are primarily excreted in the feces (90%) and approximately 5% is excreted unchanged in the urine. The elimination half-life ($t_{1/2}$) of Rosuvastatin is approximately 19 hours. The elimination half-life does not increase at higher doses.

Special Populations
Renal Insufficiency
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 (Cr_{Cl}<30mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.
Steady-state plasma concentration of Rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Insufficiency
In patients with chronic alcohol liver disease, plasma concentrations of Rosuvastatin were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Drug-Drug Relationship

Cyclosporine:
Co-administration of cyclosporine with Rosuvastatin resulted in 11 and 7-fold increase in C_{max} and AUC of Rosuvastatin respectively, compared with healthy subjects.

Gemfibrozil:
Co-administration of a single Rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in a 2.2 and 1.9-fold increase in mean C_{max} and mean AUC of Rosuvastatin, respectively.

Antacid:
Co-administration of an antacid (aluminium and magnesium hydroxide combination) with Rosuvastatin (40mg) resulted in a decrease in plasma concentrations of Rosuvastatin by approximately 50%.

Oral contraceptives:
Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with Rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

Erythromycin:
Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} 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

Microcrystalline Cellulose (Avicel PH-102),
Lactose Monohydrate,
Dibasic Calcium Phosphate Anhydrous,
Povidone K-30 (PVP K-30),
Crospovidone,
Magnesium Stearate,
Opadry II 85G210002 Green.

6.2 Incompatibilities

None

6.3 Shelf-life

3 Years
The expiration dates refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30^{o}C

Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Rovista (Rosuvastatin) Tablets 20mg are available in Alu-Alu Blister Pack of 3 x 10's tablets along with the package insert.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- To be sold on prescription of a registered medical practitioner only.
- Keep out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

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8. PRODUCT REGISTRATION NUMBER

044045

007198-EX

9. DATE OF PRODUCT REGISTRATION ISSUED

September 11, 2006

June 29, 2018