For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Biocon

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Rosuvastatin Tablets IP

BESTOR® 5/10/20

0ÉxOÉU 5/10/20

COMPOSITION:
BESTOR®-5
Each film coated tablet contains
Rosuvastatin Calcium IP
Equivalent to Rosuvastatin 5mg
Excipients q.s.

Colours: Tartrazine Lake and Titanium Dioxide IP

BESTOR®-10
Each film coated tablet contains
Rosuvastatin Calcium IP
Equivalent to Rosuvastatin 10mg
Excipients q.s.

Colours: Sunset Yellow Lake and Titanium Dioxide IP

BESTOR®-20
Each film coated tablet contains
Rosuvastatin Calcium IP
Equivalent to Rosuvastatin 20mg
Excipients q.s.

Colours: Ponceau 4R and Titanium Dioxide IP

DESCRIPTION:
Rosuvastatin is a synthetic lipid lowering agent for oral administration. The empirical formula being $(C_{22}H_{27}FN_3O_6S)$ 2. Rosuvastatin Calcium is an amorphous powder that is sparingly soluble in water and methanol and slightly soluble in ethanol.

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 co-enzyme A to mevalonate, a precursor of cholesterol.

Rosuvastatin produces its lipid-modifying effects by, it increases the number of hepatic LDL receptors on the cell-surface to enhance 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) and also inhibit the synthesis of cholesterol by inhibiting HMG CoA reductase.

Rosuvastatin reduces LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratios. 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.

Pharmacokinetic properties:
After oral administration peak plasma levels occur 5 hours after dosing. Absorption 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 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.

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However in Asian patients there is 2 fold median exposure in AUC and C_{max}.

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 drug removal.

INDICATIONS:
Rosuvastatin is indicated for patients with Hyperlipidemia and mixed dyslipidemia, Heterozygous familial hypercholesterolemia in pediatric patients of 10-17 years of age, Hypertriglyceridemia, Primary Dysbetalipoproteinemia (Type III hyperlipoproteinemia), Slowing the prognosis of atherosclerosis, Primary prevention of stroke, cardiovascular disease(without clinically evident coronary heart disease but has increased risk of cardiovascular disease based on the risk factors) and to reduce the risk during the arterial revascularization procedures. As an adjunct to diet when response to diet and exercise is inadequate.

CONTRA-INDICATIONS:
Rosuvastatin is contra-indicated in:
- patients who are hypersensitivity to any component of this product
- patients with active liver disease
- pregnancy and lactation.

INTERACTIONS:
Interaction with other medicinal products and other forms of interaction:

Cyclosporine:
Co-administration of Rosuvastatin with Cyclosporine resulted in no significant changes in Cyclosporine plasma concentration. However, Rosuvastatin steady state $AUC_{(0-t)}$ increased up to 7-fold over that seen in healthy volunteers administered the same dose.

Gemfibrozil:
Concomitant use of Rosuvastatin and Gemfibrozil resulted in a 2-fold increase in Rosuvastatin C_{max} and $AUC_{(0-t)}$ (see "Dosage and directions for use").

Protease Inhibitor:
Co-administration of Rosuvastatin with certain protease inhibitors given in combination with Ritonavir has different effects on Rosuvastatin exposure. The protease inhibitor combinations Lopinavir/Ritonavir and Atazanavir/Ritonavir increase Rosuvastatin exposure up to threefold. For these combinations the dose of Rosuvastatin is restricted to low dose.

Coumarin Anticoagulants:
Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. 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.

Niacin:
The skeletal muscle effects may be enhanced with Rosuvastatin in used with combination Niacin; a reduction in Rosuvastatin dosage should be considered.

Fenofibrate:
When Rosuvastatin was co administered with Fenofibrate, no clinally significant increase in AUC of Rosuvastatin or Fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates should be carefully weighed against the potential risks of this combination.

PREGNANCY AND LACTATION:
The safety of Rosuvastatin during pregnancy and breast-feeding 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 usual start dose is 5-

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10 mg once a day. The dosage of Rosuvastatin should be individualized 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 after 2-4 weeks. The dose can be titrated higher, depending upon the response to the lower doses.

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

Primary hypercholesterolemia (including heterozygous familial hypercholesterolemia), mixed dyslipidemia and isolated Hypertriglyceridemia:

The usual start dose is 5- 10 mg once a day.

For patients with severe hypercholesterolemia (including heterozygous familial hypercholesterolemia), a start dose of 10- 20 mg may be considered.

Homozygous familial hypercholesterolemia:
For patients with homozygous familial hypercholesterolemia a start dose 10 mg - 20 mg once a day is recommended.
Initiation of 5 mg of Rosuvastatin should be considered for Asian patients.

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 impairment. For patients with severe renal impairment the dose of Rosuvastatin should be started on 5 mg and 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 Rosuvastatin5 mg - 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 "Pharmacological action: Pharmacokinetic properties").

Concomitant therapy:
Rosuvastatin 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.

Rosuvastatin can also be used in combination with bile acid sequestrants (see "Special precautions").

ADVERSE REACTIONS:
Side-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.
The frequencies of adverse events are ranked according to the following:
Common (> 1/100, < 1/10); Uncommon (> 1/1000, < 1/100); Rare (> 1/10 000, < 1/1000).
Nervous system disorders:
Common: headache, dizziness
Gastrointestinal disorders:
Common: constipation, nausea, abdominal pain
Musculoskeletal, connective tissue and bone disorders:
Common: myalgia
Rare: myopathy, rhabdomyolysis
General disorders:
Common: asthenia
Skin disorders:
Uncommon: pruritis, rash, urticaria
Rare: hypersensitivity reactions including angio-oedema.
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").
Laboratory effects:
A dose-related increase in liver transaminases and CK has been observed in patients taking Rosuvastatin. Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen in patients taking Rosuvastatin. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on reduction of dose.
Special precautions:
Liver:
Rosuvastatin 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. It's recommended that the liver enzyme tests be performed before and after 12 weeks following both the initiation of therapy and any elevation of dose thereafter.
Renal effects:
An assessment of renal function should be considered during routine follow-up of patients treated with higher dose.
Skeletal muscle:
Effects on skeletal muscle e.g. uncomplicated myalgia, myopathy and rhabdomyolysis, have been reported in patients treated with Rosuvastatin. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. Rosuvastatin 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 Cyclosporine, fibric acid derivatives, including Gemfibrozil, Nicotinic acid, Azole antifungal 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 "Pharmacological action: Pharmacokinetic properties").
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).

KNOWN SYMPTOMS OF OVER DOSAGE 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. Hemodialysis is unlikely to be of benefit.

STORAGE INSTRUCTIONS:
Store Protected from light and moisture.
Keep out of reach of children.

PRESENTATION:
Available as Alu-Alu Blister pack of 10 tablets.

For further information please contact :
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Manufactured by:
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