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

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Rosuvastatin and Fenofibrate Tablets IP

Biocon

BESTOR FN™ 10 बेस्टोर एफएन १०

Composition:
Each film coated tablets contains:

Rosuvastatin Calcium IP equivalent to Rosuvastatin	10 mg
Fenofibrate IP	145 mg
Excipients	q.s.

Colour: Sunset Yellow

DESCRIPTION:
Rosuvastatin: Rosuvastatin is a synthetic lipid lowering agent for oral administration. The empirical formula being $(C_{22}H_{27}FN_3O_6S)_2Ca$.

Fenofibrate: Fenofibrate is also a lipid lowering agent, empirical formula is $C_{20}H_{21}O_4Cl$.

ATC CODE:
Rosuvastatin - C10BA06
Fenofibrate - C10AB05

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Mechanism of action:
Rosuvastatin: It 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 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.
Fenofibrate: By activation of peroxisome proliferator activated receptor α (PPARα), Fenofibrate increases lipolysis and elimination of triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα(Peroxisome proliferator activated receptor alpha) also induces an increase in the synthesis of apoproteins AI, AII and HDL-cholesterol.

Pharmacokinetic properties:
Rosuvastatin: After oral administration peak plasma levels occur 5 hours after dosing. The half-life is 19 hours and does not increase with increasing dose. 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.
Fenofibrate: Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, the absorption is increased when administered with food. Serum protein binding was approximately 99%, it is rapidly hydrolyzed by esterases to the active metabolite fenofibric acid; no unchanged Fenofibrate is detected in plasma. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine and its half-life is 20 hours

SPECIAL POPULATION:
Age and sex:
There was no clinically relevant effect on age or sex by this combination.

Race: 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} of rosuvatstatin.
Renal insufficiency: The lowest possible dose should be administered in renal insufficiency (mild,moderate and severe). As the drug concentration increases more than 2 fold raise in this cases.

INDICATIONS:
BESTOR FN™ is indicated for patients with Hyper-lipidemia, mixed dyslipidemia, hypercholesterolemia and hypertriglyceridemia.

CONTRA INDICATIONS:
This combination is contra indicated in:
- Patients who are hypersensitivity to any component of this product
- Patients with active liver disease or renal impairment.
- Patients with preexisting gall bladder disease
- Pregnancy and lactation.

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

Cyclosporin: Rosuvastatin steady state $AUC_{(0-6)}$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 $AUC_{(0-t)}$.

Protease Inhibitor: Coadministration of Rosuvastatin with certain protease inhibitors given in combination with ritonavir has different effects on roasuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase Rosuvastatin exposure upto threefold. For these combination the dose of Rosuvastatin is restricted to low dose.

Coumarin Anticoagulants: Rosuvastatin significantly increased INR (International Normalized Ratio) in patients receiving coumarin anticoagulants. Therefore caution should be excercised 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:
Oral Anticoagulants: Caution should be exercised when coumarin anticoagulants are given along with fenofibrate. The dosage of anticoagulant should be reduced to maintain the prothrombin time/INR.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine and because renal excretion is the primary elimination route of fibrate drugs including Fenofibrate, there is a risk that an interaction will lead to deterioration..

PREGNANCY AND LACTATION:
The safety of this combination, during pregnancy and breast-feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures.

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 and memory loss 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:

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Rhabdomyolysis, which may occasionally be associated with impairment of renal function, has been reported with Rosuvastatin. Renal effects: Proteinuria 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.

Risk of Hyperglycemia:
Increase in blood sugar levels (hyperglycemia) have been reported with rosuvastatin.

Special precautions:
Liver Dysfunction:
It is recommended that liver enzyme tests be performed before the initiation of rosuvastatin, and if signs or symptoms of liver injury occur.
Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.
In a pooled analysis of placebo-controlled trials, increases in serum transaminases to greater than 3 times the upper limit of normal occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart rosuvastatin.
Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use 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 with subjects with lower Child-Pugh scores. Its 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 cyclosporin, 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 "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).

Fenofibrate: Adverse events reported by 2% or more of patients treated with Fenofibrate during the double-blind, placebo-controlled trials, regardless of causality,are listed in the table below. Adverse events led to discontinuation of treatment in 5% of patients treated with Fenofibrate and in 3% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of Fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate (N = 439)	Placebo (N = 365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3%	1.6%
Creatine Phosphokinase Increased	3%	1.4%
SGOT Increased	3.4%	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

OVER DOSAGE:
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. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Hemodialysis is unlikely to be of benefit.

DOSAGE & ADMINISTRATION: Once in a day or as directed by the Physician.

SHELF LIFE: Please refer to Blister/Carton.

STORAGE INSTRUCTIONS: Store protected from moisture at a temperature below 30°C.
Keep out of reach of children

Special Precautions for disposal and other handling:
Any unused medicinal product should be disposed off in accordance with the local requirements.

PRESENTATION:
BESTOR FN™ 10 available in blister pack of 10 tablets.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**