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

Biocon

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Atorvastatin Tablets IP 10mg/20mg/40mg

STATIX® 10/20/40 स्टेटिक्स १०/२०/४०

Composition :

STATIX®10

Each film coated tablet contains:
Atorvastatin Calcium IP
Equivalent to Atorvastatin 10 mg
Excipients q.s.
Colour: Titanium Dioxide IP

STATIX®20

Each film coated tablet contains:
Atorvastatin Calcium IP
Equivalent to Atorvastatin 20 mg
Excipients q.s.
Colour: Erythrosine and Titanium Dioxide IP

STATIX®40

Each film coated tablet contains:
Atorvastatin Calcium IP
Equivalent to Atorvastatin 40 mg
Excipients q.s.
Colour: Tartrazine Yellow

PHARMACEUTICAL FORM: TABLETS

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic propertis

Pharmacotherapeutic group:
HMG CoA reductase inhibitors
ATC code: C10AA05

MECHANISM OF ACTION

Atorvastatin 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 sterols, Including cholesterol.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of Hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin also reduces LDL production and the number of LDL particles.

DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent.

Atorvastatin is an inhibitior of 3-Hydroxy-3-Methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate- limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*,R*)]-2-(4- Fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl -4-[(phenylamino) carbonyl] -1H- pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of Atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca.3H_2O$ and its molecular weight is 1209.42.

Atorvastatin calcium is a white to off white crystalline powder that is very slightly soluble in distilled water, slightly soluble in ethanol, and freely soluble in methanol.

Pharmacodynamics Properties:

Atorvastatin as well as some of its metabolites are pharmacologically active in humans . The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response.

Pharmacokinetic Properties

Absorption:

Atorvastatin is rapidly absorbed after oral administration, maximum plasma concentration occur within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether Atorvastatin is given with or without food. Plasma Atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution :

Mean volume of distribution of Atorvastatin is approximately 381 Liters. Atorvastatin is ≥98% bound to plasma proteins. A Blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, Atorvastatin in likely to be secreted in human milk.

Metabolism:

Atorvastatin is extensively metabolized to ortho and Parahydroxylated derivatives and various beta- oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho and Parahydroxylated metabolites is equivalent to that of Atorvastatin, approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of Atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentration of Atorvastatin in human following co-administration with Erythromycin, a known inhibitor of this isozyme. In animals the Orthohydroxy metabolite undergoes further glucuroniation.

Excretion :

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or, extra-hepatic metabolism: however, the drug does not appear to undergo enterohepatic recirculation. Mean Plasma elimination half-life of Atorvastatin in humans is approximately 14 hours but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites, less than 2% of a dose of Atorvastatin is recovered in urine following oral administration.

Special Populations:

Geriatric: Plasma concentrations of Atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age≥65 years) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Atorvastatin.

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentration of Atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC): however there is no clinically significant difference in LDL-C reduction with Arorvastatin between men and women.

Renal insufficiency: Renal diseases have no influence on the plasma concentration or LDL-C reduction of Atorvastatin: thus, dose adjustment in patients with renal dysfunction is not necessary.

Hemodialysis: While studies have not been conducted in patients with end stage renal disease, hemodialysis is not expected to significantly enhance clearance of Atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic insufficiency: In patients with chronic Alcoholic Liver Disease, plasma concentration of Atorvastatin are markedly Increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, inpatients, with childs Pugh B disease.

INDICATION

- As an adjunct to diet to reduce elevated Total Cholesterol, LDL Cholesterol, apo B and triglyceride levels in patients with primary Hypercholesterolemia (Heterozygous falmilial and nonfamilial) and Mixed dyslipidemia (Fredrickson Types IIa and IIb).
- As adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson type IV).
- For the treatment of patients with primary Dysbetalipoproteinemia (Fredrickson type III) who do not respond adequately to diet.
- To reduce Total Cholesterol and LDL-cholesterol in patients with Homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Lipid altering agents should be used in addition to diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see National Cholesterol Education Program (NCEP) Guidelines, Summarized in Table 1) At the time of hospitalization for an acute coronary event, consideration can be given initiating drug Therapy at discharge if the LDL-C levels is 130 mg/dL.

Table : 1 NCEP GUIDELINES FOR LIPID MANAGEMENT .

Definite Atherosclerotic Disease*	Two or more Other risk Factors**	LDL - Cholesterol mg/dL (mmol/L)	
		Initial Level	Minimum goal
No	No	≥190(≥4.9)	<160(<4.1)
No	Yes	>160(>4.1)	<130(<3.4)
Yes	Yes or No	≥130(≥3.4)	≤100(≤2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for Coronary Heart Disease (CHD) include: age (males ≥45 years, female ≥55 years or premature menopause without estrogen replacement therapy), family history of premature CHD, current cigarette smoking, hypertension, confirmed HDL-C ≤35mg/dL (≤0.9+1 mmol/L) and diabetes mellitus. Subtract 1 risk Factor if HDLC is ≥ 60mg/dL (≥1.6mmol/ L).

DOSAGE AND ADMINISTRATION

Hypercholesterolemia (heterozygous familial and non familial) and Mixed dyslipldemiala (Fredrickson types IIa and Iib).

The recommended starting dose of Atorvastatin is 10mg daily. The dose range is 5 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day with or without food. Therapy should be individualized according to goal of therapy and response. After initation and /or upon titration of Atorvastatin, lipid levels should be analysed with in 2 to 4 weeks and

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dosage adjusted accordingly.

Homozygous Familial hypercholesterolemia

The dosage of Atorvastatin in these patients is 10 to 80mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication active liver disease or unexplained persistent elevation of serum transaminases exceeding three times the upper limit of normal.

1.Pregnancy:

Women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of Atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins.

In rat and rabbit animal reproduction studies, Atorvastatin revealed no evidence of teratogenicity. Atorvastatin SHOULD BE ADMINISTERED TO WOMEN OF CHILD BEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHL UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, Atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

2.Nursing mothers

It is not known whether Atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin treatment should not breastfeed their infants.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE SECTION:

Erythromycin: Concurrent administration with erythromycin may result in higher plasma concentration of Atorvastatin.

Oral contraceptives: Administration of Atorvastatin with an oral contraceptive containing noretindrone and ethinyl oestradiol produces increased plasma concentration of norethindrone and ethinyl oestradiol.

Colestipol: Although plasma concentration of Atorvastatin are lower when colestipol is administered with Atorvastatin, the lipid effects are greater than when either drug is given alone.

Digoxin : Administration of multiple doses of Atorvastatin with digoxin increases the steady state plasma digoxin concentration by approximately 20%. Patients taking digoxin should be monitored appropriately.

Cyclosporine, fibric acid derivates, erthyromycin, azole antifungals or niacin: the risk of myopathy during treatment with drugs belonging to the class or HMG-CoA reductase inhibitors is increased with concurrent administration of these agents.

Antacids: Decreased plasma concentration of Atorvastatin may occur when administered along with an oral antacid suspension containing magnesium and aluminum hydroxides, however LDL-Cholesterol reduction is not altered.

Warfarin : Minimal decrease in prothrombin time may occur when warfarin and Atorvastatin are administered concurrently; patients receiving warfarin should be closely monitored when Atorvastatin is added to their therapy.

Cimetidine: Atorvastatin plasma concentration and LDL-Cholesterol reduction are not altered by co administration of Cimetidine.

Risk of Hyperglycemia:

Increase in blood sugar levels (hyperglycemia) have been reported with atorvastatin.

Liver Dysfunction:

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semi annually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin.

Myopathy/Rhabdomyolysis/Elevation of creatine kinase :

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhadbomyolysis (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Rhabdomyolsis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.

Atorvastatin may cause an increase in serum creatine phosphokinase levels. This should be considered in the differential diagnosis or chest pain in patients on therapy with Atorvastatin. Uncomplicated myalgia has been reported in Atorvastatin-treated patients. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with other drug in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin or azole anti-fungals. Patients Should be advised to report promptly any unexplained muscle pain tenderness or weakness, particularly if accompanied by malaise or fever.

Pregnancy / Lactation :

Safety of Atorvastatin in pregnancy has not been established. HMG-CoA reductase inhibitors are not recommended for use during pregnancy. An interval of 1 months should be allowed from stopping Atorvastatin treatment to conception in the event of planning a pregnancy. Use of HMG-CoA reductase inhibitors during breast feeding is not recommended, because of the potential for serious adverse effects in nursing infants.

Pediatric Use:

Safety and efficacy of Atorvastatin have not been established in Children.

Patients with hepatic dysfunction:

In patients with moderate to severe hepatic dysfunction, the therapeutic response to Atorvastatin is unaffected but exposure to the drug greatly increase the plasma concentration of Atorvastatin. Therefore caution should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Patients with renal insufficiency :

Renal disease has no influence on the plasma concentration or lipid effects of Atorvastatin: hence no adjustment of dose is required. Haemodialysis is not expected to significantly enhance the clearance of Atorvastatin since the drug is extensively bound to plasma proteins.

SIDE EFFECTS

Atorvastatin is generally well tolerated. Adverse effects reported commonly include constipation, flatulence, dyspepsia, abdominal Pain , headache, nausea, myalgia , diarrhoea, asthenia, memory loss and insomnia.

Dose- related and reversible elevated serum ALT levels have been reported in approximately 1.3% of patients receiving Atorvastatin. Elevated serum CPK levels have been reported in some patients on Atorvastatin but only rarely have patients had concurrent muscle pain, tenderness or weakness.

OVER DOSE

There is no specific treatment available for Atorvastatin over dosage. Generally supportive measures should be adopted as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not excepted to significantly enhance Atorvastatin clearance.

PHARMACEUTICAL PARTICULARS

Incompatibilities: Not applicable
Shelf life: Please refer carton / blister

Storage and Precautions:

Store protected from moisture at a temperature not exceeding 30°C.

Keep out of reach of children.

Special Precautions for Disposal and Other Handling

Any unused medicinal product or waste material should be disposed off in accordance with local requirements

Presentation: STATIX®- 10/20/40 Available as Alu-Alu 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.**