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

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Atorvastatin and Fenofibrate (Micronised) Tablets

STATIX® - F

स्टेटिक्स-एफ़

Composition:
Each uncoated tablet contains
Atorvastatin Calcium IP
equivalent to Atorvastatin 10 mg
Fenofibrate IP (micronised) 200 mg
Excipients q.s.

Description
STATIX®-F is a fixed-dose combination of Atorvastatin 10 mg and micronised Fenofibrate 200 mg. The combination provides greater improvement in all lipid parameters viz, LDL, triglycerides, HDL, non-HDL and small dense LDL, as compared to monotherapy. Also, percentage of patients achieving lipid goals is maximum with the combination. Recent evidence suggests that this combination has an acceptable safety profile, unlike previously perceived.

Clinical Pharmacology

Atorvastatin is a selective, competitive inhibitor of 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. In addition, Atorvastatin reduces VLDL and TG and increases HDL-C.

Fenofibric acid, the active metabolite of Fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides, and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with Fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII. The effects of Fenofibric acid seen in clinical practice have been explained by the activation of peroxisome proliferator activated receptor (alpha) [PPAR á].

Pharmacokinetics

Atorvastatin: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations 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%. Atorvastatin can be given with or without food.

Mean volume of distribution of Atorvastatin is approximately 381 liters.

Atorvastatin is 98% bound to plasma proteins.

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.

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.

Fenofibrate: The absolute bioavailability of Fenofibrate is not determined. However, Fenofibrate is well absorbed from the gastrointestinal tract as following administration to healthy volunteers, approximately 60% of a single dose of radiolabelled Fenofibrate appeared in urine.

Peak plasma levels of Fenofibric acid occur within 6 to 8 hours after administration. The absorption of Fenofibrate is increased when administered with food.

Steady-state plasma levels of Fenofibric acid were shown to be achieved within 5 days. There is no accumulation following multiple dose administration. Serum protein binding was approximately 99%

Following oral administration, Fenofibrate 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. After administration of radiolabelled Fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations
Geriatric:
Atorvastatin: Plasma concentrations of Atorvastatin are higher (approximately 40% for Cmax 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.

Fenofibrate: Similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Renal Insufficiency:

Atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of Atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary.

Fenofibrate: In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of Fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. Therefore, the dosage of Fenofibrate should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic Insufficiency:

Atorvastatin: In patients with chronic alcoholic liver disease, plasma concentrations of Atorvastatin are markedly increased.

Fenofibrate: No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Pediatric: Pharmacokinetic data of STATIX®-F in the pediatric population is not available.

Indication

Combined hyperlipidemia

STATIX®-F is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in these patients.

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

Dosage and Administration

The recommended dosage is one tablet once daily. STATIX® -F should be given with meals, thereby optimizing the bioavailability of the medication.

Contraindication

- Hypersensitivity to either component
- Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality
- Unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal
- Preexisting gallbladder disease
- Pregnancy and Lactation

Precautions

Liver function

The two drugs, given individually, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on two or more occasions) in serum transaminases occurred in 0.7% of patients who received Atorvastatin in clinical trials. Specifically, the incidence of these abnormalities was 0.2% for Atorvastatin 10 mg. In a pooled analysis of 10 placebo-controlled trials, increases in serum transaminases to >3 ULN occurred in 5.3% of patients taking Fenofibrate versus 1.1% of patients treated with placebo.

In a pooled safety analysis of two trials conducted on STATIX® -F, in which 82 patients received STATIX®-F for 12 weeks, none of the patients had a clinically significant drug-related increase in SGOT and SGPT, defined as an increase of > 2 times the upper limit of normal.

It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy and periodically thereafter (eg semiannually). 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, withdrawal of STATIX®-F is recommended. STATIX®-F should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Skeletal muscle

The use of STATIX®-F may occasionally be associated with myopathy since the two drugs, individually, have been shown to cause myopathy in a small percentage of patients (<1%) in international trials. In a pooled data of two trials in which 82 patients received STATIX®-F over 12 weeks, none of the patients reported myopathy. Also none of the patients showed an increase in CPK > 10 times the upper limit of normal.

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Treatment with Atorvastatin as well as Fenofibrate has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. STATIX®-F therapy should be

discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Cholelithiasis

Fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. STATIX®-F therapy should be discontinued if gallstones are found.

Renal impairment

Renal disease has no influence on the plasma concentrations or lipid effects of Atorvastatin. However, Fenofibric acid is known to be substantially excreted by the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. STATIX®-F is not recommended for use in patients with severe renal impairment.

Pregnancy

As safety in pregnant women has not been established, treatment should be immediately discontinued as soon as pregnancy is recognized.

Lactation

Satix-F is contraindicated in nursing mothers. because of the potential for adverse reactions in nursing infants, women taking STATIX®-F should not breast-feed.

Pediatric Use

Safety and efficacy of STATIX®-F in pediatric patients have not been established.

Drug Interactions

Colestipol : Plasma concentrations of Atorvastatin decreased approximately 25% when colestipol and Atorvastatin were coadministered. However, LDL-C reduction was greater when Atorvastatin and colestipol were coadministered than when either drug was given alone. Since bile acid sequestrants may bind other drugs given concurrently, patients should take STATIX®-F at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption .

Digoxin : Administration of multiple doses of Atorvastatin with digoxin increases the steady- state plasma digoxin concentrations by approximately 20%. Patients taking digoxin and STATIX® -F concomitantly should be monitored appropriately.

Erythromycin : In healthy individuals, plasma concentrations of Atorvastatin increased by approximately 40% with coadministration of Atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4. The risk of myopathy is increased when statins and erythromycin are concurrently administered. Caution should be exercised when coadministering STATIX® -F with erythromycin.

Oral Contraceptives: Coadministration of Atorvastatin and an oral contraceptive containing noreithindrone and ethinyl estradiol produces increased plasma concentrations of norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking STATIX®-F.

Oral Anticoagulants: If coumarin anticoagulants and STATIX®-F are coadministered, the dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

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. The benefits and risks of using

Statix-F with immunosuppressants and other potentially nephrotoxic agents should be carefully considered. Also, the risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine. Hence, caution should be exercised when coadministering STATIX®-F with cyclosporine.

Azole antifungals/Niacin: The risk of myopathy during treatment with statins is increased with concurrent administration of these agents. Hence caution should be exercised when these drugs are coadministered with STATIX®-F.

Adverse Reactions

The combination of Atorvastatin and Fenofibrate is generally well tolerated.

In studies conducted with STATIX®-F (n=82), the reported side effects were gastritis (2%), leg pain (6%), burning feet (2%), body ache (6%), numbness in legs (4%), joint pain (1%), pruritis (1%), hyperglycemia (1%) and dizziness (2%). All these effects were mild and transient.

Other side effects with the combination may include nausea, headache, abdominal pain, constipation, dyspepsia, flatulence, diarrhea, dizziness, insomnia, hepatitis, cholelithiasis, cholecystitis, hepatomegaly, photosensitivity, myopathy, rhabdomyolysis and eczema.

Storage

Store in a cool, dry place. Protect from light. Keep the medicine out of reach of children.

Presentation

STATIX®-F tablets are available in blister pack of 10 tablets

For further information, please contact

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