Lofat®

Fenofibrate 200 mg Capsule

Description

Lofat® is a preparation of Fenofibrate. Fenofibrate is a fibric acid derivative first synthesized in 1974 and approved by the US Food and Drug Administration in 1993 for the treatment of hyperlipidemia.

Mode of Action

Fenofibrate is a fibric acid derivative, a prodrug comprising fenofibric acid linked to an isopropyl ester. Fenofibrate is rapidly hydrolyzed after oral ingestion to its pharmacologically active form, fenofibric acid. The effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα).

It lowers lipid levels by activating peroxisome proliferator-activated receptor alpha (PPARα). PPARα activates lipoprotein lipase and reduces apoprotein CIII (an inhibitor of lipoprotein lipase activity), which increases lipolysis and elimination of triglyceride-rich particles from plasma. 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.

PPARα also increases apoproteins AI and AII, reduces VLDL- and LDL-containing apoprotein B, and increases HDL-containing apoprotein AI and AII.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Indications

Lofat® (Fenofibrate) is indicated as an adjunct to diet and other non pharmacological treatment (e.g. exercise, weight reduction) for the following:

- Treatment of severe hypertriglyceridemia with or without low HDL cholesterol.
- Mixed hyperlipidemia when a statin is contraindicated or not tolerated.
- Mixed hyperlipidemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

Dosage and Administration

Since it is less well absorbed from an empty stomach, Lofat® capsule should always be taken with food and should be swallowed as a whole with water. Dietary restrictions instituted before therapy should be continued.

Usual Adult Dose

Lofat® capsule (Fenofibrate 200 mg) once daily is recommended as the dose for the treatment of primary hypercholesterolemia, hypertriglyceridemia or mixed hyperlipidemia.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Lofat® (Fenofibrate 200 mg) capsule treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

Elderly

Normal adult dose is recommended.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients (less than 18 years of age). Therefore, the use of fenofibrate is NOT recommended in pediatric patients under 18 years.

Renal Impairment

Reduce dose to 134 mg daily if eGFR less than 60 mL/minute/1.73 m^2. Reduce dose to 67 mg daily if eGFR less than 20 mL/minute/1.73 m^2. Avoid if eGFR less than 15 mL/minute/1.73 m^2.

Hepatic Impairment

Fenofibrate is considered contraindicated in patients with hepatic failure, including biliary cirrhosis and unexplained persistent liver function abnormality.

Contraindications

Fenofibrate (Lofat®) is contraindicated in patients with

- hypersensitivity to fenofibrate or any component of this medication.
- known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal disorders.
- chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.
- pregnancy and lactation.

Special Warnings and Precautions

Secondary causes of dyslipidemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is initiated.

Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-C, triglycerides). If an adequate response has not been achieved after three months, complementary or different therapeutic measures should be considered.

Renal impairment

In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 67 mg capsules should be used, e.g. 2 Fenofibrate 67 mg capsules daily for creatinine clearance levels of < 60 mL/minute/1.73 m^2 and 1 Fenofibrate 67 mg capsule daily for creatinine clearance levels of < 20 mL/minute/1.73 m^2.

It is recommended that creatinine is measured during the first three months after initiation of treatment and thereafter periodically. Treatment should be interrupted in case of an increase in creatinine levels > 50% of ULN (upper limit of normal).

Use of Fenofibrate 67 mg capsules are also to be preferred in elderly patients with renal impairment where dosage reduction may be required.

Serum Transaminases

Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminases should be monitored every three months during the first twelve months of treatment. Treatment should be interrupted in the event of ALAT (SGPT) or ASAT (SGOT) elevations to more than 3 times the upper limit of the normal range or more than one hundred international units.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Myopathy

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminemia and previous renal insufficiency. Patients with pre-disposing factors for myopathy and/or rabdomyolysis, including age above 70 years, personal or family history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may also be at an increased risk of developing rabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be stopped.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

For hyperlipidemic patients taking estrogens or contraceptives, containing estrogen it should be ascertained whether the hyperlipidemia is of primary or secondary nature (possible elevation of lipid values caused by oral estrogen).

Drug Interactions

Oral anti-coagulants

Fenofibrate (Lofat®) has been reported to potentiate the anticoagulant effects of coumarin anti-coagulants such as warfarin. In patients receiving coumarin anti-coagulant therapy, the dose of anti-coagulant should be reduced by about one-third at the commencement of treatment and then gradually adjusted if necessary according to INR (International Normalized Ratio) monitoring.

Statins or Other Fibrates

The risk of serious muscle toxicity is increased if fenofibrate is used concomitantly with statins or other fibrates. Such combination therapy should be used with caution and liver function and creatine kinase should be monitored closely. However, the use of low-dose statins with Fenofibrate (Lofat®) appears to be well tolerated.

There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.

Resins

Since bile acid sequestrants may bind other drugs given concurrently, patients should take fenofibrate at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine

Fenofibrate (Lofat®) may increase the nephrotoxicity of cyclosporine. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered and the lowest effective dose employed. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

Other

No proven clinical interactions of fenofibrate with other drugs have been reported, although in vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites. In common with other fibrates, fenofibrate induces microsomal mixed-function oxidases involved in fatty acid metabolism in rodents and may interact with drugs metabolised by these enzymes.

Pregnancy, Lactation and Fertility

Pregnancy

Pregnancy Category C.

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

There is no data on the excretion of fenofibrate and/or its metabolites into breast milk. It is therefore recommended that Fenofibrate should not be administered to women who are pregnant or are breast feeding.

Fertility

In fertility studies, rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day.

Side Effects

Common or very common: Abdominal distension, anorexia, diarrhea, nausea.

Uncommon: Alopecia, cholestasis, dizziness, erectile dysfunction, headache, myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—special risk in renal impairment, pancreatitis, photosensitivity reactions, pruritus, pulmonary embolism, rash, renal failure, urticaria.

Rare: Hepatitis, peripheral neuropathy.

Very rare: Anemia, gallstones, increased platelet count, interstitial lung disease, leukopenia, pancytopenia, Stevens-Johnson syndrome, thrombocytopenic purpura, toxic epidermal necrolysis.

Frequency not known: Interstitial pneumopathies.

Overdose

No case of overdosage has been reported. No specific antidote is known. If overdose is suspected, treat symptomatically and institute appropriate supportive measures 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. Fenofibrate cannot be eliminated by hemodialysis because fenofibrate is highly bound to plasma proteins.

Pharmaceutical Precautions

Keep out of the reach of children. Do not store above 25°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Lofat® capsule : Box containing 30 capsules in 3 x 10 's blister strips. Each capsule contains Fenofibrate BP 200 mg.

BEXIMCO PHARMA

Manufactured by

BEXIMCO PHARMACEUTICALS LTD.

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