Nanofib®

Fenofibrate

FORMS AND PRESENTATION
Nanofib®: Film coated tablets: Box of 30.
COMPOSITION
Nanofib®: Each film coated tablet contains Fenofibrate 145mg.
Excipients: Sodium lauryl sulphate, lactose, sucrose, povidone, starch, crospovidone, colloidal anhydrous silica, magnesium stearate,polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Therapeutic class: Lipid modifying agents.
ATC code: C10AB05.
Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα).
Through activation of PPARα, Fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.
The above stated effects of Fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII.
In addition, through modulation of the synthesis and the catabolism of VLDL fractions Fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.
During clinical trials with Fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.
In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk.
Because of its effect on LDL cholesterol and triglycerides, treatment with Fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus. At the present time, no results of long-term controlled clinical trials are available to demonstrate the efficacy of Fenofibrate in the primary or secondary prevention of atherosclerotic complications.
Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during Fenofibrate therapy.
Patients with raised levels of fibrinogen treated with Fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with Fenofibrate treatment.
The uricosuric effect of Fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.
Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.
Pharmacokinetic Properties
Nanofib® film coated tablet contains 145 mg of Fenofibrate nanoparticles.
Absorption: The absolute bioavailability of Fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, Fenofibrate is well absorbed from the gastrointestinal tract. Peak plasma levels of fenofibric acid, the active metabolite of Fenofibrate, occur within 6 to 8 hours after administration.
Contrarily to previous Fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticle formulation is independent from food intake. Therefore, Nanofib® may be taken without regard to meals. A food-effect study involving administration of the new 145 mg tablet formulation of Fenofibrate to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and Cmax) to fenofibric acid is not affected by food.
Distribution: Upon multiple dosing of Fenofibrate, fenofibric acid steady state is achieved within 9 days. Plasma concentrations of fenofibric acid at steady state are approximately double those following a single dose. Fenofibric acid is strongly bound to plasma albumin (more than 99%).
Metabolism and excretion: After oral administration, Fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged Fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.
The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate.
Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis.
The plasma elimination half-life of fenofibric acid is approximately 20 hours.
Pharmacokinetics in Special Population
Geriatrics: In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.
Pediatrics: Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.
Renal Insufficiency: The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [Cr_{Cl}] ≤ 30 mL/min) showed 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (Cr_{Cl} 30-80 mL/min) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Fenofibrate should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.
Hepatic Insufficiency: No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.
INDICATIONS
Hypercholesteroleamia and hypertriglyceridaemia alone or combined (types IIa, IIb, IV dyslipidaemias, as well as types III and V dyslipidaemias) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk such as hypertension and smoking.
The treatment of secondary hyperlipoproteinaemias is indicated if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).
Appropriate dietary measures initiated before therapy should be continued.
CONTRAINDICATIONS
− hepatic insufficiency (including biliary cirrhosis),
− renal insufficiency,
− children,
− hypersensitivity to Fenofibrate or any component of this medication,
− known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen,
− gallbladder disease,
− chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.
PRECAUTIONS
Secondary cause of hypercholesterolemia, 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.
For hyperlipidaemic patients taking estrogens or contraceptives containing oestrogens it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).
Liver function: As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.
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 with the obstruction of the common bile duct.
Muscle: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents.Patients with hypoalbuminemia and renal insufficiency in their personal history have a higher incidence of myotoxicity.
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 upper normal range). In such cases treatment with Fenofibrate should be stopped.
Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, hypoalbuminaemia, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of Fenofibrate therapy should be carefully weighed up.
The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor (statins), 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 dyslipidaemia 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.
Renal function: Treatment should be interrupted in case of an increase in creatinine levels > 50% and ULN (upper limit of normal). It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.
Ability to drive and use machines:
Fenofibrate has no influence on the ability to drive and use machines.
PREGNANCY AND LACTATION
There are no adequate data from the use of Fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity. The potential risk for humans is unknown. Therefore, Fenofibrate should only be used during pregnancy after a careful benefit/risk assessment
There are no data on the excretion of Fenofibrate and/or its metabolites into breast milk. Consequently, Fenofibrate tablets should not be used in nursing mother.
DRUG INTERACTIONS
Oral anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. Therefore, this combination is not recommended.
Cyclosporin: Some severe cases of reversible renal function impairment have been reported during concomitant administration of Fenofibrate and cyclosporin. 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.
HMG-CoA reductase inhibitors and other fibrates: The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.
Cytochrome P450 enzymes: In vitro studies using human liver microsomes indicate that Fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.
ADVERSE EFFECTS
The frequencies of adverse events are ranked according to the following: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.
Gastrointestinal disorders:
Common: digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity.
Uncommon: pancreatitis *.
Hepato-biliary disorders:
Common: moderately elevated levels of serum transaminases.
Uncommon: development of gallstones.
Very rare: episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and Fenofibrate discontinued, if applicable.
Skin and subcutaneous tissue disorders:
Uncommon: rashes, pruritus, urticaria or photosensitivity reactions.
Rare: alopecia.
Very rare: cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sunlamp) in individual cases (even after many months of uncomplicated use).
Musculoskeletal, connective tissue and bone disorders:
Rare: diffuse myalgia, myositis, muscular cramps and weakness.
Very rare: rhabdomyolysis.
Cardiovascular system:
Uncommon: thromboembolism (pulmonary embolism, deep vein thrombosis)*.
Blood and lymphatic system disorders:
Rare: decrease in haemoglobin and leukocytes.
Nervous system disorders:
Rare: sexual asthenia, headache.
Respiratory, thoracic and mediastinal disorders:
Very rare: interstitial pneumopathies.
Investigation:
Uncommon: increases in serum creatinine and urea.
* In the FIELD-study, a randomized placebo-controlled trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving Fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the Fenofibrate group; p = 0.022) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0 % [48/4900 patients] versus Fenofibrate 1.4% [67/4895 patients]; p = 0.074).
DOSAGE AND ADMINISTRATION
In combination with diet, this medicinal product constitutes a long-term treatment, the efficacy of which should be monitored periodically.
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 several months (e.g. 3 months), complementary or different therapeutic measures should be considered
Posology:
Adults: The recommended dose is one tablet of Nanofib taken once daily.
Elderly patients: In elderly patients, the usual adult dose is recommended.
Patients with renal impairment: Dosage reduction is required in patients with renal impairment.
Children: The use of Nanofib® is contraindicated in children.
Hepatic disease: Patients with hepatic disease have not been studied.
Method of administration: Tablet should be swallowed whole with a glass of water.
Nanofib® tablet may be given at any time of the day, with or without food.
OVERDOSAGE
No case of overdose has been reported. No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.
STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: July 2016.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon

P1055/5