EZENOL

Fenofibrate 160mg

PRODUCT DESCRIPTION

Ezenol: An oblong, white film coated tablet with 'FENO' on one side and plain on other side.

COMPOSITION

Active ingredient: Fenofibrate 160 mg.

PHARMACODYNAMICS

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPAR α). 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 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 apoprotien β 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 and dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk of 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 significant 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 reduction in this parameter, as have those with raised levels of Lp(a). Others 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.

PHARMACOKINETICS

Ezenol Tab is a film-coated tablet containing 160 mg of micronised fenofibrate and is suprabioavailable (larger bioavailability).

Absorption: Maximum plasma concentrations occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

The absorption of fenofibrate is increased when administered with food.

Distribution: Fenofibric acid is strongly bound to plasma albumin (more 99%).

Plasma half-life: The plasma elimination half-life of fenofibric acid is approximately 20 hours.

Metabolism and excretion: No fenofibrate can be detected in the plasma where the principal metabolite is fenofibric acid. 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. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified. 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.

INDICATIONS

Hypercholesterolaemia and hypertriglyceridaemia alone or combined (types lla, llb, 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. The treatment of secondary hyperlipoproteinaemias is indicated if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).

Dietary measures initiated before therapy should be continued.

RECOMMENDED DOSAGE

The recommended dose of Ezenol Tablet 160mg is one tablet taken once daily. Tablets should be swallowed during a meal with water.

MODE OF ADMINISTRATION

Oral - Tablet

CONTRAINDICATIONS

Ezenol Tab is contra-indicated in children, during pregnancy or lactation, in patients with liver insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality), severe renal insufficiency (creatinine clearance < 20ml/min), in patients hypersensitive to fenofibrate and/or excipients, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen, chronic or acute pancreatitis with the exeption of acute pancreatitis due to severe hypertriglyceridemia, gallbladder disease. Ezenol Tab should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions.

WARNINGS AND 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.

Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-Cholesterol, triglycerides), if an adequate response has not been achieved after several months (e.g. 3 months) complementary or different therapeutic measures should be considered.

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 and thereafter periodically. 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.

Pancreatitis: One pancreatitis has been reported in patients receiving fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct effect of the medicinal product, or to a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle: Muscle toxicity, including 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 hypoalbuminaemia and previous renal insufficiency. Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, 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.

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 an HMG-CoA reductase inhibitor or another fibrate, should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease; and with a close monitoring of potential muscle toxicity.

The usual adult dose is recommended in elderly patients.

This medical product contains lactose, therefore patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Renal function: Treatment should be interrupted in case of an increase in creatinine levels > 50% ULN (upper limit of normal). It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.

INTERACTIONS WITH OTHER MEDICINES

Oral anticoagulants: The combination fenofibrate and oral anticoagulants is not recommended. Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. However if this combination is required, 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.

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 severe muscle toxicity may be increased if the drug is administered in combination with another fibrate. Concurrent use of fibrates with HMG-CoA reductase inhibitor) may cause severe myositis and myoglobinuria. This combination therapy should be used with caution and patients should be monitored closely 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.

Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

USING DURING PREGNANCY AND LACTATION

There are no adequate data from the use of fenofibrate in pregnant women. Ezenol Tablet 160mg should only be used during pregnancy after careful benefit/risk assessment. There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Ezenol Tablet 160mg should not be used during lactation.

UNDESIRABLE EFFECTS

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.

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.

Rare: alopecia, cutaneous photosensitivity reactions 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:
Uncommon: diffuse myalgia, myositis, muscular cramps and weakness.
Not known: rhabdomyolysis.
Cardiovascular system:
Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis) *
Blood and lymphatic system disorders:
Rare: decrease in haemoglobin and leukocytes.
Nervous system disorders:
Uncommon: sexual asthenia, headache.
Respiratory, thoracic and mediastinal disorders:
Not known: interstitial pneumopathies.
Investigation:
Uncommon: Increases in serum creatinine and urea.

OVERDOSE AND TREATMENT
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
Store in a dry place below 30ºC.
Protect from light.

SHELF LIFE
Please refer to outer box / blister.
DO NOT EXCEED THE EXPIRY DATE INDICATED ON THE BOX.

Keep out of the reach of children
Jauhi daripada kanak-kanak

PACKAGING
Blister of 10 tablets. 3 such blisters are packed in Box with leaflet.

Product Registration Holder:
Duopharma Marketing Sdn. Bhd.
Lot No. 2, 4, 6, 8, & 10 Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia.

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