Fenofibrate

Fenoflex®
160 mg Capsule
antihyperlipidemic

FORMULATION
Each capsule contains:
Fenofibrate ……..……...160 mg

PRODUCT DESCRIPTION
Size #0 capsule with orange cap and body, filled with white to off-white powder

CLINICAL PHARMACOLOGY
Pharmacodynamics
Fenofibrate is a prodrug and has no antilipemic activity until it is hydrolyzed by tissue and plasma esterases *in vivo* to fenofibric acid.

The lipid modifying effects of fenofibrate are mediated by the activation of peroxisome proliferator activated receptor type alpha (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The reduction in triglyceride concentrations alters the size and composition of LDL-cholesterol from small, dense particles to larger, more buoyant particles that are less atherogenic and more rapidly catabolized. PPARα activation also induces an increase in the synthesis of apo A-I, A-II, and HDL-cholesterol.

Fenofibric acid decreases total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), very low density lipoprotein cholesterol (VLDL-C), and triglycerides. In addition, fenofibric acid increases high density lipoprotein cholesterol (HDL-C), apolipoproteins A-I and A-II.

Fenofibrate has been shown to reduce serum uric acid concentrations in healthy and hyperuricemic individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics
Fenofibrate is rapidly absorbed after oral administration. The extent of fenofibrate absorption varies between fed (60 to 90%) and fasted (30 to 50%) conditions. Food increases the rate of fenofibrate absorption by approximately 55%.

The volume of distribution of fenofibric acid is 0.89 L/kg and the active metabolite is 99% protein bound.

After oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid. No unchanged fenofibrate is detected in plasma of healthy subjects after administration. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism to a significant extent.

After absorption, fenofibrate is excreted mainly in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabeled 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 approximately 20 hours, allowing once daily administration in a clinical setting.

The half-life of fenofibric acid is prolonged in the elderly (39 hours) and in the presence of hepatic dysfunction (45 to 57 hours). In severe renal failure, the half-life is markedly prolonged (143 hours) and during repeated administration of fenofibrate, fenofibric acid accumulates in the plasma. Dose adjustment is necessary in such patients.

Fenofibrate (Fenoflex) 160 mg capsule was shown to have comparable bioavailability to a single dose of fenofibrate 200 mg capsule in adults under fed conditions. After oral administration of a single dose fenofibrate (Fenoflex) 160 mg capsule, mean peak fenofibrate plasma concentration (C_{max}) of 14.3233 ± 2.1269 mcg/mL was achieved within 4.88 ± 0.9 hours (T_{max}). The area under the plasma concentration time-curve (AUC_{0-72h}) was 178.8636 ± 53.9433 mcg·h/mL.

INDICATIONS

- Adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb hyperlipidemia)
- Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)
- Treatment of secondary hyperlipoproteinemia is indicated if the hyperlipoproteinemia persists despite effective treatment of the underlying disease (e.g., dyslipidemia in diabetes mellitus)

DOSAGE AND MODE OF ADMINISTRATION

General Dosing Recommendations:

- Fenofibrate should be given with meals to optimize its bioavailability.
- Place patients on an appropriate lipid-lowering diet before receiving fenofibrate, and should continue this diet during treatment with fenofibrate.
- Monitor lipid levels periodically. Fenofibrate therapy should be withdrawn in patients who do not achieve an adequate response after two months of treatment.

Adult Dose: Orally, 160 mg once a day,
Or, as prescribed by a physician.

CONTRAINDICATIONS

- Hypersensitivity to fenofibrate or any component of the product
- Severe renal dysfunction, including patients on dialysis
- Active liver disease, hepatic dysfunction, including primary biliary cirrhosis and unexplained persistent liver function abnormality
- Preexisting gallbladder disease
- Children
- Known photoallergy or phototoxic reaction during treatment with fenofibrate or ketoprofen
- Chronic or acute pancreatitis with the exemption of acute pancreatitis due to severe hypertriglyceridemia
- Pregnancy and breastfeeding

WARNINGS AND PRECAUTIONS

Initial Therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting fenofibrate therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients. Secondary causes of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment (e.g., diuretics, beta-blockers, estrogens, progestogens, immunosuppresants, protease inhibitors) and excessive alcohol intake should be adequately treated before fenofibrate therapy is considered.

Liver Function: Abnormal liver function tests have been observed during fenofibrate administration, including elevations of serum transaminases [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST)], and decreases or, rarely, increases in alkaline phosphatase.

Perform regular periodic monitoring of liver function, including ALT, for the duration of fenofibrate therapy. Discontinue treatment if enzyme levels persist above three times the upper limit of normal (ULN).

Cholelithiasis: Fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Discontinue fenofibrate therapy if gallstones are found.

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 obstruction of the common bile duct.

Mortality and Coronary Heart Disease Morbidity: The effects of fenofibrate on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established. Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus.

Venothromboembolic Disease: In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, pulmonary embolus and deep vein thrombosis were observed at higher rates in the fenofibrate-treated group compared with the placebo-treated group.

Hematologic Changes: After initiation of fenofibrate therapy, mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been reported. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in patients treated with fenofibrate. Periodic blood counts are recommended during the first 12 months of fenofibrate therapy.

***Skeletal Muscle Effects*:** Muscle toxicity, including rare cases of rhabdomyolysis, with or without renal failure, has been observed with the use of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminemia and previous renal insufficiency. Muscle toxicity should be suspected in patients with diffuse myalgia, myositis, muscular cramps and weakness, and/or marked increases in creatinine phosphokinase (CPK) levels (> 5 times ULN). Discontinue fenofibrate in such cases.

Patients with predisposing factors for myopathy/rhabdomyolysis, including elderly (age >70 years), personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at increased risk of developing rhabdomyolysis. In such cases, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, particularly in cases of preexisting muscular disease. Thus, the coadministration 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 should be used with caution and patients should be closely monitored for signs of muscle toxicity.

Renal Function: Monitor creatinine levels during the first three months after initiation of treatment. Discontinue fenofibrate therapy in case of an increase in creatinine levels >50% ULN. Renal monitoring should also be considered in patients at risk for renal insufficiency such as the elderly and patients with diabetes.

Hypersensitivity Reactions: Fenofibrate therapy has been associated with acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids, including reports of Stevens-Johnson syndrome and toxic epidermal necrolysis. Urticaria was also reported in controlled studies.

Paradoxical Decreases in HDL-C Levels: There have been reports of severe decreases in HDL-C levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy.

The reduction was accompanied by a decrease in apo A-I concentrations, and occurred within two weeks to years after initiation of fibrate therapy. Upon discontinuance of therapy, HDL-C concentrations rapidly returned to baseline and remained at normal levels.

The clinical significance of this paradoxical decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

INTERACTIONS WITH OTHER MEDICAMENTS

Coumarin Anticoagulants: Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the prothrombin time (PT)/International normalized ratio (INR). Exercise caution when coumarin-type anticoagulants are given together with fenofibrate. Reduce dosage of the anticoagulant to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that PT/INR has stabilized.

Immunosuppressants (e.g., ciclosporin, tacrolimus): Since renal excretion is the primary elimination route of fibrate drugs including fenofibrate, concomitant administration of nephrotoxic immunosuppressants such as ciclosporin and tacrolimus, may result in deterioration of renal function. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function monitored.

HMG-CoA Reductase Inhibitors (Statins): The combined use of fenofibrate and statins should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatinine kinase levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. The use of fibrates alone, including fenofibrate, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatinine kinase level determination. Discontinue fenofibrate therapy if myopathy/myositis is suspected or diagnosed.

Bile Acid Sequestrants: Because of their potential binding effects, bile acid sequestrants may decrease absorption of fenofibrate when administered concurrently. Fenofibrate should be administered 1 hour before or 4 to 6 hours after a bile acid sequestrant.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrate coadministered with colchicine. Exercise caution when these drugs are used concomitantly.

Glitazones: Cases of reversible paradoxical reduction of HDL-C have been reported during concomitant administration of fenofibrate and glitazones. Monitor HDL-C levels. Discontinue either therapy when HDL-C is too low.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Pregnancy Category C. The safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and in rabbits when given at 9 times the MHRD (on the basis of mg/m^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should not be administered during pregnancy.

Lactation: It is not known whether fenofibrate or its metabolites are excreted into human milk. Fenofibrate should not be administered to breastfeeding women.

Children: The safety and efficacy in pediatric patients have not been established.

Elderly: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to fenofibrate may be greater in patients with renal impairment. Care should be taken in dose selection since elderly patients are more likely to have decreased renal function **(**see also **WARNINGS AND PRECAUTIONS)**.

UNDESIRABLE EFFECTS
The most frequently reported adverse events include abnormal elevation in serum transaminases (ALT and/or AST), epigastric distress, flatulence, abdominal pain, nausea, diarrhea, constipation, erythema, pruritus, urticaria, muscle pain and weakness, arthralgia, headache, dizziness, insomnia, decreased libido, hair loss, and weight loss.

Body as a whole: Back pain, asthenia, flu syndrome, chest pain, malaise, accidental injury
Cardiovascular: Thromboembolism (pulmonary embolism, deep vein thrombosis)
Gastrointestinal: Dyspepsia, gastritis, vomiting, gastrointestinal disorder, pancreatitis
Genitourinary: Acute renal failure, impotence
Hemic and Lymphatic: Anemia, agranulocytosis, thrombocytopenia
Hepatobiliary: Cirrhosis, hepatitis, jaundice, development of gallstones, complications of cholelithiasis (e.g., cholecystitis, cholangitis, biliary colic)
Metabolic and Nutritional: Elevations in the following: CPK, urea, plasma creatinine; ***Reductions in the following:*** plasma alkaline phosphatase, hematocrit, hemoglobin, leukocytes; severely depressed HDL-C levels
Musculoskeletal: Myositis, myalgia, arthralgia, muscular cramps and weakness, muscle spasm, rhabdomyolysis
Nervous: Sexual asthenia
Respiratory: Respiratory disorder, rhinitis, pharyngitis, bronchitis, sinusitis, interstitial pneumopathies
Skin and Appendages: Hypersensitivity reactions, rash, photosensitivity reactions/cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g., sun lamp), skin disorder, severe cutaneous reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), alopecia
Special Senses: Conjunctivitis

OVERDOSE AND TREATMENT
There is no specific treatment for overdose with fenofibrate. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Fenofibrate (Fenoflex®) 160 mg Capsule, in alu-alu blister pack x 6s (box of 30s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

Manufactured by **AMHERST LABORATORIES, INC.**
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines