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, low density lipoprotein (LDL)-cholesterol, apolipoprotein B (apo B), very low density lipoprotein (VLDL)-cholesterol, and triglycerides. In addition, fenofibric acid increases high density lipoprotein (HDL)-cholesterol, apoproteins 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 is comparable between fed (60 to 90%) and fasted (30 to 50%) conditions. Food increases the rate of fenofibrate absorption by approximately 55%.

After oral administration of a 160 mg capsule (Fenoflex capsule), to fasted adults, mean peak fenofibrate plasma concentration (14.3233 ± 2.1269 mcg/mL) is achieved within 4.88 ± 0.9 hours ($T_{max}$).

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 16 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.

**INDICATIONS**

- Adjunctive therapy to diet for the reduction of LDL-cholesterol, total cholesterol, triglycerides, and apo B 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 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.
- Individualize dosage according to patient response; dose should be adjusted if necessary following repeat lipid determinations at 4 to 8 weeks interval.
- **Maximum Dose:** 160 mg once daily

**Primary Hypercholesterolemia or Mixed Dyslipidemia:**

*Initial Adult Dose:* 160 mg once daily

**Hypertriglyceridemia:**

*Initial Adult Dose:* 50 to 160 mg once daily

**Dosage in Patients with Impaired Renal Function:**

*Initial Adult Dose:* 50 mg once daily

Increase dose only after evaluation of the effects on renal function and lipid levels at this dose

**Dosage in Elderly:**

*Initial Dose:* 50 mg once daily

Periodically monitor lipid levels. Consideration should be given to reducing fenofibrate’s dosage if lipid levels fall significantly below the targeted range.

Or, as prescribed by a physician.

**CONTRAINDICATIONS**

- Hypersensitivity to fenofibrate or any component of the product
- Severe renal dysfunction
- 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

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, and control of any medical problems (e.g., diabetes mellitus and hypothyroidism) that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued Therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of fenofibrate. Withdraw therapy in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 160 mg per day.

Liver Function: Fenofibrate at doses equivalent to 134 to 200 mg per day has been associated with increases in serum transaminases [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST)]. 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, like clofibrate and gemfibrozil, 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, gemfibrozil, and clofibrate. 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: The effect of fenofibrate on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate showed a non-significant 11% relative reduction in the primary outcome of coronary heart disease events [hazard ratio (HR) 0.89, 95% CI 0.75 to 1.05, p=0.1] and a significant 11% reduction in the secondary outcome of total cardiovascular disease events [HR 0.89 (0.8 to 0.99), p=0.04]. There was a non-significant 11% [HR 1.11 (0.95 to 1.29), p=0.18] and 19% [HR 1.19 (0.9 to 1.57), p=0.22] increase in total and coronary heart disease mortality, respectively, with fenofibrate compared with placebo.

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

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

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. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received in postmarketing studies. Periodic blood counts are recommended during the first 12 months of fenofibrate therapy.

Skeletal Muscle Effects: Muscle toxicity, including very rare cases of rhabdomyolysis, 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.

INTERACTIONS WITH OTHER MEDICAMENTS

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

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.

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

Ciclosporin: Some severe cases of reversible renal function have been reported. Closely monitor renal function of these patients and discontinue treatment with fenofibrate in cases of severe alteration of laboratory parameters.

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 and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MHRD (on the basis of mg/m² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Fenofibrate should not be used during breastfeeding. Because of the potential for tumorigenicity observed in animal studies, a decision should be made whether to discontinue breastfeeding or to discontinue fenofibrate.

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

**Body as a whole:** Abdominal pain, back pain, headache, asthenia, flu syndrome, chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, accidental injury

**Cardiovascular:** Angina pectoris, hypertension, vasodilatation, coronary artery disorder, abnormal electrocardiogram, ventricular extrasystoles, myocardial infarction, peripheral vascular disorder, migraine, varicose veins, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, atrial fibrillation, thromboembolism (pulmonary embolism, deep vein thrombosis)

**Gastrointestinal:** Abnormal liver function tests, diarrhea, nausea, constipation, dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, hepatitis, pancreatitis, development of gallstones

**Endocrine:** Diabetes mellitus

**Hemic and Lymphatic:** Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, thrombocytopenia

**Metabolic and Nutritional:** Weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, peripheral edema; **Elevations in the following:** alanine aminotransferase (ALT), CPK, aspartate aminotransferase (AST), urea, plasma creatinine; **Reductions in the following:** plasma alkaline phosphatase, hemoglobin, leukocytes

**Musculoskeletal:** Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, myasthenia, muscular cramps, weakness, rhabdomyolysis (rare)

**Nervous:** Dizziness, insomnia, depression, vertigo, decreased libido, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, somnolence

**Respiratory:** Respiratory disorder, rhinitis, pharyngitis, bronchitis, increased cough, dyspnea, asthma, pneumonia, laryngitis, sinusitis, interstitial pneumopathies

**Skin and Appendages:** Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, skin ulcer, photosensitivity reactions/cutaneous photosensitivity with erythema, vesication or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g., sun lamp)

**Special Senses:** Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract, refraction disorder

**Urogenital:** Urinary frequency, prostatic disorder, dysuria, abnormal kidney function, urolithiasis, gynecostasia, unintended pregnancy, vaginal moniliasis, cystitis, impotence

**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.

**STORE AT TEMPERATURES NOT EXCEEDING 30°C**

**KEEP OUT OF SIGHT AND REACH OF CHILDREN**

**AVAILABILITY**

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

**CAUTION**

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