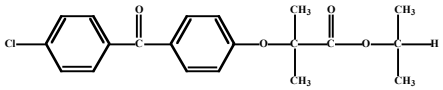
Fenoget™

(Fenofibrate Capsules)

Capsules 67mg, 200mg

DESCRIPTION

FENOGET (Fenofibrate), a fibric acid derivative, is a lipid-regulating agent. Chemically fenofibrate is 2-[4-(4 chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester. Its molecular formula is $C_{20}H_{21}O_4Cl$ and the structural formula is:



Fenofibrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

FENOGET (Fenofibrate) is available for oral administration as:

1. FENOGET Capsules 67mg
   Each capsule contains:
   Fenofibrate BP ... 67mg
   (Micronized)

2. FENOGET Capsules 200mg
   Each capsule contains:
   Fenofibrate BP ... 200mg
   (Micronized)

CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacokinetics

Absorption
Fenofibrate is well absorbed from the gastrointestinal tract. A peak plasma level of fenofibric acid occurs within 6 to 8 hours after administration. For fenofibrate capsules, the absorption is increased by approximately 35% under non-fasting as compared to fasting conditions.

Distribution
Steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67mg fenofibrate and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% bound to plasma proteins in normal and hyperlipidemic subjects.

Metabolism
Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma. 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.

Excretion
After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Renal Insufficiency
In a study in patients with renal impairment (creatinine clearance<50mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults.

Pediatrics
Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.

THERAPEUTIC INDICATIONS

Treatment of Hypercholesterolemia
FENOGET (Fenofibrate) is indicated as adjunctive therapy to diet for the reduction of LDL-C, Total-C, Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).

Treatment of Hypertriglyceridemia
FENOGET (Fenofibrate) is indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving FENOGET (Fenofibrate) capsules and should continue on this diet during treatment.
FENOGET (Fenofibrate) capsules should be given with meals, thereby optimizing the bioavailability of the medication.

Primary hypercholesterolemia or mixed hyperlipidemia:
For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of FENOGET (Fenofibrate) capsules is 200mg per day.

Hypertriglyceridemia
For adult patients with hypertriglyceridemia, the initial dose is 67 to 200mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 200mg per day.

Renal Insufficient Patients
Treatment with FENOGET (Fenofibrate) should be initiated at a dose of 67mg/day in patients with impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose.

Elderly
In the elderly, the initial dose of FENOGET (Fenofibrate) should likewise be limited to 67mg/day.
Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of FENOGET (Fenofibrate) if lipid levels fall significantly below the targeted range.

The following guidelines may be used to establish treatment goals:

NCEP Treatment Guidelines

LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129:drug optional)**
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor #	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

ADVERSE EFFECTS

The most common adverse reactions reported with fenofibrate therapy were gastrointestinal (diarrhea, constipation, dyspepsia, flatulence), muscle pain, and skin reactions.

There is a slightly increased risk of gallstones, inflamed liver (hepatitis), and muscle inflammation (myositis).

Other adverse effects include:

Headache, fatigue, muscle inflammation, inflammation of the pancreas (pancreatitis), balance problems involving the inner ear (vertigo), respiratory problems, muscle breakdown (rhabdomyolysis), hair loss (alopecia), alteration in results of liver function tests, sexual problems.

CONTRAINDICATIONS

Fenofibrate is contraindicated in patients

- With hypersensitivity to fenofibrate or any of the formulation components.
- With severe renal dysfunction.
- With hepatic dysfunction, including primary biliary cirrhosis and unexplained persistent liver function abnormality.
- Pre-existing gall bladder disease.

Fenofibrate should not be used in nursing mothers.

PRECAUTIONS

- *Initial Therapy:* Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting therapy with fenofibrate. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.
- *Continued Therapy:* Periodic determination of serum lipids should be obtained to determine the lowest effective dose of fenofibrate. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose.
- Fenofibrate therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low-density lipoprotein (VLDL).
- Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibrate, and therapy should be discontinued if enzyme levels persist above three times the normal limit.
- Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gall bladder studies are indicated and fenofibrate therapy should be discontinued if gallstones are found.
- Periodic blood counts are recommended during the first 12 months of fenofibrate administration.
- Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatinine kinase level determination. If myopathy/myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

Pregnancy

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.

Pediatric

Safety and efficacy in pediatric patients have not been established.

Drug Interactions

Oral Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

HMG-CoA Reductase Inhibitors (Statins)

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

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

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Beta-blockers, thiazides, estrogens

Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

STORAGE

Store below 30°C.

Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

FENOGET (Fenofibrate) Capsules 67mg are available in blister pack of 30's.

FENOGET (Fenofibrate) Capsules 200mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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