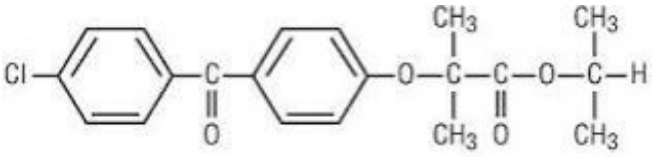
FENOFIBRATE- fenofibrate capsule
Austarpharma, LLC

Fenofibrate Capsules, USP

Rx only

DESCRIPTION

Fenofibrate capsules, USP (micronized) are a lipid regulating agent available as capsules for oral administration. The chemical name for fenofibrate is 2-[4-(4- chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is C20H21O4Cl and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79° to 82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Each 67 mg fenofibrate capsule, USP contains the following inactive ingredients: sodium lauryl sulfate, croscarmellose sodium, pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide, sodium stearyl fumarate, titanium dioxide and gelatin. The capsule shell imprinting ink contains the following inactive ingredients: shellac, black iron oxide and potassium hydroxide.

Each 134 mg fenofibrate capsule, USP contains the following inactive ingredients: sodium lauryl sulfate, croscarmellose sodium, pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide, sodium stearyl fumarate, titanium dioxide, FD&C Yellow 6, D&C Yellow 10 and gelatin. The capsule shell imprinting ink contains the following inactive ingredients: shellac, black iron oxide and potassium hydroxide.

Each 200 mg fenofibrate capsule, USP contains the following inactive ingredients: sodium lauryl sulfate, croscarmellose sodium, pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide, sodium stearyl fumarate, titanium dioxide, FD&C Yellow 6, D&C Yellow 10 and gelatin. The capsule shell imprinting ink contains the following inactive ingredients: shellac, black iron oxide and potassium hydroxide.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII.

The effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoproteins C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

Fenofibrate capsules, USP are 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). Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

Fenofibrate capsules, USP are also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

Drug 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). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia2.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet (See **WARNINGS and PRECAUTIONS**).

Fredrickson Classification of Hyperlipoproteinemias

	Lipid Elevation

Type	Lipoprotein Elevated	Lipid Elevation	
		Major	Minor
I (rare)	Chylomicrons	TG	↑↔C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	—
IV	VLDL	TG	↑↔C
V (rare)	Chylomicrons, VLDL	TG	↑↔

C = cholesterol
TG = triglycerides
LDL = low density lipoprotein
VLDL = very low density lipoprotein
IDL = intermediate density lipoprotein

The NCEP Treatment Guidelines

Definite Athlerosclerotic Disease*	Two or More Other Risk Factors†	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Goal
No	No	≥ 190 (≥ 4.9)	< 160 (< 4.1)
No	Yes	≥ 160 (≥ 4.1)	< 130 (< 3.4)
Yes	Yes or No	≥ 130‡ (≥ 3.4)	< 100 (< 2.6)

CONTRAINDICATIONS

Fenofibrate capsules are contraindicated in patients who exhibit hypersensitivity to fenofibrate.

Fenofibrate capsules are contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

Fenofibrate capsules are contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function

Fenofibrate capsules at doses equivalent to 134 mg to 200 mg fenofibrate per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminase related to fenofibrate therapy appear to be dose related. In an 8 week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 134 mg to 200 mg fenofibrate per day and was 0% in those receiving dosages equivalent to 34 mg or 67 mg of fenofibrate per day or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibrate, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

Concomitant 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/lNR 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.

Concomitant HMG-CoA Reductase Inhibitors

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.

Concomitant administration of fenofibrate (equivalent to fenofibrate 200 mg) and pravastatin (40 mg) once daily for 10 days increased the mean Cmax and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also **CLINICAL PHARMACOLOGY, Drug-drug interactions**.)

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absences of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including fenofibrate capsules 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 creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

Mortality

The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5 year randomized, placebo-controlled study of 9,795 patients with type 2 diabetes mellitus treated with fenofibrate.

Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80 to 0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p=0.18) and 19% (HR 1.19 [0.90, 1.57], p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.

In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring

surgery between the two groups (3% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between fenofibrate, clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to fenofibrate.

In a study conducted by the World Health Organization (WHO), 5,000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4,081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=0.91 to 1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07).

There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

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 such as 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 capsules. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 200 mg per day.

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.

Hypersensitivity Reactions

Acute Hypersensitivity: Anaphylaxis and angioedema have been reported postmarketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate.

Delayed Hypersensitivity: Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported postmarketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis) and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

Hematologic Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during postmarketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

Skeletal Muscle

The use of fibrates alone, including fenofibrate, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p = 0.022$).

In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; $p < 0.01$).

Serum Creatinine

Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown.

Drug Interactions

Oral Anticoagulants

CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH FENOFIBRATE CAPSULES. THE DOSAGE OF THE ANTICOAGULANTS 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

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 (see WARNINGS).

Resins

Since bile acid sequestrants may bind other drugs given concurrently, patients should take fenofibrate capsules at least 1 hour before or 4 to 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24 month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24 month rat carcinogenicity study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

A 117 week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, based on mg/m^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21 month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at 10, 60, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been

done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis in primary rat hepatocytes.

In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (~ 10 times the MRHD, based on mg/m ^{2} surface area comparisons).

Pregnancy

Teratogenic Effects

Pregnancy category C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the MRHD, based on body surface area comparisons; mg/m ^{2}.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6 to 15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m ^{2}). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6 to 18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons: mg/m ^{2}).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons: mg/m ^{2}.

Nursing Mothers

It is not known whether fenofibrate is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fenofibrate, a decision should be made whether to discontinue nursing or administration of fenofibrate taking into account the importance of the drug to the lactating woman.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. However, elderly patients have a higher incidence of renal impairment, such that dose selection for the elderly should be made on the basis of renal function (see **CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency**). Elderly patients with normal renal function should require no dose modifications.

ADVERSE REACTIONS

Photosensitivity reactions have occurred days to months after initiation; in some of these cases, patients reported a prior photosensitivity reaction to ketoprofen.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse events reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during the double-blind, placebo-controlled trials, regardless of causality, are listed in Table 3 below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

Table 3. Adverse Reactions Reported by 2% or More of Patients Treated withFenofibrate and Greater than Placebo During the Double-Blind, Placebo-Controlled Trials

BODY SYSTEM Adverse Reaction	Fenofibrate* (N=439)	PLACEBO (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
DIGESTIVE		
Abnormal Liver Function Tests	7.5%†	1.4%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
Increased ALT	3%	1.6%
Increased CPK	3%	1.4%
Increased AST	3.4%†	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of fenofibrate: myalgia, rhabdomyolysis, pancreatitis, acute renal failure, muscle spasm, hepatitis, cirrhosis, anemia, arthralgia, decreases in hemoglobin, decreases in hematocrit, white blood cell decreases and asthenia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

OVERDOSAGE

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.

DOSAGE AND ADMINISTRATION

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

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of fenofibrate capsules is 200 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 67 mg to 200 mg 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 200 mg per day.

Treatment with fenofibrate capsules, should be initiated at a dose of 67 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 67 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of fenofibrate capsules if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

Fenofibrate capsules, USP (micronized) 67 mg are opaque white cap and body, hard gelatin capsules, printed in black ink “CL” and “22” on opposing cap and body portions of the capsule. They are supplied as follows:

NDC 35561-345-11 Bottles of 90 capsules

Fenofibrate capsules, USP (micronized) 134 mg are opaque white cap and opaque yellow body, hard gelatin capsules, printed in black ink “CL” and “23” on opposing cap and body portions of the capsule. They are supplied as follows:

NDC 35561-346-11 Bottles of 90 capsules

Fenofibrate capsules, USP (micronized) 200 mg are opaque yellow cap and body, hard gelatin capsules, printed in black ink “CL” and “24” on opposing cap and body portions of the capsule. They are supplied as follows:

NDC 35561-347-11 Bottles of 90 capsules

STORAGE

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture. Dispense in tight, light-resistant container as defined in USP with a child-resistant closure (as required).

REFERENCES

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2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV, et al. Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

Manufactured by:
AustarPharma, LLC
Edison, NJ 08837 USA
Revised: 10/22/2019
LBL342

PRINCIPAL DISPLAY PANEL - 67 mg Capsule Bottle Label

NDC 35561- **345**-11

Fenofibrate Capsules, USP

67 mg

Rx Only 90 Capsules

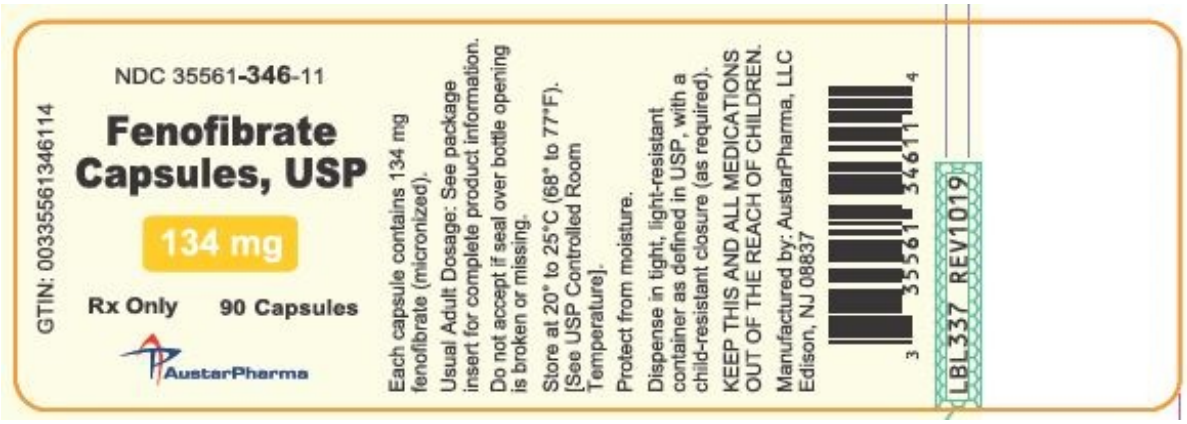
PRINCIPAL DISPLAY PANEL - 134 mg Capsule Bottle Label

NDC 35561- **346**-11

Fenofibrate Capsules, USP

134 mg

Rx Only 90 Capsules



PRINCIPAL DISPLAY PANEL - 200 mg Capsule Bottle Label

NDC 35561- -11

Fenofibrate Capsules, USP

200 mg

Rx Only 90 Capsules

FENOFIBRATE

fenofibrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:35561-345
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENOFIBRATE (UNII: U202363UOS) (FENOFIBRIC ACID - UNII:BGF9MN2HU1)	FENOFIBRATE	67 mg

Product Characteristics			
Color	white (opaque white)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	CL;22
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:35561-345-11	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/17/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207805	11/17/2017	

FENOFIBRATE

fenofibrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:35561-346
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENOFIBRATE (UNII: U202363UOS) (FENOFIBRIC ACID - UNII:BGF9MN2HU1)	FENOFIBRATE	134 mg

Product Characteristics			
Color	white (white-cap) , yellow (yellow-body)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	CL;23
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:35561-346-11	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/17/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207805	11/17/2017	

FENOFIBRATE

fenofibrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:35561-347
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENOFIBRATE (UNII: U202363UOS) (FENOFIBRIC ACID - UNII:BGF9MN2HU1)	FENOFIBRATE	200 mg

Product Characteristics			
Color	yellow	**Score**	no score

Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	CL;24
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:35561-347-11	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/17/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207805	11/17/2017	

Labeler - Austarpharma, LLC (362785011)

Establishment

Name	Address	ID/FEI	Business Operations
Austarpharma, LLC		362785011	manufacture(35561-345, 35561-346, 35561-347)

Revised: 5/2020 Austarpharma, LLC