HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FIBRICOR™ (fenofibric acid) Tablets safely and effectively. See full prescribing information for FIBRICOR.

FIBRICOR™ (fenofibric acid)
Initial U.S. Approval: 2009

---------- INDICATIONS AND USAGE ----------
FIBRICOR is a peroxisome proliferator receptor alpha (PPARα) activator indicated:

- To reduce triglyceride (TG) levels in patients with severe hypertriglyceridemia (≥ 500 mg/dl) (1.1).
- To reduce elevated total cholesterol (TC), low-density-lipoprotein cholesterol (LDL-C), TG and apolipoprotein (Apo) B and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia or mixed dyslipidemia (1.2).

General Considerations for Treatment: The active moiety of FIBRICOR is fenofibric acid. The pharmacological effects of fenofibric acid have been extensively studied through oral administration of fenofibrate, which is converted *in vivo* to fenofibric acid (1.3).

Limitations of use: Fenofibrate as a dose equivalent to 105 mg of FIBRICOR was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus (1.3).

---------- DOSAGE AND ADMINISTRATION ----------
- FIBRICOR may be taken without regards to meals (2.1).
- Severe hypertriglyceridemia: 35 to 105 mg/day; the dose should be adjusted according to patient response (2.2).
- Primary hyperlipidemia or mixed dyslipidemia: 105 mg/day (2.2).

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 35 mg and 105 mg (3)

---------- CONTRAINDICATIONS ----------
- Severe renal dysfunction, including patients receiving dialysis (4)
- Active liver disease (4)
- Gallbladder disease (4)
- Nursing Mothers (4)
- Known hypersensitivity to fenofibric acid or fenofibrate (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Fenofibrate can increase serum transaminases. Monitor liver tests periodically (5.1).
- Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.2).
- Exercise caution in concomitant treatment with oral coumarin anticoagulants. Adjust the dosage of coumarin anticoagulant to maintain the prothrombin time/INR at the desired level to prevent bleeding complications (5.3).
- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks of myopathy and rhabdomyolysis appears to be increased in elderly patients and patients with diabetes, renal failure, or hypothyroidism (5.4).
- Fenofibrate can reversibly increase serum creatinine levels. Monitor renal function periodically in patients with renal insufficiency (5.5).

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (> 2% and greater than placebo) are increased liver tests, abdominal pain, back pain, and headache (6).

To report SUSPECTED ADVERSE REACTIONS, contact Mutual Pharmaceutical Company, Inc. at 1-888-351-3786 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS ----------
- Oral Anticoagulants (7.1)
- Bile-Acid Binding Resins (7.2)
- Immunosuppressants (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pediatric use: The safety and effectiveness in pediatric patients have not been established (8.4).
- Geriatric use: Determine dose selection based on renal function (8.5).
- Renal impairment: Avoid in patients with severe renal impairment; dose reduction required in patients with mild to moderate renal impairment (8.6).
- Hepatic impairment: FIBRICOR has not been evaluated in patients with hepatic impairment (8.7).

Revised: 8/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Severe Hypertriglyceridemia
1.2 Primary Hyperlipidemia or Mixed Dyslipidemia
1.3 Considerations of Treatment
2 DOSAGE AND ADMINISTRATION
2.1 Dosing Information
2.2 Recommended Adult Dose
2.3 Renal Impairment
2.4 Geriatric Patients
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Abnormal Liver Tests
5.2 Cholelithiasis
5.3 Concomitant Use with Oral Anticoagulants
5.4 Myopathy
5.5 Elevated Serum Creatinine
5.6 Coronary Heart Disease Morbidity and Mortality
5.7 Pancreatitis
5.8 Venothromboembolic Disease
5.9 Hypersensitivity Reactions
5.10 Hematological Changes
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Oral Anticoagulants
7.2 Bile-Acid Binding Resins
7.3 Immunosuppressants
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Severe Hypertriglyceridemia
14.2 Primary Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Severe Hypertriglyceridemia

FIBRICOR is indicated as adjunctive therapy to diet for treatment of severe hypertriglyceridemia (≥ 500 mg/dl). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacologic intervention.

Levels of serum triglycerides > 1000 mg/dl may increase the risk of developing pancreatitis. The effect of FIBRICOR on reducing this risk has not been studied.

1.2 Primary Hyperlipidemia or Mixed Dyslipidemia

FIBRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total-C, TG, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.

1.3 Considerations of Treatment

Fenofibrate at a dose equivalent to 105 mg of FIBRICOR was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus [*see Warnings and Precautions (5.6)*].

The active moiety of FIBRICOR is fenofibric acid. The pharmacological effects of fenofibric acid have been extensively studied through oral administration of fenofibrate, which is converted *in vivo* to fenofibric acid.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

FIBRICOR can be given without regard to meals.

Patients should be placed on an appropriate lipid-lowering diet before receiving FIBRICOR and should continue this diet during treatment with fenofibric acid.

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting FIBRICOR 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.

Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of FIBRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 105 mg per day.

Consideration should be given to reducing the dosage of FIBRICOR if lipid levels fall significantly below the targeted range.

2.2 Recommended Adult Dose

Severe Hypertriglyceridemia: The initial dose is 35 to 105 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.

Primary Hyperlipidemia or Mixed Dyslipidemia: The dose of FIBRICOR is 105 mg per day.

The maximum dose of FIBRICOR is 105 mg per day.

2.3 Renal Impairment

In patients with mild-to-moderate renal impairment, treatment with FIBRICOR should be initiated at a dose of 35 mg/day, and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of FIBRICOR should be avoided in patients with severe renal impairment [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.4 Geriatric Patients

Dose selection for the elderly should be made on the basis of renal function [*see Use in Specific Populations (8.6)*].

3 DOSAGE FORMS AND STRENGTHS

- 35 mg: White, round tablets. Debossed “AR 787”.
- 105 mg: White, modified oval tablets. Debossed “AR 788”.

4 CONTRAINDICATIONS

FIBRICOR is contraindicated in patients with:

- severe renal impairment, including those receiving dialysis [*see Clinical Pharmacology (12.3)*].
- active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities [*see Warnings and Precautions (5.3)*].
- preexisting gallbladder disease.
- known hypersensitivity to fenofibric acid or fenofibrate [*see Warnings and Precautions (5.9)*].
- FIBRICOR is also contraindicated in nursing mothers [*see Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Abnormal Liver Tests

Fenofibrate (administered over a range of doses with the higher dose equivalent to 105 mg fenofibric acid) 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 of ALT occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. The incidence of increases in transaminases observed with fenofibrate therapy may be dose related.

Chronic active hepatocellular 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.

Periodic monitoring of liver tests (e.g., ALT) should be performed for the duration of therapy with FIBRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

5.2 Cholelithiasis

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

5.3 Concomitant Use with Oral Anticoagulants

Caution should be exercised when FIBRICOR is given in conjunction with oral anticoagulants. FIBRICOR may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time/INR. Frequent monitoring of prothrombin time/INR and dose adjustment of the anticoagulant are recommended until the prothrombin time/INR has stabilized in order to prevent bleeding complications [*see Drug Interactions (7.1)*].

5.4 Myopathy

Fibrates increase the risk for myopathy and have been associated with rhabdomyolysis. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.

Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are co-administered with an HMG-CoA reductase inhibitor (statin).

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 FIBRICOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

5.5 Elevated 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. Renal monitoring should be considered for patients with renal impairment and for patients at risk for renal insufficiency, such as the elderly and patients with diabetes.

5.6 Coronary Heart Disease Morbidity and Mortality

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

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 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 [0.80–0.99], 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.

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 fenofibric acid.

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 (3.0% vs. 1.8%).

In a study conducted by the World Health Organization (WHO), 5000 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=4081) 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 = 0.91–1.64). 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 (relative risk=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 (HR 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).

5.7 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.

5.8 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 4,875 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).

5.9 Hypersensitivity Reactions

Acute hypersensitivity reactions including severe skin rashes such as Stevens-Johnson syndrome and toxic epidermal necrolysis requiring patient hospitalization and treatment with steroids have been reported in individuals treated with fenofibrate.

5.10 Hematological Changes

Mild-to-moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrate. Periodic monitoring of red and white blood cell counts is recommended during the first 12 months of FIBRICOR administration.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

Adverse reactions reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during the double-blind, placebo-controlled trials are listed in Table 1. Adverse reactions led to discontinuation of treatment in 5% of patients treated with fenofibrate and in 3% treated with placebo. Increases in liver tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients.

Table 1. Adverse Reactions Reported by 2% or More of Patients Treated with Fenofibrate* During the Double-Blind, Placebo-Controlled Trials

BODY SYSTEM Adverse Reactions	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		
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
Abnormal Liver Tests	7.5%	1.4%
Increased ALT	3%	1.6%
Creatine Phosphokinase Increased	3%	1.4%
Increased AST	3.4%	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Fenofibric acid is the active moiety of fenofibrate; Fenofibrate dosage equivalent to 105 mg fenofibric acid.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fenofibrate. 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: myalgia, rhabdomyolysis, increased creatinine phosphokinase, pancreatitis, increased alanine aminotranaminase, increased aspartate aminotranaminase, muscle spasm, acute renal failure, hepatitis, cirrhosis, nausea, abdominal pain, anemia, headache, arthralgia and asthenia.

7 DRUG INTERACTIONS

7.1 Oral Anticoagulants

Caution should be exercised when FIBRICOR is given in conjunction with coumarin anticoagulants. FIBRICOR may potentiate the anticoagulant effect of these agents resulting in prolongation of the prothrombin time/INR. Frequent monitoring of prothrombin time/INR and dose adjustment of the oral anticoagulant are recommended until the prothrombin time/INR has stabilized in order to prevent bleeding complications [*see Warnings and Precautions (5.3)*].

7.2 Bile-Acid Binding Resins

Since bile-acid binding resins may bind other drugs given concurrently, patients should take FIBRICOR at least 1 hour before or 4 to 6 hours after taking another drug.

7.3 Immunosuppressants

Immunosuppressant agents such as cyclosporine and tacrolimus can impair renal function. When immunosuppressants and other potentially nephrotoxic agents are co-administered with FIBRICOR, the lowest effective dose of FIBRICOR should be employed and renal function should be monitored.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Safety in pregnant women has not been established. There are no adequate and well controlled studies of FIBRICOR in pregnant women. FIBRICOR 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 a dose that results in exposure to fenofibric acid that is 50 times that at the MRHD of fenofibric acid.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6–15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (a dose that results in exposure to fenofibric acid that is approximately twice that at the MRHD of fenofibric acid). 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 6–18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (20 times that at the MRHD of fenofibric acid). No developmental findings were observed at 15 mg/kg/day (an exposure to fenofibric acid that is 7 times that at the MRHD of fenofibric acid).

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 an exposure to fenofibric acid that is approximately 50 times that at the MRHD of fenofibric acid [*see Nonclinical Toxicology (13.1)*].

8.3 Nursing Mothers

FIBRICOR should not be used by nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug [*see Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness of FIBRICOR in pediatric patients have not been established.

8.5 Geriatric Use

FIBRICOR is substantially excreted by the kidney as fenofibric acid and fenofibric acid glucuronide, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, the dose selection for the elderly should be made on the basis of renal function [*see Dosage and Administration (2.3) Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

The use of FIBRICOR should be avoided in patients who have severe renal impairment. Dose reduction is required in patients with mild-to-moderate renal impairment. Monitoring renal function in patients with renal impairment is recommended. [*See Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

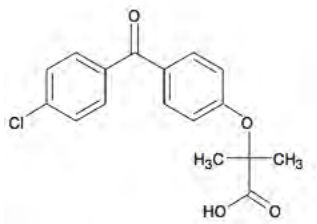
The use of FIBRICOR has not been evaluated in patients with hepatic impairment [*see Contraindications (4)*].

10 OVERDOSAGE

There is no specific treatment for overdose with FIBRICOR. 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 FIBRICOR is highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION

FIBRICOR is a lipid regulating agent available as tablets for oral administration. Each tablet contains 35 mg or 105 mg of fenofibric acid. The chemical name for fenofibric acid is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid with the following structural formula:



Fenofibric acid is a white to almost white crystalline powder that is stable under ordinary conditions, and has a melting point of 179 – 183°C. Its empirical formula is $C_{17}H_{15}ClO_4$ and molecular weight 318.75. Fenofibric acid is insoluble in water; its solubility increases with pH in buffered media.

Inactive Ingredients: Each tablet contains copovidone, crospovidone, magnesium stearate and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein 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 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.

12.2 Pharmacodynamics

Elevated levels of Total-C, LDL-C, and Apo B, and decreased levels of HDL-C and its transport complex, Apo AI and Apo AII, are risk factors for atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the levels of Total-C, LDL-C, and TG, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

The extent and rate of absorption of fenofibric acid after administration of 105 mg FIBRICOR tablets are equivalent to those after administration of 145 mg fenofibrate tablets (TriCor) under fasted conditions.

Absorption

The absolute bioavailability of FIBRICOR has not been determined. Following oral administration of FIBRICOR in healthy volunteers, median peak plasma levels of fenofibric acid occur by approximately 2.5 hours after administration. Exposure after administration of 3 X 35 mg FIBRICOR tablets is comparable to 1 X 105 mg FIBRICOR tablets.

A food-effect study involving administration of FIBRICOR to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased by approximately 35% while the AUC remained unchanged. This decrease in exposure is not considered clinically significant, and therefore FIBRICOR can be taken without regards to meals.

Distribution

Upon multiple dosing of fenofibrate, fenofibric acid steady state is achieved within 9 days. Plasma concentrations of fenofibric acid at steady state are slightly more than double those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

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 vitro and *in vivo* metabolism data indicate that fenofibric acid does not undergo oxidative metabolism (e.g. cytochrome P450) to a significant extent. The enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 do not play a role in the metabolism of fenofibric acid.

Elimination

Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once-daily dosing.

Specific Populations

Geriatrics: In five elderly volunteers 77 – 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an equivalent dose of FIBRICOR can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites *[see Use in Specific Populations (8.5)*].

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

Gender: No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race: The influence of race on the pharmacokinetics of fenofibric acid has not been studied, however fenofibric acid is not metabolized by enzymes known for exhibiting inter-ethnic variability.

Renal Impairment: The pharmacokinetics of fenofibric acid were examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl ≤ 30 mL/min) showed a 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild (CrCl 50–80 mL/min) to-moderate (CrCl 30–50 mL/min) renal impairment had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of fenofibric acid should be avoided in patients who have severe renal impairment and dose reduction is required in patients with mild-to-moderate renal impairment.

Hepatic Impairment: No pharmacokinetic studies of fenofibric acid have been conducted in patients with hepatic impairment.

Drug-Drug Interactions: An *in vitro* study using human hepatocytes indicates that fenofibric acid does not induce CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

In -vitro studies using human liver microsomes indicate that fenofibric acid is not an inhibitor of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2.

Table 2 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 3 describes the effects of co-administered fenofibric acid on exposure to other drugs.

Table 2. Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from FIBRICOR or Fenofibrate Administration

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	C_{max}
No dosing adjustment required for FIBRICOR with the following co-administered drugs				
Lipid-lowering agents				
Atorvastatin	20 mg QD for 10 days	Fenofibrate 160 mg[1] QD for 10 days	↓2%	↓4%
Pravastatin	40 mg as a single dose	Fenofibrate 3 x 67 mg[2] as a single dose	↓1%	↓2%
Fluvastatin	40 mg as a single dose	Fenofibrate 160 mg[1] as a single dose	↓2%	↓10%
Simvastatin	80 mg QD for 7 days	Fenofibrate 160 mg[1] QD for 7 days	↓5%	↓11%
Ezetimibe	10 mg QD for 10 days	Fenofibrate 145 mg[1] QD for 10 days	0%	↑3%
Anti-diabetic agents				
Glimepiride	1 mg as a single dose	Fenofibrate 145 mg[1] QD for 10 days	↑1%	↓1%
Metformin	850 mg TID for 10 days	Fenofibrate 54 mg[1] TID for 10 days	↓9%	↓6%
Rosiglitazone	8 mg QD for 5 days	Fenofibrate 145 mg[1] QD for 14 days	↑10%	↑3%

[1] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

Table 3. Effects of FIBRICOR or Fenofibrate Co-Administration on Systemic Exposure of Other Drugs

Dosage Regimen of Fenofibrate	Dosage Regimen of Co-Administered Drug	Change in Co-Administered Drug Exposure		
		Analyte	AUC	C_{max}
No dosing adjustments required for these co-administered drugs with FIBRICOR				
Lipid-lowering agents				
Fenofibrate 160 mg[1] QD for 10 days	Atorvastatin, 20 mg QD for 10 days	Atorvastatin	↓17%	0%
Fenofibrate 3 x 67 mg[2] as a single dose	Pravastatin, 40 mg as a single dose	Pravastatin	↑13%	↑13%
		3α-Hydroxyl-iso-pravastatin	↑26%	↑29%
Fenofibrate 160 mg[1] QD for 10 days	Pravastatin, 40 mg QD for 10 days	Pravastatin	↑28%	↑36%
		3α-Hydroxyl iso-pravastatin	↑39%	↑55%
Fenofibrate 160 mg[1] as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑15%	↑16%
Fenofibrate 160 mg[1] QD for 7 days	Simvastatin, 80 mg QD for 7 days	Simvastatin acid	↓36%	↓11%
		Simvastatin	↓11%	↓17%
		Active HMG-CoA Inhibitors	↓12%	↓1%
		Total HMG-CoA Inhibitors	↓8%	↓10%
Fenofibrate 145 mg[1] QD for 10 days	Ezetimibe, 10 mg QD for 10 days	Total Ezetimibe	↑43%	↑33%
		Free Ezetimibe	↑3%	↑11%
		Ezetimibe Glucuronide	↑49%	↑34%
Anti-diabetic agents				
Fenofibrate 145 mg[1] QD for 10 days	Glimepiride, 1 mg as a single dose	Glimepiride	↑35%	↑18%
Fenofibrate 54 mg[1] TID for 10 days	Metformin, 850 mg TID for 10 days	Metformin	↑3%	↑6%
Fenofibrate 145 mg[1] QD for 14 days	Rosiglitazone, 8 mg QD for 5 days	Rosiglitazone	↑6%	↓1%
Anti-viral agents				
FIBRICOR 105 mg QD for 10 days	Efavirenz, 600 mg as a single dose	Efavirenz	↓11%	↓2%

[1] TriCor (fenofibrate) oral tablet

[2] TriCor (fenofibrate) oral micronized capsule

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, Wistar rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, (approximately 0.3, 1, and 6 times the maximum recommended human (MRHD) dose on the basis of mg/sq meter surface area). At a dose of 200 mg/kg/day (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 45, and 200 mg/kg/day (approximately 1, and 6 times the human dose on the basis of mg/sq meter surface area), an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed in males at a dose that results in exposure to fenofibric acid that is 6 times the human dose. In a second 24-month rat carcinogenicity study in a different strain of rats (Sprague-Dawley), doses of 10 and 60 mg/kg/day (1.2 and 16.5 times the MRHD of fenofibric acid, based upon exposure) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 16.5 times the MRHD of fenofibrate (60 mg/kg/day).

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 of fenofibrate), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/meter^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 CF-1 mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the human dose on the basis of mg/sq meter surface area) significantly increased the liver carcinomas in both sexes at doses that result in exposure to fenofibric acid that is 3.7 times the MRHD of fenofibric acid. 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 of fenofibrate.

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.

Mutagenesis

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 and *in vivo* in the mouse micronucleus assay.

Impairment of Fertility

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 (approximately 10 times the MRHD of fenofibrate, based on mg/m^2 surface area comparisons).

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one protocol entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL.

In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 105 mg of FIBRICOR decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of some with elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 4).

Table 4: Effects of Fenofibrate in Patients with Elevated Triglycerides

Study 1	**Placebo**				**Fenofibrate**			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	7	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	9	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	7	252	227	-9.1*
HDL Cholesterol	28	35	36	4	7	34	40	19.6*
LDL Cholesterol	28	120	129	12	7	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	7	92	46	-44.7*
Study 2	**Placebo**				**Fenofibrate**			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = $p < 0.05$ vs. Placebo

14.2 Primary Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

The effects of fenofibrate at doses equivalent to 105 mg of FIBRICOR were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 5).

Table 5: Mean Percent Change in Lipid Parameters at End of Fenofibrate Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C >160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C >160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months.

* p = < 0.05 vs. Placebo

In a subset of the subjects, measurement of Apo B was conducted. Fenofibrate treatment significantly reduced Apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p < 0.0001, n=213 and 143 respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

FIBRICOR (fenofibric acid) Tablets 35 mg, are white, round tablets, debossed "AR 787" on one side and blank on the other side.

Bottles of 30	NDC 13310-101-07
Bottles of 60	NDC 13310-101-06
Bottles of 90	NDC 13310-101-90
Bottles of 100	NDC 13310-101-01
Bottles of 250	NDC 13310-101-03
Bottles of 500	NDC 13310-101-05
Bottles of 1000	NDC 13310-101-10

FIBRICOR (fenofibric acid) Tablets 105 mg, are white, modified oval tablets, debossed "AR 788" on one side and blank on the other side.

Bottles of 30	NDC 13310-102-07
Bottles of 60	NDC 13310-102-06
Bottles of 90	NDC 13310-102-90
Bottles of 100	NDC 13310-102-01
Bottles of 250	NDC 13310-102-03
Bottles of 500	NDC 13310-102-05
Bottles of 1000	NDC 13310-102-10

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

- of the potential benefits and risks of FIBRICOR [*see Clinical Studies (14); Contraindications (4); Warnings and Precautions (5); Adverse Reactions (6)*].
- of medications that should not be taken in combination with FIBRICOR [*see Drug Interactions (7)*].
- to continue to follow an appropriate lipid-modifying diet while taking FIBRICOR *[see Dosing Information (2.1)*].
- to take FIBRICOR once daily, without regard to food, at the prescribed dose [*see Dosage and Administration (2)*].
- to inform their physician of all medications, supplements, and herbal preparations they are taking and any change to their medical condition. Patients should also be advised to inform their physicians prescribing a new medication that they are taking FIBRICOR.
- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms [*see Myopathy (5.4)*].

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Manufactured for:
AR SCIENTIFIC, INC.
Philadelphia, PA 19124 USA

Manufactured by:
MUTUAL PHARMACEUTICAL COMPANY, INC.
Philadelphia, PA 19124 USA

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