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) Tablets, for oral use
Initial U.S. Approval: 1993

INDICATIONS AND USAGE

FIBRICOR is a peroxisome proliferator receptor alpha (PPARα) activator indicated as an adjunct to diet:

- to reduce triglyceride (TG) levels in adult 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 adult patients with primary hypercholesterolemia or mixed dyslipidemia (1.2).

Important Limitations of Use: Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in 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 hypercholesterolemia or mixed dyslipidemia: 105 mg/day (2.3).
- Renally impaired patients: Initial dose of 35 mg once daily (2.4).
- Geriatric patients: Select the dose on the basis of renal function (2.5).

DOSAGE FORMS AND STRENGTHS

Oral 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

- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks of myopathy and rhabdomyolysis appears to be increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil), particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism (5.2).
- Fenofibrate can increase serum transaminases. Monitor liver tests, including ALT, periodically during therapy (5.3).
- Fenofibrate can reversibly increase serum creatinine levels. Monitor renal function periodically in patients with renal insufficiency (5.4).
- Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.5).
- 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 (5.6).
- Acute hypersensitivity reactions, including anaphylaxis and angioedema, and delayed hypersensitivity reactions, including severe cutaneous adverse drug reactions have been reported postmarketing. Some cases, were life-threatening and required emergency treatment. Discontinue fenofibrate and treat patients appropriately if reactions occur (5.9).

ADVERSE REACTIONS

Most common adverse reactions (> 2% and at least 1% greater than placebo) are abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6).

To report SUSPECTED ADVERSE REACTIONS, contact Athena Bioscience at 1-833-284-3622 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Coumarin Anticoagulants (7.1)
- Bile-Acid Binding Resins (7.2)
- Immunosuppressants (7.3)
- Colchicine (7.4)

USE IN SPECIFIC POPULATIONS

- 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).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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.

Markedly elevated levels of serum triglycerides > 2000 mg/dL may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

1.2 Primary Hypercholesterolemia or Mixed Dyslipidemia

FIBRICOR is indicated as adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), triglycerides (TG), and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia or mixed dyslipidemia.

1.3 Important Limitations of Use

Fenofibrate at a dose equivalent to 105 mg of FIBRICOR was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus [*see Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

FIBRICOR can be given without regard to meals. Patients should be advised to swallow FIBRICOR tablets whole. Do not crush, dissolve or chew tablets.

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

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, thiazide diuretics and beta-blockers, are 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.

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 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. The maximum dose is 105 mg once daily.

2.3 Primary Hypercholesterolemia or Mixed Dyslipidemia

The dose of FIBRICOR is 105 mg per day.

2.4 Impaired Renal Function

In patients with mild-to-moderate renal impairment, treatment with FIBRICOR should be initiated at a dose of 35 mg once daily, 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)*].

2.5 Geriatric Patients

Dose selection for the elderly should be made on the basis of renal function [*see Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.3)*].

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)*].
- patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities [*see Warnings and Precautions (5.3)*].
- patients with preexisting gallbladder disease [*see Warnings and Precautions (5.5)*].
- patients with known hypersensitivity to fenofibric acid or fenofibrate [*see Warnings and Precautions (5.9)*].
- nursing mothers [*see Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Mortality and Coronary Heart Disease Morbidity

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

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major

adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79–1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI 0.69–0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98–1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

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).

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).

5.2 Skeletal Muscle

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). The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination [*see Clinical Pharmacology (12.3)*].

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/myositis is suspected or diagnosed.

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co-administered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine [*see Drug Interactions (7.4)*].

5.3 Liver Function

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.

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 transaminases observed with 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 35 mg to 105 mg FIBRICOR per day and was 0% in those receiving dosages equivalent to 35 mg or less FIBRICOR 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.

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

5.4 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.

5.5 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.

5.6 Coumarin Anticoagulants

Caution should be exercised when coumarin anticoagulants are given in conjunction with FIBRICOR. FIBRICOR may potentiate the anticoagulant effects of these agents resulting in prolongation of the

prothrombin time/International Normalized Ratio (PT/INR). To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the anticoagulant are recommended until the PT/INR has stabilized [*see Drug Interactions (7.1)*].

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 Hematological 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. 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.

5.9 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.

5.10 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; $p<0.01$).

5.11 Paradoxical Decreases in HDL Cholesterol Levels

There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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 function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

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**[1] **(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%[2]	1.4%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
Increased ALT	3.0%	1.6%
Increased CPK	3.0%	1.4%
Increased AST	3.4%[2]	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

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

[2] Significantly different from Placebo.

Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval 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, pancreatitis, muscle spasm, acute renal failure, hepatitis, cirrhosis, anemia, headache, arthralgia, decreases in hemoglobin, decreases in hematocrit, white blood cell decreases, asthenia, severely depressed HDL-cholesterol levels, and interstitial lung disease. Photosensitivity reactions have

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

7 DRUG INTERACTIONS

7.1 Coumarin Anticoagulants

Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the PT/INR. Caution should be exercised when coumarin anticoagulants are given in conjunction with FIBRICOR. 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 [*see Warnings and Precautions (5.6)*].

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 a bile-acid binding resin to avoid impeding its absorption.

7.3 Immunosuppressants

Immunosuppressant agents such as cyclosporine and tacrolimus 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 FIBRICOR, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using FIBRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function monitored.

7.4 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co-administered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine.

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 fenofibrate 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 0.3 times the maximum recommended human dose (MRHD), based on body surface area comparisons; mg per m^2.

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 (less than 1 times the MRHD, based on body surface area comparisons; mg per 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 6–18 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 per m^2). No developmental findings were observed at 15 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg per 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 per m^2 [*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, taking into account the importance of the drug to the mother [*see Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

FIBRICOR is 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. Since elderly patients have a higher incidence of renal impairment, dose selection for the elderly should be made on the basis of renal function [*see Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)*]. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking FIBRICOR.

8.6 Renal Impairment

The use of FIBRICOR should be avoided in patients who have severe renal impairment [*see Contraindications (4)*]. Dose reduction is required in patients with mild-to-moderate renal impairment [*see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. Monitoring renal function in patients with renal impairment is recommended.

8.7 Hepatic Impairment

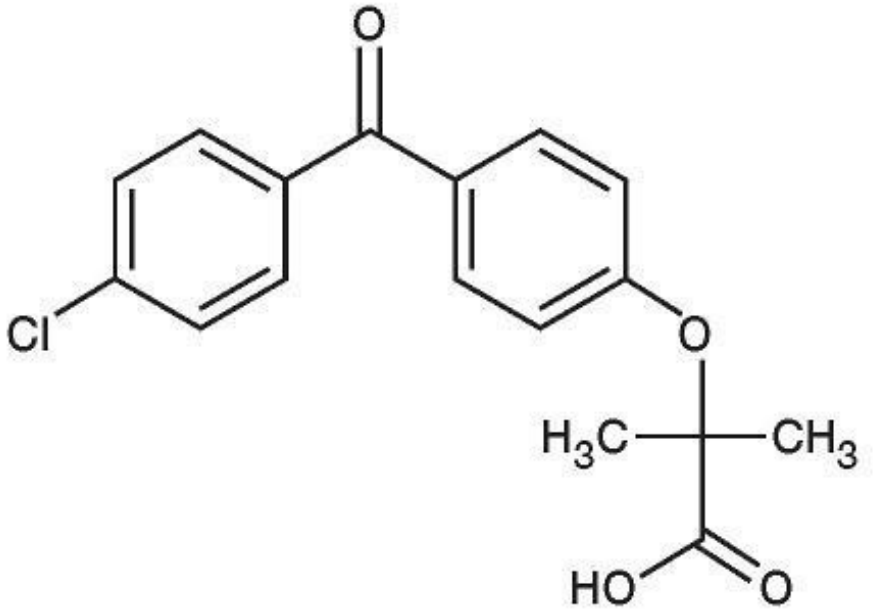
The use of FIBRICOR has not been evaluated in patients with hepatic impairment [*see Contraindications (4)*].

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 active moiety of FIBRICOR is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying 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 decrease in TG 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.

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

12.2 Pharmacodynamics

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B, an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of 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 TG, 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 apolipoproteins apo AI and apo AII.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of FIBRICOR has not been determined as the compound is virtually insoluble in aqueous media suitable for injection. 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 × 35 mg FIBRICOR tablets is comparable to 1 × 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.

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.

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

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

Specific Populations

Geriatrics: In five elderly volunteers 77 to 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)* and *Dosage and Administration (2.5)*].

Pediatrics: The pharmacokinetics of FIBRICOR has not been studied in pediatric populations.

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 was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (Estimated glomerular filtration rate [eGFR]<30 mL/min/1.73m^2) 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-to-moderate (eGFR 30 – 59 mL/min/1.73m^2) 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 FIBRICOR 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: In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C8, CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

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 once daily for 10 days	Fenofibrate 160 mg[1] once daily 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%
Anti-diabetic agents				
Glimepiride	1 mg as a single dose	Fenofibrate 145 mg[1] once daily for 10 days	↑ 1%	↓ 1%
Metformin	850 mg three times daily for 10 days	Fenofibrate 54 mg[1] three times daily for 10 days	↓ 9%	↓ 6%
Rosiglitazone	8 mg once daily for 5 days	Fenofibrate 145 mg[1] once daily 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 adjustment required for these co-administered drugs with FIBRICOR				
Lipid-lowering agents				
Fenofibrate 160 mg[1] once daily for 10 days	Atorvastatin, 20 mg once daily 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] once daily for 10 days	Pravastatin, 40 mg once daily 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%
Anti-diabetic agents				
Fenofibrate 145 mg[1] once daily for 10 days	Glimepiride, 1 mg as a single dose	Glimepiride	↑ 35%	↑ 18%
Fenofibrate 54 mg[1] three times daily for 10 days	Metformin, 850 mg three times daily for 10 days	Metformin	↑ 3%	↑ 6%
Fenofibrate 145 mg[1] once daily for 14 days	Rosiglitazone, 8 mg once daily for 5 days	Rosiglitazone	↑ 6%	↓ 1%
Anti-viral agents				
FIBRICOR 105 mg once daily for 10 days	Efavirenz, 600 mg as a single dose	Efavirenz	↓ 8%	↑ 1%

[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, based on body surface area comparisons (mg/m^2). 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 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 (Sprague-Dawley), 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 of fenofibrate), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, 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, 1, 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 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 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.

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 Severe Hypertriglyceridemia

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	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	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 Hypercholesterolemia (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[1]

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% [2]	-20.6% [2]	+11.0% [2]	-28.9% [2]
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% [2]	-31.4% [2]	+9.8% [2]	-23.5% [2]
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% [2]	-20.1% [2]	+14.6% [2]	-35.9% [2]
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

1 Duration of study treatment was 3 to 6 months.

2 $p = < 0.05$ 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).

The effect of FIBRICOR on cardiovascular morbidity and mortality has not been determined.

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 71511-501-30

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 71511-502-30

Store at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF)

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

- of the potential benefits and risks of FIBRICOR.
- not to use FIBRICOR if there is a known hypersensitivity to fenofibrate or fenofibric acid.
- that if they are taking coumarin anticoagulants, FIBRICOR may increase their anticoagulant effect, and increased monitoring may be necessary.
- of medications that should not be taken in combination with FIBRICOR.
- to continue to follow an appropriate lipid-modifying diet while taking FIBRICOR.
- to take FIBRICOR once daily, without regard to food, at the prescribed dose, swallowing each tablet whole.
- 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.
- to return to their physician's office for routine monitoring.

Manufactured for: Athena Bioscience LLC
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