HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use fenofibric acid delayed-release capsules safely and effectively. See full prescribing information for fenofibric acid delayed-release capsules.

Fenofibric acid delayed-release capsules for oral use

Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Warnings and Precautions, Skeletal Muscle **(5.2)** **09/2012**
Warnings and Precautions, Paradoxical Decreased in HDL Cholesterol Levels **(5.11)** **09/2012**

INDICATIONS AND USAGE

Fenofibric acid delayed-release capsules are a peroxisome proliferator receptor alpha (PPARα) activator indicated:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal **(1.1)**.
- As monotherapy to reduce TG in patients with severe hypertriglyceridemia **(1.2)**.
- As monotherapy 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)**.

Important Limitations of Use: No incremental benefit of fenofibric acid delayed-release capsules on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established. Fenofibrate at a dose equivalent to 135 mg of fenofibric acid delayed-release capsules was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION

- Mixed dyslipidemia: 135 mg once daily **(2.2)**.
- Hypertriglyceridemia: 45 to 135 mg once daily **(2.3)**.
- Renally impaired patients: 45 mg once daily **(2.5)**.
- Maximum dose: 135 mg once daily **(2.1)**.
- May be taken without regard to food **(2.1)**.
- May be taken at the same time as a statin **(2.2)**.
- Coadministration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks **(2.2)**.

DOSAGE FORMS AND STRENGTHS

Oral Delayed Release Capsules: 45 mg and 135 mg **(3)**.

CONTRAINDICATIONS

- Severe renal dysfunction, including patients receiving dialysis **(4, 12.3)**.
- Active liver disease **(4, 5.3)**.
- Gallbladder disease **(4, 5.4)**.
- Nursing mothers **(4, 8.3)**.
- Known hypersensitivity to fenofibric acid or fenofibrate **(4, 5.9)**.

WARNINGS AND PRECAUTIONS

- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks for myopathy and rhabdomyolysis are increased when fibrates are coadministered with a statin (with a significantly higher rate observed for gemfibrozil), particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism **(5.1)**.
- Fenofibric acid delayed-release capsules can increase serum transaminases. Liver tests should be monitored periodically **(5.3)**.
- Fenofibric acid delayed-release capsules can reversibly increase serum creatinine levels **(5.2)**. Renal function should be monitored periodically in patients with renal insufficiency **(8.6)**.
- Fenofibric acid delayed-release capsules increase cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated **(5.4)**.
- 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 **(5.5)**.

ADVERSE REACTIONS

The most common adverse events (≥ 3% of patients receiving fenofibric acid delayed-release capsules or fenofibric acid delayed-release capsules coadministered with statins) are headache, back pain, nasopharyngitis, nausea, myalgia, diarrhea, and upper respiratory tract infection **(6.1)**.

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 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)**.

USE IN SPECIFIC POPULATIONS

- Geriatric Use: Dose selection for the elderly should be made on the basis of renal function **(8.5)**.
- Renal Impairment: Fenofibric acid delayed-release capsules should be avoided in patients with severe renal impairment. Dose adjustment is required in patients with mild to moderate renal impairment **(8.6)**.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

010209A-02

FENOFIBRIC ACID
DELAYED-RELEASE CAPSULES
R06/13

010209A-02

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Coadministration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Fenofibric acid delayed-release capsules are indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD > 20%

1.2 Treatment of Severe Hypertriglyceridemia

Fenofibric acid delayed-release capsules are indicated as adjunctive therapy to diet to reduce TG in patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacological intervention. Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibric acid delayed-release capsules therapy on reducing this risk has not been adequately studied.

1.3 Treatment of Primary Hypercholesterolemia or Mixed Dyslipidemia

Fenofibric acid delayed-release capsules are 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.

1.4 Important Limitations of Use

No incremental benefit of fenofibric acid delayed-release capsules on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established. Fenofibrate at a dose equivalent to 135 mg of fenofibric acid delayed-release capsules was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus.

1.5 General Considerations for Treatment

Laboratory studies should be performed to establish that lipid levels are abnormal before instituting fenofibric acid delayed-release capsules therapy.

Every reasonable attempt should be made to control serum lipids with non-drug methods including appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that may be contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible, and excessive alcohol intake should be addressed before triglyceride-lowering drug therapy is considered. If the decision is made to use lipid-altering drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Drug therapy is not indicated for patients who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of VLDL.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Patients should be placed on an appropriate lipid-lowering diet before receiving Fenofibric Acid Delayed-Release Capsules as monotherapy or coadministered with a statin, and should continue this diet during treatment. Fenofibric acid delayed-release capsules can be taken without regard to meals. Patients should be advised to swallow fenofibric acid delayed-release capsules whole. Do not open, crush, dissolve, or chew capsules. Serum lipids should be monitored periodically.

2.2 Coadministration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Fenofibric acid delayed-release capsules 135 mg may be coadministered with an HMG-CoA reductase inhibitor (statin) in patients with mixed dyslipidemia. For convenience, the daily dose of fenofibric acid delayed-release capsules may be taken at the same time as a statin, according to the dosing recommendations for each medication. Coadministration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks.

2.3 Severe Hypertriglyceridemia

The initial dose of fenofibric acid delayed-release capsules is 45 to 135 mg once daily. 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 135 mg once daily.

2.4 Primary Hypercholesterolemia or Mixed Dyslipidemia

The dose of fenofibric acid delayed-release capsules is 135 mg once daily.

2.5 Impaired Renal Function

Treatment with fenofibric acid delayed-release capsules should be initiated at a dose of 45 mg once daily in patients with mild to moderate renal impairment and should only be increased after evaluation of the effects on renal function and lipid levels at this dose. The use of fenofibric acid delayed-release capsules should be avoided in patients with severely impaired renal function *[see* **Use in Specific Populations (8.6)** *and* **Clinical Pharmacology (12.3)***]*.

2.6 Geriatric Patients

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

3 DOSAGE FORMS AND STRENGTHS

- 45 mg fenofibric acid delayed-release capsules with a dark brown opaque cap and yellow opaque body imprinted with "Par" on the cap and "C209" on the body in black ink.
- 135 mg fenofibric acid delayed release capsules with a light blue opaque cap and yellow opaque body imprinted with "Par" on the cap and "C210" on the body in black ink.

4 CONTRAINDICATIONS

Fenofibric acid delayed-release capsules are 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)***]*.
- nursing mothers *[see* **Use in Specific Populations (8.3)***]*.
- patients with hypersensitivity to fenofibric acid or fenofibrate *[see* **Warnings and Precautions (5.9)***]*.

When fenofibric acid delayed-release capsules are coadministered with a statin, refer to the *Contraindications* section of the respective statin labeling.

5 WARNINGS AND PRECAUTIONS

5.1 Mortality and Coronary Heart Disease Morbidity

The effect of fenofibric acid delayed-release capsules on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. Because of similarities between fenofibric acid delayed-release capsules and fenofibrate, clofibrate, and gemfibrozil, the findings in the following large randomized, placebo-controlled clinical studies with these fibrate drugs may also apply to fenofibric acid delayed-release capsules.

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 to 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 to 0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98 to 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 to 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 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 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 WHO study (RR = 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 (hazard ratio 2.2, 95% confidence interval: 0.94 to 5.05).

5.2 Skeletal Muscle

Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are coadministered with a statin (with a numerically higher rate observed with gemfibrozil/statin combination use compared to fenofibrate/statin combination use). Refer to the respective statin labeling for important drug-drug interactions that increase statin levels and could increase this risk. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.

In phase 3 clinical trials with fenofibric acid delayed-release capsules, myalgia was reported in 3.3% of patients treated with fenofibric acid delayed-release capsules monotherapy and 3.1% to 3.5% of patients treated with fenofibric acid delayed-release capsules coadministered with statins compared to 4.7% to 6.1% of patients treated with statin monotherapy. Increases in creatine phosphokinase (CPK) to > 5 times upper limit of normal occurred in no patients treated with fenofibric acid delayed-release capsules monotherapy and 0.2% to 1.2% of patients treated with fenofibric acid delayed-release capsules coadministered with statins compared to 0.4% to 1.3% of patients treated with statin monotherapy.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibric acid delayed-release capsules and statin therapy should be discontinued if markedly elevated CPK levels occur or myopathy or myositis is suspected or diagnosed.

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

5.3 Liver Function

Fenofibric acid delayed-release capsules at a dose of 135 mg once daily administered as monotherapy or coadministered with low to moderate doses of statins has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of three double-blind controlled studies of fenofibric acid delayed-release capsules administered as monotherapy or in combination with statins, increases to > 3 times the upper limit of normal on two consecutive occasions in ALT and AST occurred in 1.9% and 0.2%, respectively, of patients receiving fenofibric acid delayed-release capsules monotherapy and in 1.3% and 0.4%, respectively, of patients receiving fenofibric acid delayed-release capsules coadministered with statins. Increases to > 3 times the upper limit of normal in ALT and AST occurred in no patients receiving low- to moderate-dose statin monotherapy. Increases to > 3 times the upper limit of normal in ALT and AST occurred in 0.8% and 0.4%, respectively in patients receiving high-dose statin monotherapy. In a long-term study of fenofibric acid delayed-release capsules coadministered with statins for up to 52 weeks, increases of > 3 times the upper limit of normal on two consecutive occasions of ALT and AST occurred in 1.2% and 0.5% of patients, respectively. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. Increases in ALT and/or AST were not accompanied by increases in bilirubin or clinically significant increases in alkaline phosphatase.

In a pooled analysis of 10 placebo-controlled trials of fenofibrate, increases to > 3 times the upper limit of normal in 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. In an 8- week dose-ranging study of fenofibrate in hypertriglyceridemia, the incidence of ALT or AST elevations ≥ 3 times the upper limit of normal was 13% in patients receiving dosages equivalent to 90 mg to 135 mg fenofibric acid delayed-release capsules once daily and was 0% in those receiving dosages equivalent to 45 mg fenofibric acid delayed-release capsules once daily or less, or placebo. Hepatocellular, chronic active, and cholestatic hepatitis observed 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 monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibric acid delayed-release capsules, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal.

5.4 Serum Creatinine

Reversible elevations in serum creatinine have been reported in patients receiving fenofibric acid delayed-release capsules as monotherapy or coadministered with statins as well as patients receiving fenofibrate. In the pooled analysis of three double- blind controlled studies of fenofibric acid delayed-release capsules administered as monotherapy or in combination with statins, increases in creatinine to > 2 mg/dL occurred in 0.8% of patients treated with fenofibric acid delayed-release capsules monotherapy and 1.1% to 1.3% of patients treated with fenofibric acid delayed-release capsules coadministered with statins compared to 0% to 0.4% of patients treated with statin monotherapy. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long-term therapy and tended to return to baseline following discontinuation of treatment. The clinical significance of these observations is unknown. Monitoring renal function in patients with renal impairment taking fenofibric acid delayed-release capsules is suggested. Renal monitoring should be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

5.5 Cholelithiasis

Fenofibric acid delayed-release capsules, like fenofibrate, clofibrate, and gemfibrozil, may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibric acid delayed-release capsules therapy should be discontinued if gallstones are found.

5.6 Coumarin Anticoagulants

Caution should be exercised when fenofibric acid delayed-release capsules is given in conjunction with oral coumarin anticoagulants. Fenofibric acid delayed-release capsules may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time/International Normalized Ratio (PT/INR). Frequent monitoring of PT/INR and dose adjustment of the oral anticoagulant are recommended until the PT/INR has stabilized in order to prevent bleeding complications *[see* **Drug Interactions (7.1)***]*.

5.7 Pancreatitis

Pancreatitis has been reported in patients taking drugs of the fibrate class, including fenofibric acid delayed-release capsules. 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 fenofibric acid delayed-release capsules and fenofibrate therapy. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrates. Periodic monitoring of red and white blood cell counts are recommended during the first 12 months of fenofibric acid delayed-release capsules administration.

5.9 Hypersensitivity Reactions

Acute hypersensitivity reactions such as Stevens-Johnson syndrome and toxic necrolysis requiring patient hospitalization and treatment with steroids have been reported in individuals treated with fenofibrates.

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 PE 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 studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug.

Fenofibric acid delayed-release capsules

Monotherapy

Treatment-emergent adverse events reported in 3% or more of patients treated with fenofibric acid delayed-release capsules during the randomized controlled trials are listed in **Table 1** below.

Coadministration Therapy with Statins (Double-blind Controlled Trials)

Treatment-emergent adverse events reported in 3% or more of patients treated with fenofibric acid delayed-release capsules coadministered with statins during the randomized controlled trials are listed in **Table 1** below.

Table 1. Treatment-Emergent Adverse Events Reported in ≥3% of Patients Receiving Fenofibric Acid Delayed-Release Capsules or Fenofibric Acid Delayed-Release Capsules Coadministered with a Statin During Double-Blind Controlled Studies [Number (%)]

Adverse Event	Fenofibric Acid Delayed-Release Capsules (N = 490)	Low-Dose Statin (N = 493)	Fenofibric Acid Delayed-Release Capsules + Low-Dose Statin (N = 490)	Moderate-Dose Statin (N = 491)	Fenofibric Acid Delayed-Release Capsules + Moderate-Dose Statin (N = 489)	High-Dose Statin (N = 245)
Gastrointestinal Disorders						
Constipation	16 (3.3)	11 (2.2)	16 (3.3)	13 (2.6)	15 (3.1)	6 (2.4)
Diarrhea	19 (3.9)	16 (3.2)	15 (3.1)	24 (4.9)	18 (3.7)	17 (6.9)
Dyspepsia	18 (3.7)	13 (2.6)	13 (2.7)	17 (3.5)	23 (4.7)	6 (2.4)
Nausea	21 (4.3)	18 (3.7)	17 (3.5)	22 (4.5)	27 (5.5)	10 (4.1)
General Disorders and Administration Site Conditions						
Fatigue	10 (2.0)	13 (2.6)	13 (2.7)	13 (2.6)	16 (3.3)	5 (2.0)
Pain	17 (3.5)	9 (1.8)	16 (3.3)	8 (1.6)	7 (1.4)	8 (3.3)
Infections and Infestations						
Nasopharyngitis	17 (3.5)	29 (5.9)	24 (4.7)	16 (3.3)	21 (4.3)	9 (3.7)
Sinusitis	16 (3.3)	4 (0.8)	14 (2.9)	8 (1.6)	17 (3.5)	4 (1.6)
Upper Respiratory Tract Infection	26 (5.3)	13 (2.6)	18 (3.7)	23 (4.7)	23 (4.7)	7 (2.9)
Investigations						
ALT Increased	6 (1.2)	2 (0.4)	15 (3.1)	2 (0.4)	12 (2.5)	4 (1.6)
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	19 (3.9)	22 (4.5)	21 (4.3)	21 (4.3)	17 (3.5)	12 (4.9)
Back Pain	31 (6.3)	31 (6.3)	30 (6.3)	32 (6.5)	20 (4.1)	8 (3.3)
Muscle Spasms	8 (1.6)	18 (3.7)	12 (2.4)	24 (4.9)	15 (3.1)	6 (2.4)
Myalgia	16 (3.3)	24 (4.9)	17 (3.5)	23 (4.7)	15 (3.1)	15 (6.1)
Pain in Extremity	22 (4.5)	24 (4.9)	14 (2.9)	21 (4.3)	13 (2.7)	9 (3.7)
Nervous System Disorders						
Dizziness	20 (4.1)	8 (1.6)	19 (3.9)	11 (2.2)	16 (3.3)	2 (0.8)
Headache	62 (12.7)	64 (13.0)	64 (13.1)	82 (16.7)	58 (11.9)	32 (13.1)

Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg

Coadministration Therapy with Statins (Long-Term Exposure for up to 64 Weeks)

Patients successfully completing any one of the three double-blind, controlled studies were eligible to participate in a 52-week long-term extension study where they received fenofibric acid delayed-release capsules coadministered with the moderate dose statin. A total of 2201 patients received at least one dose of fenofibric acid delayed-release capsules coadministered with a statin in the double-blind controlled study or the long-term extension study for up to a total of 64 weeks of treatment. Additional treatment-emergent adverse events (not listed in **Table 1** above) reported in 3% or more of patients receiving fenofibric acid delayed-release capsules coadministered with a statin in either the double-blind controlled studies or the long-term extension study are provided below.

Infections and Infestations
Bronchitis, influenza, and urinary tract infection.

Investigations
AST increased, blood CPK increased, and hepatic enzyme increased.

Musculoskeletal and Connective Tissue Disorders
Musculoskeletal pain.

Psychiatric Disorders
Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders
Cough and pharyngolaryngeal pain.

Vascular Disorders
Hypertension.

Fenofibrate

Fenofibric acid is the active metabolite of fenofibrate. Adverse events reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials are listed in **Table 2**. 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 tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

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

BODY SYSTEM Adverse Event	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%
INVESTIGATIONS		
Abnormal Liver Tests	7.5%	1.4%
Increased AST	3.4%	0.5%
Increased ALT	3.0%	1.6%
Increased Creatine Phosphokinase	3.0%	1.4%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 135 mg fenofibric acid delayed-release capsules

6.2 Postmarketing Experience

The following adverse events have been identified during postapproval use of fenofibrate: myalgia, rhabdomyolysis, pancreatitis, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, anemia, arthralgia, asthenia, and severely depressed HDL-cholesterol levels.

Because these events 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.

7 DRUG INTERACTIONS

7.1 Coumarin Anticoagulants

Potentiation of coumarin-type anticoagulant effect has been observed with prolongation of the PT/INR.

Caution should be exercised when oral coumarin anticoagulants are given in conjunction with fenofibric acid delayed-release capsules. The dosage of the anticoagulant should be reduced to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that the PT/INR has stabilized *[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 fenofibric acid delayed-release capsules at least 1 hour before or 4 to 6 hours after a bile acid resin to avoid impeding its absorption.

7.3 Immunosuppressants

Immunosuppressants 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 drugs of the fibrate class including fenofibric acid delayed-release capsules, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using fenofibric acid delayed-release capsules with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

7.4 Colchicine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category: C

The safety of fenofibric acid delayed-release capsules in pregnant women has not been established. There are no adequate and well controlled studies of fenofibric acid delayed-release capsules in pregnant women. Fenofibric acid delayed-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When fenofibric acid delayed-release capsules are administered with a statin in a woman of childbearing potential, refer to pregnancy category and product labeling for the statin. All statins are contraindicated in pregnant women.

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 maximum recommended human dose [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/m^2). 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.

8.3 Nursing Mothers

Fenofibric acid delayed-release capsules should not be used in 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.

8.4 Pediatric Use

The safety and effectiveness of fenofibric acid delayed-release capsules monotherapy or coadministration with a statin in pediatric patients have not been established.

8.5 Geriatric Use

Fenofibric acid delayed-release capsules are 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. 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 (2.6)** *and* **Clinical Pharmacology (12.3)***]*. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking fenofibric acid delayed-release capsules.

8.6 Renal Impairment

The use of fenofibric acid delayed-release capsules 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 (2.5)** *and* **Clinical Pharmacology (12.3)***]*. Monitoring renal function in patients with renal impairment is recommended.

8.7 Hepatic Impairment

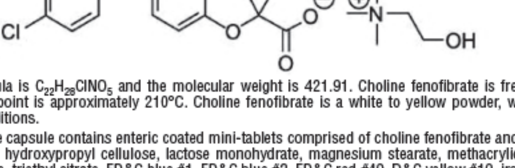
The use of fenofibric acid delayed-release capsules has not been evaluated in subjects with hepatic impairment *[see* **CONTRAINDICATIONS (4)** *and* **Clinical Pharmacology (12.3)***]*.

10 OVERDOSAGE

There is no specific treatment for overdose with fenofibric acid delayed-release capsules. 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 fenofibric acid delayed-release capsules are highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION

Fenofibric Acid Delayed-Release Capsules are a lipid regulating agent available as delayed release capsules for oral administration. Each delayed release capsule contains choline fenofibrate, equivalent to 45 mg or 135 mg of fenofibric acid. The chemical name for choline fenofibrate is ethanaminium, 2-hydroxy-N,N,N-trimethyl, 2-{4-(4-chlorobenzoyl)phenoxy] -2-methylpropanoate (1:1) with the following structural formula:



The empirical formula is $C_{22}H_{28}ClNO_5$ and the molecular weight is 421.91. Choline fenofibrate is freely soluble in water. The melting point is approximately 210°C. Choline fenofibrate is a white to yellow powder, which is stable under ordinary conditions.

Each delayed release capsule contains enteric coated mini-tablets comprised of choline fenofibrate and the following inactive ingredients: hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer, stearic acid, talc, triethyl citrate, FD&C blue #1, FD&C blue #2, FD&C red #40, D&C yellow #10, iron oxide black, propylene glycol, and shellac. Additionally, the 45 mg capsule shell contains black iron oxide, D&C yellow #10, FD&C yellow #6, gelatin, red iron oxide, titanium dioxide and yellow iron oxide. The 135 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C yellow #6, gelatin and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active moiety of fenofibric acid delayed-release capsules 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 Apo CIII (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 (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 HDL-C and Apo AI and AII.

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 human 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.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in TC, LDL-C, Apo B, TG, and triglyceride-rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibric acid results in increases in HDL-C and Apo AI and Apo AII.

12.3 Pharmacokinetics

Fenofibric acid delayed-release capsules contain fenofibric acid, which is the only circulating pharmacologically active moiety in plasma after oral administration of fenofibric acid delayed-release capsules. Fenofibric acid is also the circulating pharmacologically active moiety in plasma after oral administration of fenofibrate, the ester of fenofibric acid.

Plasma concentrations of fenofibric acid after administration of one 135 mg fenofibric acid delayed-release capsule are equivalent to those after one 200 mg capsule of micronized fenofibrate administered under fed conditions.

Absorption

Fenofibric acid is well absorbed throughout the gastrointestinal tract. The absolute bioavailability of fenofibric acid is approximately 81%.

Peak plasma levels of fenofibric acid occur within 4 to 5 hours after a single dose administration of fenofibric acid delayed-release capsule under fasting conditions.

Fenofibric acid exposure in plasma, as measured by C_{max} and AUC, is not significantly different when a single 135 mg dose of fenofibric acid delayed-release capsules is administered under fasting or nonfasting conditions.

Distribution

Upon multiple dosing of fenofibric acid delayed-release capsules, fenofibric acid levels reach steady state within 8 days. Plasma concentrations of fenofibric acid at steady state are approximately slightly more than double those following a single dose. Serum protein binding is approximately 99% in normal and dyslipidemic 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 vivo metabolism data after fenofibrate administration indicate that fenofibric acid does not undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Elimination

After absorption, fenofibric acid delayed-release capsules are primarily excreted in the urine in the form of fenofibric acid and fenofibric acid glucuronide.

Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once daily administration of fenofibric acid delayed-release capsules.

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 fenofibric acid delayed-release capsules 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

The pharmacokinetics of fenofibric acid delayed-release capsules have not been studied in pediatric populations.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibric acid delayed-release capsules.

Race

The influence of race on the pharmacokinetics of fenofibric acid delayed-release capsules 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/1.73 m^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 renal impairment (eGFR 30-59 mL/min/1.73 m^2) 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 delayed-release capsules should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment *[see* **Dosage and Administration (2.5)***]*.

Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic impairment.

Drug-drug Interactions

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. It is a weak inhibitor of CYP2C8, CYP2C19, and CYP2A6, and mild-to-moderate inhibitor of CYP2C9 at therapeutic concentrations.

Comparison of atorvastatin exposures when atorvastatin (80 mg once daily for 10 days) is given in combination with fenofibric acid (fenofibric acid delayed-release capsules 135 mg once daily for 10 days) and ezetimibe (10 mg once daily for 10 days) versus when atorvastatin is given in combination with ezetimibe only (ezetimibe 10 mg once daily and atorvastatin, 80 mg once daily for 10 days): The C_{max} decreased by 1% for atorvastatin and ortho-hydroxy-atorvastatin and increased by 2% for parahydroxy-atorvastatin. The AUC decreased 6% and 9% for atorvastatin and orthohydroxy-atorvastatin, respectively, and did not change for para-hydroxy-atorvastatin.

Comparison of ezetimibe exposures when ezetimibe (10 mg once daily for 10 days) is given in combination with fenofibric acid (fenofibric acid delayed-release capsules 135 mg once daily for 10 days) and atorvastatin (80 mg once daily for 10 days) versus when ezetimibe is given in combination with atorvastatin only (ezetimibe 10 mg once daily and atorvastatin, 80 mg once daily for 10 days): The C_{max} increased by 26% and 7% for total and free ezetimibe, respectively. The AUC increased by 27% and 12% for total and free ezetimibe, respectively.

Table 3 describes the effects of coadministered drugs on fenofibric acid systemic exposure.

Table 4 describes the effects of coadministered fenofibric acid on other drugs.

Table 3. Effects of Coadministered Drugs on Fenofibric Acid Systemic Exposure from Fenofibric Acid Delayed-Release Capsules or Fenofibrate Administration

Coadministered Drug	Dosage Regimen of Coadministered Drug	Dosage Regiment of Fenofibric Acid Delayed-Release Capsules or Fenofibrate	Changes in Fenofibric Acid Exposure: AUC	C_{max}
Lipid-lowering agents				
Rosuvastatin	40 mg once daily for 10 days	Fenofibric Acid Delayed-Release Capsules 135 mg once daily for 10 days	↓2%	↓2%
Atorvastatin	20 mg once daily for 10 days	Fenofibrate 160 mg[1] once daily for 10 days	↓2%	↓4%
Atorvastatin + ezetimibe	Atorvastatin, 80 mg once daily and ezetimibe, 10 mg once daily for 10 days	Fenofibric Acid Delayed-Release Capsules 135 mg once daily for 10 days	↑5%	↑5%
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 once daily for for 7 days	Fenofibrate 160 mg[1] once daily for 7 days	↓5%	↓11%
Anti-diabetic agents				
Glimepiride	1 mg as a single dose	Fenofibrate 145 mg[1] once daily for 10 days	↑1%	↓1%
Metformin	850 mg 3 times daily for 10 days	Fenofibrate 54 mg[1] 3 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%
Gastrointestinal agents				
Omeprazole	40 mg once daily for 5 days	Fenofibric Acid Delayed-Release Capsules 135 mg as a single dose fasting	↑6%	↑17%
Omeprazole	40 mg once daily for 5 days	Fenofibric Acid Delayed-Release Capsules 135 mg as a single dose with food	↑4%	↓2%

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

Table 4. Effects of Fenofibric Acid Delayed-Release Capsules or Fenofibrate Coadministration on Systemic Exposure of Other Drugs

Dosage Regimen of Fenofibric Acid Delayed-Release Capsules or Fenofibrate	Dosage Regimen of Coadministered Drug	Changes in Coadministered Exposure: Analyte	AUC	C_{max}
Lipid-lowering agents				
Fenofibric Acid Delayed-Release Capsules 135 mg once daily for 10 days	Rosuvastatin, 40 mg once daily for 10 days	Rosuvastatin	↑6%	↑20%
Fenofibrate 160 mg[1] once daily for 10 days	Atorvastatin, 20 mg once daily for 10 days	Atorvastatin	↓17%	0%
Fenofibrate once daily 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 as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑15%	↑16%
Fenofibrate 160 mg[1] once daily for 7 days	Simvastatin, 80 mg once daily for 7 days	Simvastatin acid	↓36%	↓11%
		Simvastatin	↓11%	↓17%
		Active HMG-CoA Inhibitors	↓12%	↓1%
		Total HMG-CoA Inhibitors	↓8%	↓10%
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] 3 times daily for 10 days	Metformin, 850 mg 3 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%

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fenofibric acid delayed-release capsules

No carcinogenicity and fertility studies have been conducted with choline fenofibrate or fenofibric acid. However, because fenofibrate is rapidly converted to its active metabolite, fenofibric acid, either during or immediately following absorption both in animals and humans, studies conducted with fenofibrate are relevant for the assessment of the toxicity profile of fenofibric acid. A similar toxicity spectrum is expected after treatment with either fenofibric acid delayed-release capsules or fenofibrate.

Fenofibrate

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 dose (MRHD), 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 interstitial cell tumors of the testes 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 MRHD). 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 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 and 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.

Mutagenesis: Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, and micronucleus *in vivo*/rat. In addition, fenofibric acid, has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and sister chromatid exchange in human lymphocytes, and unscheduled DNA synthesis in primary rat hepatocytes.

Impairment of Fertility: In a fertility study, rats were given oral dietary doses of fenofibrate. Males received doses for 61 days prior to mating and females for 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).

14 CLINICAL STUDIES

14.1 Coadministration Therapy with Statins

Efficacy and safety of fenofibric acid delayed-release capsules coadministered with statins were assessed in three 12-week, double-blind, controlled Phase 3 studies and one 52-week, long-term, open-label extension study in 2698 patients with mixed dyslipidemia. Patients were required to meet the following fasting lipid entry criteria: TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL (males) and < 50 mg/dL (females), and LDL-C ≥ 130 mg/dL. The three multicenter, randomized, double-blind, controlled studies had similar designs, differing primarily in the statin used for combination therapy/monotherapy. Each study compared the effects of 135 mg fenofibric acid delayed-release capsules coadministered with either a low dose or a moderate dose of statin with fenofibric acid delayed-release capsules monotherapy and statin monotherapy at the corresponding dose on CHD lipid risk factors. A smaller group of patients received a high dose of statin monotherapy. In study 1, patients received fenofibric acid delayed-release capsules coadministered with 10 mg or 20 mg rosuvastatin. In study 2, patients received fenofibric acid delayed-release capsules coadministered with 20 mg or 40 mg simvastatin. In study 3, patients received fenofibric acid delayed-release capsules coadministered with 20 mg or 40 mg atorvastatin.

Patients were enrolled for a total of approximately 22 weeks, consisting of a 6-week diet run-in/washout period, a 12-week treatment period, and a 30-day safety follow up period. Patients who completed the 12- week treatment period were eligible to participate in the 52-week long-term extension study. Of the 2698 randomized and treated subjects in the controlled studies, 51.6% were female and 48.4% were male; 92.6% of all subjects were White, 4.7% were Black, and 2.8% were of other races. Hispanics comprised 9.9% of the study population. Mean age was 54.9 years.

The primary efficacy endpoints for all three studies were mean percent changes from baseline to final value in HDL-C, TG, and LDL-C. For each statin dose coadministered with fenofibric acid delayed-release capsules, there were three primary comparisons. For HDL-C and TG, fenofibric acid delayed-release capsules coadministered with each statin dose was compared with statin monotherapy at the corresponding dose. For LDL-C, fenofibric acid delayed-release capsules coadministered with each statin dose was compared with fenofibric acid delayed-release capsules monotherapy. In order to declare combination therapy successful for a particular statin dose, all three primary comparisons were required to demonstrate superiority of the combination therapy over the corresponding monotherapy. The primary efficacy results were consistent in the three studies and were confirmed by the pooled analysis of the three studies. The results from the individual studies and the pooled analysis demonstrated that fenofibric acid delayed-release capsules coadministered with low-dose statins and moderate-dose statins was superior to the corresponding monotherapy. Statistically significant differences were observed for all three primary efficacy comparisons for both doses of combination therapy in all three double-blind, controlled studies as well as the pooled analysis.

In the pooled analysis, fenofibric acid delayed-release capsules coadministered with both low-dose statins and moderate-dose statins resulted in mean percent increases (18.1% and 17.5%) in HDL-C and mean percent decreases (-43.9% and -42.0%) in TG that were significantly greater than the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C; -16.8% and -23.7% for TG). In addition, both doses of combination therapy resulted in mean percent decreases (-33.1% and -34.6%) in LDL-C that were significantly greater than fenofibric acid delayed-release capsules monotherapy (-5.1%). The results of the pooled analysis are described in **Table 5**.

Table 5. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C (Pooled Double-Blind, Controlled Studies)

	Fenofibric Acid Delayed-Release Capsules	Low-Dose Statin	Fenofibric Acid Delayed-Release Capsules + Low-Dose Statin	Between-Groups Δ (p-value)	Moderate-Dose Statin	Fenofibric Acid Delayed-Release Capsules + Moderate-Dose Statin	Between-Groups Δ (p-value)	High Dose Statin
HDL-C (mg/dL)	(N = 420)	(N = 455)	(N = 423)		(N = 430)	(N = 422)		(N = 217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Mean %Δ	16.3%	7.4%	18.1%	10.7%[a] (<0.001)	8.7%	17.5%	8.8%[a] (<0.001)	7.9%
TG (mg/dL)	(N = 459)	(N = 477)	(N = 470)		(N = 472)	(N = 462)		(N = 235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Mean %Δ	-31.0%	-16.8%	-43.9%	-27.2%[a] (<0.001)	-23.7%	-42.0%	-18.3%[a] (<0.001)	-28.1%
LDL-C (mg/dL)	(N = 427)	(N = 463)	(N = 436)		(N = 439)	(N = 434)		(N = 225)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Mean %Δ	-5.1%	-33.9%	-33.1%	-28.0%[b] (<0.001)	-40.6%	-34.6%	-29.5%[b] (<0.001)	-47.1%

[a] Combination therapy vs. corresponding statin monotherapy
[b] Combination therapy vs. fenofibric acid delayed-release capsules monotherapy
Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg
BL = Baseline
%Δ = Percent change from baseline to final value

Secondary efficacy endpoints in all three double-blind, controlled studies were percent changes in non-HDL-C (fenofibric acid delayed-release capsules coadministered with statin compared to fenofibric acid delayed-release capsules monotherapy and corresponding statin monotherapy), and percent changes in VLDL-C, Total-C, and Apo B (fenofibric acid delayed-release capsules coadministered with statin compared to corresponding statin monotherapy). Coadministration of fenofibric acid delayed-release capsules with statins resulted in the following changes in secondary parameters (**Table 6**).

Table 6. Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, and Apo B (Pooled Double-Blind, Controlled Studies)

Secondary Endpoints	Fenofibric Acid Delayed-Release Capsules	Low-Dose Statin	Fenofibric Acid Delayed-Release Capsules + Low-Dose Statin	Between-Groups Δ	Moderate-Dose Statin	Fenofibric Acid Delayed-Release Capsules + Moderate-Dose Statin	Between-Groups Δ	High-Dose Statin
Non HDL-C (mg/dL)	(N = 420)	(N = 454)	(N = 422)		(N = 431)	(N = 420)		(N = 217)
BL mean	222.5	217.6	219.9		222.4	218.9		220.2
Mean %Δ	-17.3%	-34.9%	-40.4%	-23.1%[a] -5.5%[b]	-42.4%	-42.0%	-24.8%[a] 0.4%[b]	-47.3%
VLDL-C (mg/dL)	(N = 449)	(N = 463)	(N = 455)		(N = 458)	(N = 449)		(N = 232)
BL mean	65.0	66.0	65.5		67.8	64.5		66.1
Mean %Δ	-34.2%	-32.1%	-50.0%	-18.0%[b]	-38.9%	-51.2%	-12.3%[b]	-42.1%
Total-C (mg/dL)	(N = 459)	(N = 477)	(N = 469)		(N = 472)	(N = 462)		(N = 235)
BL mean	260.9	257.0	258.6		261.3	257.3		258.8
Mean %Δ	-12.4%	-28.7%	-31.5%	-2.8%[b]	-34.7%	-33.3%	1.4%[b]	-39.5%
Apo B (mg/dL)	(N = 455)	(N = 470)	(N = 465)		(N = 468)	(N = 455)		(N = 229)
BL mean	146.2	145.0	146.1		147.1	145.0		146.0
Mean %Δ	-15.6%	-31.1%	-36.3%	-5.2%[b]	-36.9%	-36.7%	0.2%[b]	-42.4%

[a] Fenofibric acid delayed-release capsules + statin vs. fenofibric acid delayed-release capsules monotherapy
[b] Fenofibric acid delayed-release capsules + statin vs. corresponding statin monotherapy
Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg
BL = Baseline
% Δ = Percent change from baseline to final value

A total of 1895 patients who completed 12 weeks of treatment in the double-blind, controlled studies were treated in the 52-week, long-term extension study. Patients received fenofibric acid delayed-release capsules coadministered with the moderate-dose of the statin that had been used in the double-blind, controlled study in which they were enrolled. Whether combination therapy was initiated during the double-blind, controlled studies or introduced during the long-term extension study, the treatment effect of combination therapy was observed within four weeks, and was sustained over the duration of treatment in the long-term study. A total of 568 patients completed 52 weeks of treatment with fenofibric acid delayed-release capsules coadministered with statins. Mean 52-week values and mean percent change from baseline (at time of enrollment in randomized controlled trials) were 91.7 mg/dL (-38.2%) for LDL-C, 47.3 mg/dL (+24.0%) for HDL-C, 135.5 mg/dL (-47.6%) for TG, 117.9 mg/dL (-45.7%) for non-HDL-C, 26.2 mg/dL (-53.1%) for VLDL-C, 165.2 mg/dL (-35.4%) for Total-C, and 81.4 mg/dL (-43.6%) for Apo B.

14.2 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 entered patients with baseline 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 135 mg once daily of fenofibric acid delayed-release capsules decreased primarily VLDL-TG and VLDL-C. Treatment of patients with elevated TG often results in an increase of LDL-C (**Table 7**).

Table 7. Effects of Fenofibrate in Patients With Severe Hypertriglyceridemia

Study 1	**Placebo**				**Fenofibrate**			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
Triglycerides	28	449	450	-0.5	27	432	223	-42.6*
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 (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
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

14.3 Primary Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

The effects of fenofibrate at a dose equivalent to fenofibric acid delayed-release capsules 135 mg once daily 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 **(Table 8)**.

Table 8. Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Pooled Cohort				
Mean baseline lipid values (n = 646)	306.9	213.8	52.3	191.0
All Fenofibrate (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				
Mean baseline lipid values (n = 646)	307.7	227.7	58.1	101.7
All Fenofibrate (n = 361)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n = 285)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL				
Mean baseline lipid values (n = 646)	312.8	219.8	46.7	231.9
All Fenofibrate (n = 361)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n = 285)	-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, measurements of Apo B were 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

Fenofibric Acid Delayed-Release Capsules are supplied in two dose strengths as follows:

- 45 mg fenofibric acid delayed-release capsules have a dark brown opaque cap and yellow opaque body imprinted with "Par" on the cap and "C209" on the body in black ink. Each hard gelatin capsule contains enteric coated white to off white round mini-tablets. The delayed release capsules are available in bottles of 90-count (NDC 10370-209-09) and 1000-count (NDC 10370-209-10).
- 135 mg fenofibric acid delayed-release capsules have a light blue opaque cap and yellow opaque body imprinted with "Par" on the cap and "C210" on the body in black ink. Each hard gelatin capsule contains enteric coated white to off white round mini-tablets. The delayed release capsules are available in bottles of 90-count (NDC 10370-210-09) and 500-count (NDC 10370-210-05).

Storage and Handling

Store fenofibric acid delayed-release capsules, 45 and 135 mg between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Patient Counseling

Patients should be advised:

- of the potential benefits and risks of fenofibric acid delayed-release capsules.
- to read the Medication Guide before starting fenofibric acid delayed-release capsules therapy and to reread it each time the prescription is renewed.
- of medications that should not be taken in combination with fenofibric acid delayed-release capsules.
- to continue to follow an appropriate lipid-modifying diet while taking fenofibric acid delayed-release capsules.
- to take fenofibric acid delayed-release capsules once daily, without regard to food, at the prescribed dose, swallowing each capsule whole. If fenofibric acid delayed-release capsules are coadministered with a statin, they may be taken together.
- to return for routine monitoring.
- 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 fenofibric acid delayed-release capsules.
- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms.

MEDICATION GUIDE

Fenofibric Acid Delayed-Release Capsules

Read this Medication Guide before you start taking fenofibric acid delayed-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about fenofibric acid delayed-release capsules?

Fenofibric acid delayed-release capsules can be used with other cholesterol-lowering medicines called statins. Statins include:

- atorvastatin (Lipitor, Caduet)
- fluvastatin (Lescol, Lescol XL)
- lovastatin (Altoprev, Mevacor, Advicor)
- pitavastatin (Livalo)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastatin (Zocor, Simcor, Vytorin)

Statins can cause muscle pain, tenderness or weakness, which may be symptoms of a rare but serious muscle condition called rhabdomyolysis. In some cases rhabdomyolysis can cause kidney damage and death. The risk of rhabdomyolysis may be higher when fenofibric acid delayed-release capsules are given with statins. If you take a statin, tell your healthcare provider.

Other medicines or large amounts of grapefruit juice (more than a quart) may raise the levels of statins in your body, and could then raise the risk of muscle problems. Tell your healthcare provider if you are taking any medicines listed below.

- Heart medicine
- Stomach medicine
- Antibiotics
- Anti-fungal
- Cholesterol-lowering medicine
- Hormones
- HIV/AIDS medicine
- Antidepressant
- Immunosuppressant
- Anti-seizure medicine

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Tell your healthcare provider if you drink grapefruit juice.

What are fenofibric acid delayed-release capsules?

Fenofibric acid delayed-release capsules are a prescription medicine used to treat cholesterol in the blood by lowering the total amount of triglycerides and LDL (bad) cholesterol, and increasing the HDL (good) cholesterol. **Fenofibric acid delayed-release capsules have not been shown to lower your risk of having heart problems or a stroke.** You should be on a low fat and low cholesterol diet while you take fenofibric acid delayed-release capsules.

The safety and effectiveness of fenofibric acid delayed-release capsules in children is not known.

Who should not take fenofibric acid delayed-release capsules?

Do not take fenofibric acid delayed-release capsules if you:

- are allergic to fenofibric acid, or any of the ingredients in fenofibric acid delayed-release capsules. See the end of this Medication Guide for a list of all the ingredients in fenofibric acid delayed-release capsules.
- have severe kidney disease.
- have liver disease.
- have gallbladder disease.
- are a nursing mother.

Talk to your healthcare provider before you take fenofibric acid delayed-release capsules if you have any of these conditions.

What should I tell my healthcare provider before taking fenofibric acid delayed-release capsules?

Before taking fenofibric acid delayed-release capsules, tell your healthcare provider about all your medical conditions, including if you:

- are allergic to any medicines.
- have ever had kidney problems.
- have ever had liver problems.
- have ever had gallbladder problems.
- are pregnant or if you plan to become pregnant. It is not known if fenofibric acid delayed-release capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if fenofibric acid delayed-release capsules passes into your breast milk. You and your healthcare provider should decide if you will take fenofibric acid delayed-release capsules or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Using fenofibric acid delayed-release capsules with certain other medicines can affect the way these medicines work and other medicines may affect how fenofibric acid delayed-release capsules works. In some cases, using fenofibric acid delayed-release capsules with other medicines can cause serious side effects.

Know all the medicines you take. Keep a list of them and show it to your healthcare provider when you get a new medicine.

It is especially important to tell your healthcare provider if you take any of the medicines mentioned in, "What is the most important information I should know about fenofibric acid delayed-release capsules?" or any of the medicines listed below:

- **anticoagulants**, also known as blood thinners (warfarin, Coumadin)
- **bile acid resins**
- **cyclosporine**

Ask your healthcare provider if you are not sure if your medicine is one of these.

How should I take fenofibric acid delayed-release capsules?

- You should be on a low fat and low cholesterol diet while you take fenofibric acid delayed-release capsules.
- Take fenofibric acid delayed-release capsules one time each day as prescribed by your healthcare provider.
- Take fenofibric acid delayed-release capsules with or without food.
- Swallow fenofibric acid delayed-release capsules whole. Do not break, crush, dissolve, or chew fenofibric acid delayed-release capsules before swallowing. If you cannot swallow fenofibric acid delayed-release capsules whole, tell your healthcare provider, you may need a different medicine.
- If you take a medicine called a statin, you can take fenofibric acid delayed-release capsules and your statin at the same time of day.
- If you miss a dose of fenofibric acid delayed-release capsules, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. If you are not sure about your dosing, call your healthcare provider. **Do not take more than one dose of fenofibric acid delayed-release capsules a day unless your healthcare provider tells you to.**
- If you take too much fenofibric acid delayed-release capsules, contact your healthcare provider or your local emergency department.
- Do not change your dose or stop fenofibric acid delayed-release capsules unless your healthcare provider tells you to.
- Your healthcare provider may do blood tests before you start taking fenofibric acid delayed-release capsules and during treatment. See your healthcare provider regularly to check your cholesterol and triglyceride levels and to check for side effects.

What are the possible side effects with fenofibric acid delayed-release capsules?

Fenofibric acid delayed-release capsules may cause serious side effects, including:

- **muscle pain, tenderness, or weakness.** See "What is the most important information that I should know about fenofibric acid delayed-release capsules?"
- **tiredness and fever.**
- **abdominal pain, nausea, or vomiting.** These may be signs of inflammation (swelling) of the gallbladder or pancreas.

Call your healthcare provider right away if you have any of these serious side effects.

The most common side effects with fenofibric acid delayed-release capsules include:

- headache
- heartburn (indigestion)
- nausea
- muscle aches
- increases in muscle or liver enzymes that are measured by blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of fenofibric acid delayed-release capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store fenofibric acid delayed-release capsules?

- Store fenofibric acid delayed-release capsules between 20° to 25°C (68° to 77°F).
- Protect fenofibric acid delayed-release capsules from moisture.

Keep fenofibric acid delayed-release capsules and all medicines out of the reach of children.

General information about the safe and effective use of fenofibric acid delayed-release capsules

Medicines are sometimes prescribed for conditions that are not mentioned in the Medication Guide. Do not use fenofibric acid delayed-release capsules for a condition for which it was not prescribed. Do not give fenofibric acid delayed-release capsules to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about fenofibric acid delayed-release capsules. If you would like more information, talk to your healthcare provider. You can also ask your pharmacist or healthcare provider for information that is written for health professionals.

For more information go to www.parpharm.com or call 1-800-828-9393.

What are the ingredients in fenofibric acid delayed-release capsules?

Active Ingredient: Fenofibric acid

Inactive Ingredients: Hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer, stearic acid, talc, triethyl citrate, FD&C blue #1, FD&C blue #2, FD&C red #40, D&C yellow #10, iron oxide black, propylene glycol, and shellac. Additionally, the 45 mg capsule shell contains black iron oxide, D&C yellow #10, FD&C yellow #6, gelatin, red iron oxide, titanium dioxide and yellow iron oxide. The 135 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C yellow #6, gelatin and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Revised: 06/13 OS209A-01-1-02

MEDICATION GUIDE

Fenofibric Acid Delayed-Release Capsules

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- fluvastatin (Lescol, Lescol XL)
- lovastatin (Altoprev, Mevacor, Advicor)
- pitavastatin (Livalo)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastatin (Zocor, Simcor, Vytorin)

Statins can cause muscle pain, tenderness or weakness, which may be symptoms of a rare but serious muscle condition called rhabdomyolysis. In some cases rhabdomyolysis can cause kidney damage and death. The risk of rhabdomyolysis may be higher when fenofibric acid delayed-release capsules are given with statins. If you take a statin, tell your healthcare provider.

Other medicines or large amounts of grapefruit juice (more than a quart) may raise the levels of statins in your body, and could then raise the risk of muscle problems. Tell your healthcare provider if you are taking any medicines listed below.

- Heart medicine
- Stomach medicine
- Antibiotics
- Anti-fungal
- Cholesterol-lowering medicine
- Hormones
- HIV/AIDS medicine
- Antidepressant
- Immunosuppressant
- Anti-seizure medicine

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- have liver disease.
- have gallbladder disease.
- are a nursing mother.

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- have ever had liver problems.
- have ever had gallbladder problems.
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- are breastfeeding or plan to breastfeed. It is not known if fenofibric acid delayed-release capsules passes into your breast milk. You and your healthcare provider should decide if you will take fenofibric acid delayed-release capsules or breastfeed. You should not do both.

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- **abdominal pain, nausea, or vomiting.** These may be signs of inflammation (swelling) of the gallbladder or pancreas.

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This Medication Guide summarizes the most important information about fenofibric acid delayed-release capsules. If you would like more information, talk to your healthcare provider. You can also ask your pharmacist or healthcare provider for information that is written for health professionals.

For more information go to www.parpharm.com or call 1-800-828-9393.

What are the ingredients in fenofibric acid delayed-release capsules?

Active Ingredient: Fenofibric acid

Inactive Ingredients: Hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer, stearic acid, talc, triethyl citrate, FD&C blue #1, FD&C blue #2, FD&C red #40, D&C yellow #10, iron oxide black, propylene glycol, and shellac. Additionally, the 45 mg capsule shell contains black iron oxide, D&C yellow #10, FD&C yellow #6, gelatin, red iron oxide, titanium dioxide and yellow iron oxide. The 135 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C yellow #6, gelatin and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

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/s/

BETTY B TURNER
06/11/2013

CHI-ANN Y WU
06/11/2013
For Wm. Peter Rickman