HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Fenofibric Acid Delayed-release Capsule, for Oral use

Initial U.S. Approval: 2008

WARNINGS AND PRECAUTIONS

- **Known hypersensitivity to fenofibric acid or fenofibrate (4, 5.9)**
- **Nursing mothers (4, 8.3).**
- **Active liver disease (4, 5.3).**

Recent Major Changes

- [2012] Warnings and Precautions, Skeletal Muscle
- [2012] Warnings and Precautions, Paradoxical Decreased in HDL Cholesterol Levels (5.11)

INDICATIONS AND USAGE

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

Dosage and Administration

- **Coadministration with the maximum dose of a statin has not been evaluated in clinical studies.**
- **May be taken at the same time as a statin (2.2).**
- **May be taken without regard to food (2.1).**
- **Maximum dose: 135 mg once daily (2.1).**

Dosage Forms and Strengths

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

Recent Major Changes

- **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

- **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 hyperlipidemia (5.1).**
- **Fenofibric acid can increase serum transaminases. Liver tests should be monitored periodically (5.3).**
- **Fenofibric acid can reversibly increase serum creatinine levels (5.2). Renal function should be monitored periodically in patients with renal insufficiency (8.6).**
- **Fenofibric acid increases 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).**

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 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 the FDA-approved Medication Guide.

FEBRUARY 2013

FENC.R1mt/MG:FENC.R1m/MG:FENC.R1mt

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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 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 on reducing this risk has not been adequately studied.

1.2 Treatment of Primary Hypercholesterolemia or Mixed Dyslipidemia
Fenofibric acid delayed-release capsules are indicated as adjunctive therapy to diet to reduce 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 Treatment of Primary Hypertriglyceridemia or Mixed Dyslipidemia
Fenofibric acid delayed-release capsules are indicated as adjunctive therapy to diet to reduce 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.

2 DOSAGE AND ADMINISTRATION
2.1 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 nondrug methods including appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypertriglyceridemia 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.

2.2 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 concomitant use, the 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 mg 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 weeks 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 (8.6)).

3 DOSAGE FORMS AND STRENGTHS
• 45 mg choline fenofibrate delayed-release capsules have a brown-pink opaque cap and light yellow opaque body imprinted axially on the cap and body with MYLAN over CF 45 in black ink.
• 135 mg choline fenofibrate delayed-release capsules have a powder blue opaque cap and light yellow opaque body imprinted axially on the cap and body with MYLAN over CF 135 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 increases in transaminase levels (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, choline fenofibrate or fenofibrate (see Warnings and Precautions (5.5)).

When fenofibric acid is 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 on coronary heart disease morbidity and mortality and non-carboxylic acid and fenofibrate, clofibrate and gemfibrozil, the findings in the following large randomized, placebo-controlled clinical studies with these fibrates drugs may also apply to fenofibric acid.

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5,518 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 1.34) (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 9,755 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the composite outcome of coronary heart disease death 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 15% (HR 1.19 [0.90, 1.57], p = 0.22) increase in the 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 cholecystectomy requiring surgery between the two groups (3% vs. 1.8%).

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

The Helsinki Heart Study was a large (n = 4,081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 5-year follow-up. A total of 21,640 patient-years of intervention were accrued in this study (5 years of randomized use and 5 years of clofibrate follow-up). There was no difference in the rate 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 trends 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 trends 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 risk 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, Mylagon was reported in 3.3% of patients treated with fenofibric acid monotherapy and 3.1% to 3.5% of patients treated with fenofibric acid 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 0.2% to 1.2% of patients treated with fenofibric acid coadministered with statins compared to 0.4% to 1.3%
of patients treated with statin monotherapy.

Mypathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, particularly if accompanied by malaise or fever. Muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever, may be apparent in 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 coadministered with statins for up to 52 weeks, increases of > 3 times the upper limit of normal of ALT and AST occurred in 12.2% and 0.5% of patients, respectively. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal levels 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 ten 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 fenofibrate once daily and was 0% in those receiving dosages equivalent to 45 mg fenofibrate 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 fenofibrate 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 fenofibrate as monotherapy or coadministered with statins as well as patients receiving fenofibrate therapy. In the pooled analysis of three double-blind controlled studies of fenofibrate administered as monotherapy or in combination with statins, increases in serum creatinine to > 2 mg/dL occurred in 0.8% of patients treated with fenofibrate and 1.1% of patients treated with fenofibrate 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 increases is unclear. Monitoring renal function in patients with renal impairment taking fenofibrate 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, 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 therapy should be discontinued if gallstones are found.

5.6 Cumarin Anticoagulants

Caution should be exercised when fenofibric acid is given in conjunction with oral cumarin anticoagulants. Fenofibric acid may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time. In International Normalized Ratio (PT/INR) controlled studies of another drug.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fenofibric Acid (n = 490)</th>
<th>Low-Dose Statin (n = 493)</th>
<th>Fenofibric Acid + Low-Dose Statin (n = 498)</th>
<th>Fenofibric Acid + Moderate-Dose Statin (n = 491)</th>
<th>Fenofibric Acid + High-Dose Statin (n = 489)</th>
<th>Total (n = 2,431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (3.3)</td>
<td>11 (2.2)</td>
<td>16 (3.2)</td>
<td>13 (2.6)</td>
<td>15 (3.1)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>19 (3.9)</td>
<td>16 (3.2)</td>
<td>15 (3.1)</td>
<td>24 (4.9)</td>
<td>18 (3.7)</td>
<td>17 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (3.7)</td>
<td>13 (2.6)</td>
<td>17 (3.4)</td>
<td>23 (4.7)</td>
<td>24 (4.9)</td>
<td>23 (4.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (4.3)</td>
<td>18 (3.7)</td>
<td>15 (3.1)</td>
<td>22 (4.5)</td>
<td>27 (5.5)</td>
<td>19 (0.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
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<td></td>
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<tr>
<td>Fatigue</td>
<td>18 (3.7)</td>
<td>13 (2.6)</td>
<td>17 (3.4)</td>
<td>16 (3.2)</td>
<td>18 (3.7)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>22 (4.5)</td>
<td>21 (4.2)</td>
<td>20 (4.0)</td>
<td>16 (3.2)</td>
<td>16 (3.3)</td>
<td>3 (1.2)</td>
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<tr>
<td>Infections and infestations</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (3.5)</td>
<td>29 (5.9)</td>
<td>23 (4.7)</td>
<td>16 (3.2)</td>
<td>21 (4.3)</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>18 (3.7)</td>
<td>14 (2.8)</td>
<td>14 (2.8)</td>
<td>20 (4.1)</td>
<td>17 (3.5)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>26 (5.3)</td>
<td>13 (2.6)</td>
<td>18 (3.7)</td>
<td>24 (4.7)</td>
<td>24 (4.7)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ALT increased</td>
<td>6 (1.2)</td>
<td>2 (0.4)</td>
<td>15 (3.1)</td>
<td>2 (0.4)</td>
<td>12 (2.5)</td>
<td>4 (1.6)</td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
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<tr>
<td>Arthritis</td>
<td>19 (3.9)</td>
<td>22 (4.5)</td>
<td>21 (4.3)</td>
<td>21 (4.3)</td>
<td>17 (3.5)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>21 (4.3)</td>
<td>31 (6.3)</td>
<td>30 (6.1)</td>
<td>32 (6.5)</td>
<td>20 (4.1)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>8 (1.6)</td>
<td>18 (3.7)</td>
<td>12 (2.4)</td>
<td>24 (4.9)</td>
<td>15 (3.1)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (3.3)</td>
<td>24 (4.9)</td>
<td>17 (3.5)</td>
<td>23 (4.7)</td>
<td>15 (3.1)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14 (2.9)</td>
<td>14 (2.9)</td>
<td>14 (2.9)</td>
<td>21 (4.3)</td>
<td>13 (2.7)</td>
<td>9 (0.4)</td>
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<tr>
<td>Nervous System Disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20 (4.1)</td>
<td>8 (1.6)</td>
<td>19 (3.9)</td>
<td>11 (2.2)</td>
<td>16 (3.3)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>62 (12.7)</td>
<td>64 (13.3)</td>
<td>64 (13.3)</td>
<td>67 (13.7)</td>
<td>58 (11.9)</td>
<td>32 (13.1)</td>
</tr>
</tbody>
</table>

5.7 Pancreatitis

Pancreatitis has been reported in patients taking drugs of the fibrate class, including fenofibric acid. 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.
fenofibric acid 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 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

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>Fenofibrate (n = 439)</th>
<th>Placebo (n = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABDOMINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>DIGESTIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>INVESTIGATIONS</strong></td>
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<td></td>
</tr>
<tr>
<td>Abnormal Liver Tests</td>
<td>7.5%</td>
<td>1.4%</td>
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<tr>
<td>Increased ALT</td>
<td>3.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Increased Creatine</td>
<td>3.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Phosphokinase</td>
<td>3%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
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<td></td>
</tr>
<tr>
<td>Respiratory Disorder</td>
<td>6.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.3%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

1 Dosage equivalent to 135 mg fenofibric acid

6.2 Post-Marketing 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 casual 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. 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 at least one 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 nephotoxicity 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, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using fenofibric acid with immunosuppressants and other potentially nephotoxic 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

Teratogenic Effects. Pregnancy Category C: The safety of fenofibric acid in pregnant women has not been established. There are no adequate and well controlled studies of fenofibric acid in pregnant women. Fenofibric acid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When fenofibric acid is 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/m²). At higher multiples of human doses evidence of maternal toxicity was observed.

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

In pregnant rats given oral gavage 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/m².

8.3 Nursing Mothers

Fenofibric acid 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 monotherapy or coadministration with a statin in pediatric patients have not been established.

8.5 Geriatric Use

Fenofibric acid is substantially excreted by the kidney as fenofibric acid and fenofibric acid glucuronide, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. Since elderly patients have a higher incidence of renal impairment, the dose selection for the elderly should be made on the basis of renal function [see Dosage and Administration (2.6) 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.

8.6 Renal Impairment

The use of fenofibric acid 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 (2.3) and Clinical Pharmacology (12.3)]. Monitoring renal function in patients with renal impairment is recommended.

8.7 Hepatic Impairment

The use of fenofibric acid 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. 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 is highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION

Fenofibric acid is 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-4-(R)-2'-methyl-3-phenyl-3-methylpropionic acid (1:1) with the following structural formula:

The molecular formula is C_{32}H_{39}C_{10}NO_{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 almost white crystalline powder, which is stable under ordinary conditions. Each delayed-release capsule contains enteric coated pellets comprised of choline fenofibrate and the following inactive ingredients: colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, hypromellose, methacrylic acid copolymer type C, polyethylene glycol 8000, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, triethyl citrate and yellow iron oxide. The 45 mg capsules also contain red iron oxide. The 135 mg capsules also contain FD&C Blue No. 2. The black imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

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 by 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 CII (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. 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 fenofibrate capsules under fasting conditions. Fenofibric acid exposure in plasma, as measured by Cmax and AUC, is not significantly different when a single 135 mg dose of fenofibrate is administered under fasting or non-fasting conditions.

Distribution: Upon multiple dosing of fenofibric acid, 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 95% 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.

Excretion: After absorption, fenofibric acid is primarily excreted in the urine in the form of fenofibrate and fenofibric acid glucuronide.

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

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 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 has not been studied in pediatric populations.

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

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 < 30 mL/min/1.73 m²) showed a 2.1-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 to 59 mL/min/1.73 m²) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of fenofibric acid should be avoided in patients who have severe renal impairment and dose reduction is required in patients 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) 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 Cmax decreased by 1% 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.

1 Fenofibrate oral tablet
2 Fenofibrate oral micronized capsule

Table 4. Effects of Fenofibric Acid or Fenofibrate Coadministration on Systemic Exposure of Other Drugs

1 Dosage Regimen Dosage Regimen Change in Coadministered Drug Exposure

Lipid-lowering agents

| Dosage Regimen of Fenofibric Acid or Fenofibrate |
| Dosage Regimen of Coadministered Drug |
| Change in Coadministered Drug Exposure |
| Analyte | AUC | Cmax |
| Fenofibrate 145 mg1 Glimepiride, 1 mg as Glimepiride | Rosuvastatin, 40 mg once daily for 10 days | Rosuvastatin | ↑ 6% | ↑ 20% |
| Fenofibrate 160 mg1 Simvastatin, 80 mg once daily for 10 days | Fenofibrate 160 mg once daily for 10 days | Fenofibrate 160 mg once daily for 10 days | ↓ 6% | ↓ 14% |

Anti-diabetic agents

| Dosage Regimen Dosage Regimen Change in Coadministered Drug Exposure |
| Analyte | AUC | Cmax |
| Fenofibrate 160 mg1 Metformin, 850 mg 3 times daily for 10 days | Fenofibrate 160 mg once daily for 10 days | Fenofibrate 160 mg once daily for 10 days | ↓ 6% | ↓ 14% |

Active HMG-CoA Inhibitors

| Dosage Regimen Dosage Regimen Change in Coadministered Drug Exposure |
| Analyte | AUC | Cmax |
| Fenofibrate 160 mg1 Pravastatin, 40 mg once daily for 10 days | Fenofibrate 160 mg once daily for 10 days | Fenofibrate 160 mg once daily for 10 days | ↓ 14% | ↓ 14% |

1 Fenofibrate oral tablet
2 Fenofibrate oral micronized capsule

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fenofibric acid: 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 fenofibric acid 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/day, approximately 0.3, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m²). At a dose of 200 mg/200 mg/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, 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)), fenofibrate 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 dosed compared and gemplifib (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. Gemplibro- dil 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 mg²/m² 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 performed 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, fenofibrate, 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. Male doses received for 61 days prior to mating and females for 15 days prior to mating observed in humans after treatment with other members of the fibrate class when liver biopsies were performed before and after treatment in the same individual.

Secondary efficacy endpoints in all three double-blind, controlled studies were percent changes in non-HDL-C (fenofibrate acid coadministered with statin compared to fenofibrate acid monotherapy and corresponding change in control), and percent changes in VLDL-C, Total-C, and Apo B (fenofibrate acid coadministered with statin compared to corresponding statin monotherapy). Co-administration of fenofibrate acid with statins resulted in the following changes in secondary parameters (Table 6).

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th>Fenofibrate Acid</th>
<th>Low-Dose Statin</th>
<th>Fenofibrate Acid + Low-Dose Statin</th>
<th>Between-Group</th>
<th>Moderate-Dose Statin</th>
<th>Fenofibrate Acid + Moderate-Dose Statin</th>
<th>Between-Group</th>
<th>High-Dose Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>(n = 426)</td>
<td>(n = 454)</td>
<td>(n = 422)</td>
<td>(n = 433)</td>
<td>(n = 428)</td>
<td>(n = 420)</td>
<td>(n = 217)</td>
<td>(n = 228)</td>
</tr>
<tr>
<td>BL mean</td>
<td>227.5</td>
<td>214.3</td>
<td>219.1</td>
<td>222.4</td>
<td>218.9</td>
<td>240.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean %</td>
<td>-17.3%</td>
<td>-34.9%</td>
<td>-40.4%</td>
<td>-23.1%</td>
<td>-5.5%</td>
<td>-42.4%</td>
<td>-24.8%</td>
<td>-42.4%</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>(n = 449)</td>
<td>(n = 463)</td>
<td>(n = 445)</td>
<td>(n = 436)</td>
<td>(n = 445)</td>
<td>(n = 449)</td>
<td>(n = 224)</td>
<td>(n = 228)</td>
</tr>
<tr>
<td>BL mean</td>
<td>59.1</td>
<td>66.0</td>
<td>65.5</td>
<td>81.8</td>
<td>64.5</td>
<td>66.0</td>
<td>61.0</td>
<td></td>
</tr>
<tr>
<td>Mean %</td>
<td>-24.2%</td>
<td>-21.1%</td>
<td>-56.0%</td>
<td>-16.9%</td>
<td>-16.5%</td>
<td>-51.2%</td>
<td>-12.3%</td>
<td>-42.1%</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>(n = 436)</td>
<td>(n = 450)</td>
<td>(n = 432)</td>
<td>(n = 446)</td>
<td>(n = 445)</td>
<td>(n = 447)</td>
<td>(n = 230)</td>
<td>(n = 235)</td>
</tr>
<tr>
<td>BL mean</td>
<td>70.4</td>
<td>73.0</td>
<td>73.1</td>
<td>76.3</td>
<td>74.3</td>
<td>75.4</td>
<td>72.0</td>
<td></td>
</tr>
<tr>
<td>Mean %</td>
<td>-12.4%</td>
<td>-26.0%</td>
<td>-28.0%</td>
<td>-23.4%</td>
<td>-33.0%</td>
<td>-33.4%</td>
<td>-21.4%</td>
<td></td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>(n = 438)</td>
<td>(n = 452)</td>
<td>(n = 434)</td>
<td>(n = 447)</td>
<td>(n = 444)</td>
<td>(n = 447)</td>
<td>(n = 229)</td>
<td>(n = 235)</td>
</tr>
<tr>
<td>BL mean</td>
<td>146.2</td>
<td>140.6</td>
<td>148.0</td>
<td>147.3</td>
<td>146.1</td>
<td>148.0</td>
<td>146.0</td>
<td></td>
</tr>
<tr>
<td>Mean %</td>
<td>-13.6%</td>
<td>-31.1%</td>
<td>-36.3%</td>
<td>-5.9%</td>
<td>-36.9%</td>
<td>-36.7%</td>
<td>0.7%</td>
<td>-42.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># Combination therapy vs. corresponding statin monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, atorvastatin 20 mg</td>
</tr>
<tr>
<td>Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, atorvastatin 40 mg</td>
</tr>
<tr>
<td>High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, atorvastatin 80 mg</td>
</tr>
<tr>
<td>BL = Baseline</td>
</tr>
<tr>
<td># % = Change from baseline to final value</td>
</tr>
</tbody>
</table>

4. Combination therapy vs. corresponding statin monotherapy |
5. Combination therapy vs. fenofibrate acid monotherapy |
6. Mean 52-week values and mean percent change from baseline to final value in HDL-C, TG and LDL-C (Pooled Double-Blind, Controlled Studies)
The effects of fenofibrate at a dose equivalent to fenofibric acid 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 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate also lowered triglycerides and raised HDL-C (Table 8).

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

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total-C (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled Cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline lipid values (n = 646)</td>
<td>306.9</td>
<td>213.8</td>
<td>52.3</td>
<td>191</td>
</tr>
<tr>
<td>All Fenofibrate (n = 261)</td>
<td>-18.7%*</td>
<td>-20.6%*</td>
<td>+11.3%</td>
<td>-28.9%*</td>
</tr>
<tr>
<td>Placebo (n = 285)</td>
<td>-8.4%</td>
<td>-2.2%</td>
<td>+0.7%</td>
<td>+7.7%</td>
</tr>
<tr>
<td><strong>Baseline LDL-C &gt; 160 mg/dL and TG &lt; 150 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline lipid values (n = 334)</td>
<td>307.7</td>
<td>227.7</td>
<td>58.1</td>
<td>101.7</td>
</tr>
<tr>
<td>All Fenofibrate (n = 133)</td>
<td>-22.4%*</td>
<td>-31.4%*</td>
<td>+9.8%</td>
<td>-23.5%*</td>
</tr>
<tr>
<td>Placebo (n = 141)</td>
<td>-4.2%</td>
<td>+2.2%</td>
<td>+2.6%</td>
<td>+11.7%</td>
</tr>
<tr>
<td><strong>Baseline LDL-C = 160 mg/dL and TG ≥ 150 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline lipid values (n = 242)</td>
<td>312.8</td>
<td>215.8</td>
<td>46.7</td>
<td>231.9</td>
</tr>
<tr>
<td>All Fenofibrate (n = 126)</td>
<td>-16.8%*</td>
<td>-20.1%*</td>
<td>+4.6%</td>
<td>-35.9%*</td>
</tr>
<tr>
<td>Placebo (n = 116)</td>
<td>-3%</td>
<td>-6.6%</td>
<td>+2.3%</td>
<td>+0.9%</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Placebo

1. Duration of study treatment was 3 to 6 months
2. % 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. -9.8%, p < 0.001, n = 213 and 143, respectively).

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

The effects of fenofibrate are dose dependent. A dose of 135 mg once daily was more effective than 45 mg in lowering the total cholesterol (TC) and LDL-C, increasing the HDL-C, and reducing the triglycerides in patients with hyperlipidemia. The effects on TC, LDL-C, HDL-C, and triglycerides were additive at doses of 135 mg and 100 mg once daily, and the effects of 135 mg once daily were similar to those of 45 mg twice daily. The effects were similar in men and women.

### How Supplied/Storage and Handling

Fenofibric Acid Delayed-release Capsules are hard-shell gelatin capsules with a brown-pink opaque body and light yellow opaque capsule filled with white to off-white enteric coated pellets. The capsule is axially printed with MYLAN over CO 45 in black ink on the cap and body. The 45 mg capsules are hard-shell gelatin capsules with a brown-pink opaque cap and light yellow opaque body filled with white to off-white enteric coated pellets. The capsule is axially printed with MYLAN over CO 135 in black ink on the cap and body.

NDC 0378-2589-93 bottles of 30 capsules
NDC 0378-2589-77 bottles of 90 capsules
NDC 0378-2589-05 bottles of 500 capsules


### 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:

- 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 breast-feeding 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 breast-feed. 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 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 at 20° to 25°C (68° to 77°F).
• Protect fenofibric acid delayed-release capsules from moisture.