

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-118**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### Fenofibrate Tablets

Initial U.S. Approval: 1993

#### INDICATIONS AND USAGE

Fenofibrate is a peroxisome proliferator receptor alpha (PPAR $\alpha$ ) activator indicated:

- as an adjunct to diet to reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia when response to diet and non-pharmacological interventions alone has been inadequate. (1.1)
- as an adjunct to diet to treat patients with hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacologic intervention. (1.2)

Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus. (1.3).

#### DOSAGE AND ADMINISTRATION

- Primary hyperlipidemia and mixed dyslipidemia: 120 mg /day (2.1)
- Hypertriglyceridemia: 40 to 120 mg/day; the dose should be adjusted according to patient response (2.2)
- Renally impaired patients: 40 mg/day; the dose should be increased according to the effect on renal function and lipid levels (2.4)

Fenofibrate Tablets should be taken with meals.

#### DOSAGE FORMS AND STRENGTHS

- 40 mg: White to off white oval tablets. Debossed "FLO".
- 120 mg: White to off white oval tablets. Debossed "FHI".

#### CONTRAINDICATIONS

- Severe renal dysfunction, including patients receiving dialysis (4, 12.3)
- Active liver disease (4, 5.1)
- Gallbladder disease (4, 5.2)
- Nursing mothers (4, 8.3)

#### WARNINGS AND PRECAUTIONS

- Fenofibrate can increase serum transaminases. Liver tests should be periodically monitored (5.1).
- Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. (5.2)
- Exercise caution in concomitant treatment with coumarin anticoagulants. Reduce the dosage of coumarin to maintain the prothrombin time/INR at the desired level to prevent bleeding complications (5.3).
- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism (5.4)
- Fenofibrate reversibly increases serum creatinine levels (5.5)

#### ADVERSE REACTIONS

The most common adverse reactions (> 2% and at least 1% greater than placebo) are abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact the Drug Safety Department of LifeCycle Pharma at 1-800-849-9707 ext. 1454 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Coumarin Anticoagulants (7.1)
- Cyclosporine (7.2)
- HMG-CoA Reductase Inhibitors (7.3)
- Bile-Acid Resins (7.4)

#### USE IN SPECIFIC POPULATIONS

- Renal impairment: Fenofibrate should be avoided in patients with severe renal impairment and dose reduction is required in patients with mild to moderate renal impairment (8.5).
- Geriatric Use: Dose selection for the elderly should be made on the basis of renal function (8.6).

Revised: 08/2007

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Hyperlipidemia and Mixed Dyslipidemia

Fenofibrate is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, and Apo B, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate.

#### 1.2 Hypertriglyceridemia

Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

#### 1.3 General Guidelines

Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus. [see *Warnings and Precautions* (5.5).]

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

Drug therapy is not indicated for patients with who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing these patients from those with elevated VLDL.<sup>2</sup>

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Hyperlipidemia and Mixed Dyslipidemia

The initial dose of Fenofibrate Tablets is 120 mg per day.

#### 2.2 Hypertriglyceridemia

The initial dose is 40 to 120 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 120 mg per day.

#### 2.3 Renally Impaired Patients

Treatment with fenofibrate should be initiated at a dose of 40 mg/day in patients with mild to moderately impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of fenofibrate should be avoided in patients with severe renal function.

#### 2.4 Elderly Patients

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

#### 2.5 General Dosing Information

Fenofibrate Tablets should be taken with meals.

### 3 DOSAGE FORMS AND STRENGTHS

- 40 mg: White to off white oval tablets. Debossed "FLO".
- 120 mg: White to off white oval tablets. Debossed "FHI".

### 4 CONTRAINDICATIONS

- Fenofibrate is contraindicated in patients with severe renal dysfunction, including those receiving dialysis [see *Clinical Pharmacology* (12.3)].
- Fenofibrate is contraindicated in patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities [see *Warnings and Precautions* (5.1)].
- Fenofibrate is contraindicated in patients with gallbladder disease [see *Warnings and Precautions* (5.2)].
- Fenofibrate is contraindicated in nursing mothers [see *Use in Specific Populations* (8.3)].
- Fenofibrate is contraindicated in patients who have a known hypersensitivity to fenofibrate, such as severe skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis. [see *Warnings and Precautions* (5.9)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Liver Tests

Fenofibrate at doses equivalent to 87 mg to 130 mg fenofibrate per day [at the highest dose, comparable to Fenofibrate Tablets, 120 mg] can increase serum transaminases [AST (SGOT) or ALT (SGPT)].

In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 87 mg to 130 mg fenofibrate per day and was 0% in those receiving dosages equivalent to 43 mg or less fenofibrate per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

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

#### 5.2 Cholelithiasis

Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

#### 5.3 Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anti-coagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized. [See *Drug Interactions* (7.1).]

#### 5.4 Skeletal Muscle

Treatment with fenofibrate increases risk of myopathy. Treatment with fenofibrate increases risk of rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase (CPK) levels.

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

#### 5.5 Serum Creatinine

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

#### 5.6 Mortality and Coronary Heart Disease Morbidity

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p=0.41) and 19% (HR 1.19 [0.90, 1.57], p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.

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

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=0.91-1.64). 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 the 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: 0.94-5.05).

### 5.7 Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

### 5.8 Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,875 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ( $p = 0.074$ ); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ( $p = 0.022$ ).

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

### 5.9 Hypersensitivity Reactions

Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis.

### 5.10 Hematologic Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy.

### 5.11 Concomitant HMG-CoA Reductase Inhibitors

The combined use of fenofibric acid derivatives, particularly gemfibrozil, and HMG-CoA reductase inhibitors results in an increased risk of rhabdomyolysis and myoglobinuria leading in a high proportion of cases to acute renal failure.

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. [see Drug Interactions(7.3).]

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies Experience

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

Adverse reactions reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials are listed in Table 1. Adverse reactions 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 1. Adverse Reactions Reported by 2% or More of Patients Treated with Fenofibrate and Greater than Placebo During the Double-Blind, Placebo-Controlled Trials**

| BODY SYSTEM<br>Adverse Reaction  | Fenofibrate*<br>(N=439) | Placebo<br>(N=365) |
|----------------------------------|-------------------------|--------------------|
| <b>BODY AS A WHOLE</b>           |                         |                    |
| Abdominal Pain                   | 4.6%                    | 4.4%               |
| Back Pain                        | 3.4%                    | 2.5%               |
| Headache                         | 3.2%                    | 2.7%               |
| <b>DIGESTIVE</b>                 |                         |                    |
| Nausea                           | 2.3%                    | 1.9%               |
| Constipation                     | 2.1%                    | 1.4%               |
| <b>INVESTIGATIONS</b>            |                         |                    |
| 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%               |
| <b>RESPIRATORY</b>               |                         |                    |
| Respiratory Disorder             | 6.2%                    | 5.5%               |
| Rhinitis                         | 2.3%                    | 1.1%               |

\* Dosage equivalent to 130 mg fenofibrate

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fenofibrate: myalgia, rhabdomyolysis, increased creatinine phosphokinase, pancreatitis, increased alanine aminotransaminase, increased aspartate aminotransaminase, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, nausea, abdominal pain, anemia, headache, arthralgia, and asthenia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

## 7 DRUG INTERACTIONS

### 7.1 Coumarin Anticoagulants

Caution should be exercised when coumarin anticoagulants are given in conjunction with fenofibrate. The dosage of the anticoagulants should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized. [see Concomitant Coumarin Anticoagulants (5.3).]

### 7.2 Cyclosporine

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

### 7.3 HMG-CoA Reductase Inhibitors

The combined use of fenofibric acid derivatives, particularly gemfibrozil, and HMG-CoA reductase inhibitors results in an increased risk of rhabdomyolysis and myoglobinuria leading in a high proportion of cases to acute renal failure. [See Concomitant HMG-CoA Reductase Inhibitors (5.11)]

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of fenofibrate and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin, or its active metabolite 3 $\alpha$ -hydroxy iso-pravastatin when compared to either drug given alone.

### 7.4 Bile-Acid Resins

Since bile acid sequestrants may bind other drugs given concurrently, patients should take Fenofibrate Tablets at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Fenofibrate is classified as pregnancy category C. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter<sup>2</sup> surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. [see Nonclinical Toxicology (13)].

### 8.3 Nursing Mothers

Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

### 8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

### 8.5 Renal Impairment

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibrate should be avoided in patients with severe renal impairment and dose reduction is required in patients with mild to moderate renal impairment.

### 8.6 Geriatric Use

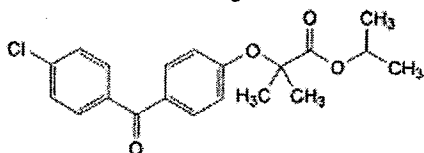
Fenofibric acid exposure is not influenced by age. However, elderly patients have a higher incidence of renal impairment. Dose selection for the elderly should be made on the basis of renal function.

## 10 OVERDOSAGE

There is no specific treatment for overdose with fenofibrate. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

## 11 DESCRIPTION

Fenofibrate Tablets, is a lipid regulating agent available as tablets for oral administration. Each tablet contains 40 mg or 120 mg fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is  $C_{20}H_{21}O_4Cl$  and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is  $79^\circ$  to  $82^\circ\text{C}$ . Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains lactose monohydrate, NF; Polyethylene Glycol 6000, NF; Poloxamer 188, NF; and magnesium stearate, NF.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor  $\alpha$  (PPAR $\alpha$ ).

Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apolipoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR $\alpha$  also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

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

### 12.2 Pharmacodynamics

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

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

### 12.3 Pharmacokinetics

Plasma concentrations of fenofibric acid after single-dose administration of Fenofibrate Tablets, 120 mg are equivalent to those of Fenofibrate 130 mg capsules under high-fat conditions.

A high-fat meal did not affect the fenofibric acid AUC after Fenofibrate Tablets administration but did increase the mean  $C_{max}$  by 44% compared to fasting conditions.

- Absorption:** The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from fenofibrate occur, on average, within 2 to 3 hours after administration.

Doses of three Fenofibrate Tablets, 40 mg are considered to be equivalent to single doses of Fenofibrate Tablets, 120 mg.

- Distribution:** In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.
- Metabolism:** Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

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 indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

- Excretion:** After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibrate acid from Fenofibrate Tablets is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

- Geriatrics:** In 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 a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites. [See *Dosage and Administration* (2.4) and *Use in Specific Populations* (8.5).]
- Pediatrics:** Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.
- Gender:** No pharmacokinetic difference between males and females has been observed for fenofibrate.
- Race:** The influence of race on the pharmacokinetics of fenofibrate has not been studied; however, fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.
- Renal Insufficiency:** The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance  $[CrCl] \leq 30$  mL/min or estimated glomerular filtration rate  $[eGFR] < 30$  mL/min/1.73m<sup>2</sup>) showed 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 ( $CrCl$  30-80 mL/min or  $eGFR$  30-59 mL/min/1.73m<sup>2</sup>) 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 fenofibrate 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* (2.3).]
- Hepatic Insufficiency:** No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.
- Drug-Drug Interactions:** *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potential of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR. [See *Concomitant Coumarin Anticoagulants* (5.3).]

Bile-acid resins have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption. [See *Drug Interactions* (7.3).]

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter<sup>2</sup> of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter<sup>2</sup> surface area), there were 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 maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter<sup>2</sup> surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter<sup>2</sup> surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

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

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternbrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

### 14 CLINICAL STUDIES

#### 14.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

The effects of fenofibrate at a dose equivalent to 120 mg fenofibrate per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 2).

Table 2. Mean Percent Change in Lipid Parameters at End of Treatment<sup>†</sup>

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

<sup>†</sup> 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).

#### 14.2 Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials<sup>1</sup> of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 120 mg Fenofibrate Tablets per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 3).

Table 3. Effects of Fenofibrate in Patients With Hypertriglyceridemia

| Study 1                              | Placebo |                 |                 |                 | Fenofibrate |                 |                 |                 |
|--------------------------------------|---------|-----------------|-----------------|-----------------|-------------|-----------------|-----------------|-----------------|
|                                      | N       | Baseline (Mean) | Endpoint (Mean) | % Change (Mean) | N           | Baseline (Mean) | Endpoint (Mean) | % Change (Mean) |
| Baseline TG levels 350 to 499 mg/dL  |         |                 |                 |                 |             |                 |                 |                 |
| Triglycerides                        | 28      | 449             | 450             | -0.5            | 27          | 432             | 223             | -46.2*          |
| VLDL Triglycerides                   | 19      | 367             | 350             | 2.7             | 19          | 350             | 178             | -44.1*          |
| Total Cholesterol                    | 28      | 255             | 261             | 2.8             | 27          | 252             | 227             | -9.1*           |
| HDL Cholesterol                      | 28      | 35              | 36              | 4               | 27          | 34              | 40              | 19.6*           |
| LDL Cholesterol                      | 28      | 120             | 129             | 12              | 27          | 128             | 137             | 14.5            |
| VLDL Cholesterol                     | 27      | 99              | 99              | 5.8             | 27          | 92              | 46              | -44.7*          |
| Study 2                              | Placebo |                 |                 |                 | Fenofibrate |                 |                 |                 |
|                                      | N       | Baseline (Mean) | Endpoint (Mean) | % Change (Mean) | N           | Baseline (Mean) | Endpoint (Mean) | % Change (Mean) |
| Baseline TG levels 500 to 1500 mg/dL |         |                 |                 |                 |             |                 |                 |                 |
| 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

### 15 HOW SUPPLIED/STORAGE AND HANDLING

- NDC 59630-490-30: 40 mg White to off white oval tablets. Debossed "FLO"; bottle of 30 tablets
- NDC 59630-490-10: 40 mg White to off white oval tablets. Debossed "FLO"; bottle of 100 tablets
- NDC 59630-495-30: 120 mg White to off white oval tablets. Debossed "FHI"; bottle of 30 tablets
- NDC 59630-495-10: 120 mg White to off white oval tablets. Debossed "FHI"; bottle of 100 tablets

Manufactured by:  
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