

FENOFIBRATE- fenofibrate capsule

Sun Pharmaceutical Industries, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FENOFIBRATE capsules, for oral use

Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Indications and Usage (1) 07/2024

Dosage and Administration (2) 07/2024

Warnings and Precautions, Mortality and Coronary

Heart Disease Morbidity (5.1) 07/2024

INDICATIONS AND USAGE

Fenofibrate capsules, USP are peroxisome proliferator receptor (PPAR) alpha agonist indicated as an adjunct to diet: (1)

- To reduce triglyceride (TG) levels in adults with severe hypertriglyceridemia (TG greater than or equal to 500 mg/dL) (1).
- To reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia when use of recommended LDL-C lowering therapy is not possible (1).

Limitations of Use: (1)

- 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 determined (1).
- Fenofibrate did not reduce coronary heart disease morbidity and mortality in two large, randomized controlled trials of patients with type 2 diabetes mellitus (1).

DOSAGE AND ADMINISTRATION

- Severe Hypertriglyceridemia: 43 mg to 130 mg orally once daily; the dose should be adjusted according to patient response (2.2).
- Primary hyperlipidemia: 130 mg orally once daily (2.2).
- Administer as a single dose, at any time of day, with or without food (2.2).
- Assess TG when clinically appropriate, as early as 4 to 8 weeks after initiating fenofibrate capsules. Discontinue fenofibrate capsules in patients who do not have an adequate response after two months of treatment (2.2).
 - Renal impairment: Initial dosage of 43 mg orally once daily (2.3).
 - Geriatric patients: Select the dosage on the basis of renal function (2.4).

DOSAGE FORMS AND STRENGTHS

- Capsules: 43 mg and 130 mg (3) (3)

CONTRAINDICATIONS

- Severe renal impairment, including those with end-stage renal disease (ESRD) and those receiving dialysis (4)
- Active liver disease, including those with unexplained persistent liver function abnormalities (4)
- Pre-existing gallbladder disease (4)
- Hypersensitivity to fenofibrate fenofibric acid, or any of the excipients in fenofibrate capsules (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Serious drug-induced liver injury, including liver transplantation and death, has been reported with fenofibrate. Monitor patient's liver function, including serum ALT, AST, and total bilirubin, at baseline and periodically for the duration of therapy. Discontinue if signs or symptoms of liver injury develop or if elevated enzyme levels persist (5.2).
- Myopathy and rhabdomyolysis: Have been reported in patients taking fenofibrate. Risks are increased during co-administration with a statin, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. Discontinue fenofibrate capsules if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Temporarily discontinue fenofibrate capsules in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to

rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the fenofibrate dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (5.3).

- *Serum creatinine*: Increases in serum creatinine have been reported in patients on fenofibrate capsules. Monitor renal function in patients with renal impairment taking fenofibrate capsules. Consider monitoring renal function in patients at risk for renal impairment (5.4).
- *Cholelithiasis*: Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.5).
- *Hypersensitivity Reactions*: Acute hypersensitivity reactions, including anaphylaxis and angioedema, and delayed hypersensitivity reactions, including severe cutaneous adverse drug reactions have been reported postmarketing. Some cases were life-threatening and required emergency treatment. Discontinue fenofibrate and treat patients appropriately if reactions occur (5.9).

ADVERSE REACTIONS

Most common adverse reactions (> 2% and greater than 1% in placebo) are abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6.1). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Consider if the benefit of concomitant use of statins or colchicine outweighs the increased risk of myopathy and rhabdomyolysis. Monitor patients for signs and symptoms of myopathy (7).
- Exercise caution in concomitant treatment with coumarin anticoagulants.
- Reduce the dosage of coumarin to maintain the PT/INR at the desired level to prevent bleeding complications (7).
 - Consider the benefits and risks of concomitant use with immunosuppressants and other potentially nephrotoxic agents. Use the lowest effective dosage and monitor renal function (7).
 - Administer fenofibrate capsules at least 1 hour before or 4 to 6 hours after the bile acid resins to avoid impeding its absorption (7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Prior to Initiation of Fenofibrate Capsule
- 2.2 Recommended Dosage and Administration
- 2.3 Recommended Dosage in Patients with Renal Impairment
- 2.4 Recommended Dosage in Geriatric Patients

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Mortality and Coronary Heart Disease Morbidity
- 5.2 Hepatotoxicity
- 5.3 Myopathy and Rhabdomyolysis
- 5.4 Increases in Serum Creatinine
- 5.5 Cholelithiasis
- 5.6 Increased Bleeding Risk with Coumarin Anticoagulants
- 5.7 Pancreatitis
- 5.8 Hematologic Changes
- 5.9 Hypersensitivity Reactions
- 5.10 Venothromboembolic Disease

5.11 Paradoxical Decreases in HDL Cholesterol Levels

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

14.2 Clinical Trials in Adults with Hypertriglyceridemia

14.3 Clinical Trials in Adults with Primary Hyperlipidemia

14.4. Lack of Efficacy in Cardiovascular Outcomes Trials

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fenofibrate Capsules are indicated as adjunctive therapy to diet:

- To reduce triglyceride (TG) levels in adults with severe hypertriglyceridemia (TG greater than or equal to 500 mg/dL).
- To reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia when use of recommended LDL-C lowering therapy is not possible.

Limitations of Use

- 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 determined [*see Warnings and Precautions (5.7)*].
- Fenofibrate did not reduce coronary heart disease morbidity and mortality in two large, randomized controlled trials of patients with type 2 diabetes mellitus [*see Warnings and Precautions (5.1) and Clinical Studies (14.4)*].

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of Fenofibrate Capsule

- Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
- Patients should be placed on an appropriate lipid-lowering diet before receiving fenofibrate capsules and should continue this diet during treatment with fenofibrate capsules.
- In patients with diabetes and fasting chylomicronemia, improve glycemic control prior to considering starting fenofibrate capsules.

2.2 Recommended Dosage and Administration

- Severe hypertriglyceridemia:
 - o The recommended dosage of fenofibrate capsules is 43 mg or 130 mg orally once daily.
 - o Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals.
- Primary hyperlipidemia:
 - o The recommended dosage of fenofibrate capsule is 130 mg orally once daily.
 - Administer fenofibrate capsules as a single dose at any time of day, with or without food.
 - Advise patients to swallow fenofibrate capsules whole. Do not crush, break, dissolve, or chew capsules.
 - Assess TG when clinically appropriate, as early as 4 to 8 weeks after initiating fenofibrate capsules. Discontinue fenofibrate capsules in patients who do not have an adequate response after two months of treatment.
 - If a dose is missed, advise patients not to take an extra dose. Resume treatment with the next dose.
 - Advise patients to take fenofibrate capsules at least 1 hour before or 4 hours to 6 hours after a bile acid binding resin to avoid impeding its absorption.

2.3 Recommended Dosage in Patients with Renal Impairment

- Assess renal function prior to initiation of fenofibrate capsules and periodically thereafter [*see Warnings and Precautions (5.4)*].
- Treatment with fenofibrate capsules should be initiated at a dosage of 43 mg orally once daily in patients with mild to moderately impaired renal function (eGFR 30 to <60 mL/min/1.73m²), and increased only after evaluation of the effects on renal function and TG levels at this dose.
- Fenofibrate capsules are contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m²), including those with end-stage renal disease (ESRD) and those receiving dialysis [*see Contraindications (4), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.4 Recommended Dosage in Geriatric Patients

Dosage selection for the elderly should be made on the basis of renal function [*see Use*

in *Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- Fenofibrate capsules, 43 mg are white to off-white granular powder filled in **size '4'** white opaque cap and white opaque body hard gelatin capsule imprinted with '**RG78**' on cap and body in black ink.
- Fenofibrate capsules, 130 mg are white to off-white granular powder filled in **size '0'** white opaque cap and white opaque body hard gelatin capsule imprinted with '**RG79**' on cap and body in black ink.

4 CONTRAINDICATIONS

Fenofibrate is contraindicated in the following conditions:

- Severe renal impairment, including those with end-stage renal disease (ESRD) and those receiving dialysis [see *Clinical Pharmacology (12.3)*].
- Active liver disease, including those with unexplained persistent liver function abnormalities [see *Warnings and Precautions (5.2)*].
- Pre-existing gallbladder disease [see *Warnings and Precautions (5.5)*].
- Hypersensitivity to fenofibric acid, fenofibrate, or any of the excipients in fenofibrate capsules. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with fenofibrate [see *Warnings and Precautions (5.9)*].

5 WARNINGS AND PRECAUTIONS

5.1 Mortality and Coronary Heart Disease Morbidity

Fenofibrate did not reduce cardiovascular disease morbidity or mortality in two large, randomized controlled trials of patients with type 2 diabetes mellitus [see *Clinical Studies (14.4)*].

Because of chemical, pharmacological, and clinical similarities between fenofibrate, pemafibrate, clofibrate, and gemfibrozil, findings in 5 large randomized, placebo-controlled clinical trials with these other fibrate drugs may also apply to fenofibrate.

Pemafibrate did not reduce cardiovascular disease morbidity or mortality in a large, randomized, placebo-controlled trial of patients with type 2 diabetes mellitus on background statin therapy [see *Clinical Studies (14.4)*].

In the Coronary Drug Project, a large trial conducted from 1965 to 1985 in men post myocardial infarction, there was no difference in mortality or nonfatal myocardial infarction between the clofibrate group and the placebo group after 5 years of treatment (NCT00000482).

In a trial conducted by the World Health Organization (WHO) from 1965 to 1976, men 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%, $p \leq 0.01$). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis.

The Helsinki Heart Study, conducted from 1982 to 1987, was a large (n = 4,081) trial 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 but not statistically higher in the gemfibrozil randomization group versus placebo [95% confidence interval (CI) of the hazard ratio (HR) 0.91 to 1.64].

A secondary prevention component of the Helsinki Heart Study treated middle-aged men with gemfibrozil or placebo for 5 years. The HR for cardiac deaths was 2.2, 95% CI, 0.94 to 5.05.

5.2 Hepatotoxicity

Serious drug-induced liver injury (DILI), including liver transplantation and death, has been reported postmarketing with fenofibrate. DILI has been reported within the first few weeks of treatment or after several months of therapy and in some cases has reversed with discontinuation of fenofibrate treatment. Patients with DILI have experienced signs and symptoms including dark urine, abnormal stool, jaundice, malaise, abdominal pain, myalgia, weight loss, pruritus, and nausea. Many patients had concurrent elevations of total bilirubin, serum alanine transaminase (ALT), and aspartate transaminase (AST). DILI has been characterized as hepatocellular, chronic active, and cholestatic hepatitis, and cirrhosis has occurred in association with chronic active hepatitis.

In clinical trials, fenofibrate at dosages comparable to 43 mg or 130 mg of fenofibrate per day has been associated with increases in serum AST or ALT. The incidence of increases in transaminases may be dose related [see *Adverse Reactions (6.1)*].

Fenofibrate is contraindicated in patients with active liver disease, including those with unexplained persistent liver function abnormalities [see *Contraindications (4)*]. Monitor patient's liver function, including serum ALT, AST, and total bilirubin, at baseline and periodically for the duration of therapy with fenofibrate. Discontinue fenofibrate if signs or symptoms of liver injury develop or if elevated enzyme levels persist (ALT or AST > 3 times the upper limit of normal, or if accompanied by elevation of bilirubin). Do not restart fenofibrate in these patients if there is no alternative explanation for the liver injury.

5.3 Myopathy and Rhabdomyolysis

Fenofibrate may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, and concomitant use with certain other drugs [see *Drug Interaction (7) and Uses in Specific Populations (8.6)*].

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Data from observational studies indicate that the risk for rhabdomyolysis is increased when fibrates are co-administered with a statin. Avoid concomitant use unless the benefit of further alterations in TG levels is likely to outweigh the increased risk of this drug combination [see *Drug Interactions (7) and Clinical Pharmacology (12.3)*].

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrate co-administered with colchicine. Consider whether the benefit of using colchicine concomitantly with fenofibrate outweighs the increased risk of myopathy. [see *Drug Interactions (7)*].

Discontinue fenofibrate if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if fenofibrate is discontinued. Temporarily discontinue fenofibrate in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the fenofibrate dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.4 Increases in Serum Creatinine

Increases in serum creatinine have been reported in patients on fenofibrate. These increases tend to return to baseline following discontinuation of fenofibrate. The clinical significance of this finding is unknown. Monitor renal function in patients with renal impairment taking fenofibrate. Renal monitoring should also be considered for patients taking fenofibrate at risk for renal insufficiency such as the elderly and patients with diabetes. Fenofibrate is contraindicated in patients with severe renal impairment, including those with end-stage renal disease (ESRD) and those receiving dialysis [see *Dosage and Administration (2.3)*, *Contraindications (4)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

5.5 Cholelithiasis

Fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found. Fenofibrate is contraindicated in patients with pre-existing gallbladder disease.

5.6 Increased Bleeding Risk with 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/International Normalized Ratio (PT/INR). To prevent bleeding complications, frequent monitoring of PT/INR and dosage adjustment of the anticoagulant are recommended until PT/INR has stabilized [see *Drug Interactions (7)*].

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 Hematologic Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been

observed in patients following initiation of fenofibrate. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrate. Periodic monitoring of red and white blood cell counts is recommended during the first 12 months of fenofibrate administration.

5.9 Hypersensitivity Reactions

Acute Hypersensitivity

Anaphylaxis and angioedema have been reported postmarketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate. Fenofibrate capsules are contraindicated in patients with a hypersensitivity to fenofibrate, fenofibric acid, or any of the ingredients in fenofibrate capsules.

Delayed Hypersensitivity

Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported postmarketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis) and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

5.10 Venothromboembolic Disease

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1.4%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1.1%) 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; $p < 0.01$).

In the cardiovascular outcome trial with pemafibrate, pulmonary embolism was reported for 37 (0.7%) subjects in the pemafibrate group and 16 (0.3%) subjects in the placebo group. Deep vein thrombosis was reported for 36 (0.7%) subjects in the pemafibrate group and 13 (0.2%) subjects in the placebo group.

5.11 Paradoxical Decreases in HDL Cholesterol Levels

There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in patients with and without diabetes initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and

sustained. The clinical significance of this decrease in HDL-C is unknown. Check HDL-C levels within the first few months after initiation of fenofibrate. If a severely depressed HDL-C level is detected, discontinue fenofibrate and monitor HDL-C until it has returned to baseline. Fenofibrate should not be re-initiated.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Mortality and coronary heart disease morbidity [see Warnings and Precautions (5.1)]
- Hepatotoxicity [see Warnings and Precautions (5.2)]
- Myopathy and Rhabdomyolysis [see Warnings and Precautions (5.3)]
- Increases in Serum Creatinine [see Warnings and Precautions (5.4)]
- Cholelithiasis [see Warnings and Precautions (5.5)]
 - Increased Bleeding Risk with Coumarin Anticoagulants [see Warnings and Precautions (5.6)]
 - Pancreatitis [see Warnings and Precautions (5.7)]
 - Hematologic Changes [see Warnings and Precautions (5.8)]
 - Hypersensitivity reactions [see Warnings and Precautions (5.9)]
 - Venothromboembolic disease [see Warnings and Precautions (5.10)]

6.1 Clinical Trials 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.

The safety of fenofibrate has been established in adults with hypertriglyceridemia or primary hyperlipidemia based on adequate and well-controlled trials of other formulations of fenofibrate, referenced below as “fenofibrate” [see Clinical Studies (14)]. Dosages of fenofibrate used in these trials were comparable to fenofibrate 90 mg per day [see Clinical Pharmacology (12.3)].

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 1. Adverse reactions led to discontinuation of treatment in 5% of patients treated with fenofibrate and in 3% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

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

Adverse Reaction	Placebo (N = 365)	Fenofibrate (N = 439)
Abnormal Liver Tests	1%	8%
Abdominal Pain	4%	5%
Increased ALT	2%	3%
Increased AST	1%	3%

Increased Creatine Phosphokinase	1%	3%
Constipation	1%	2%
Rhinitis	1%	2%

Other Adverse Reactions

Urticaria

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

Increases in Liver Enzymes

In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal in ALT occurred in 5.3% of patients taking fenofibrate at doses comparable to 130 mg fenofibrate daily versus 1.1% of patients treated with placebo. In an 8-week study, the incidence of ALT or AST elevations \geq 3 times the upper limit of normal was 13% in patients receiving

dosages comparable to 60 mg to 90 mg fenofibrate daily and was 0% in those receiving dosages comparable to 30 mg or less fenofibrate daily or placebo.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fenofibrate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood Disorders: Anemia

Gastrointestinal Disorders: Pancreatitis

General Disorder: Asthenia

Hepatobiliary Disorders: Increased total bilirubin, hepatitis, cirrhosis

Immune System Disorders: Anaphylaxis, angioedema

Lipid Disorders: Severely depressed HDL-cholesterol levels

Musculoskeletal Disorders: Myalgia, muscle spasms, rhabdomyolysis, arthralgia

Renal and Urinary Disorders: Acute renal failure *Respiratory Disorders:* Interstitial lung disease

Skin and Subcutaneous Tissue Disorders: Photosensitivity reactions. This may occur in patients who report a prior photosensitivity reaction to ketoprofen.

7 DRUG INTERACTIONS

Table 2. Clinically Important Drug Interactions with Fenofibrate

Statins

Clinical Fibrates may cause myopathy when given alone. The risk of myopathy and

Impact: rhabdomyolysis is increased with concomitant use of fibrates with statins.
Intervention: Consider if the benefit of using fenofibrate concomitantly with statin therapy outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of statin therapy.

Colchicine

Clinical Cases of myopathy and rhabdomyolysis have been reported with

Impact: concomitant use of colchicine with fenofibrates.

Intervention: Consider if the benefit of using colchicine concomitantly with fenofibrate outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dosage titration of colchicine.

Coumarin Anticoagulants

Clinical Fibrates may cause potentiation of coumarin-type anticoagulant effects with

Impact: prolongation of the PT/INR.

Intervention: Caution should be exercised when coumarin anticoagulants are given in conjunction with fenofibrate. The dosage of the anticoagulants 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

Immunosuppressants

Clinical Immunosuppressants such as cyclosporine and tacrolimus can produce

Impact: 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.

Intervention: The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dosage employed and renal function monitored.

Bile-Acid Binding Resins

Clinical Bile-acid binding resins may bind other drugs given concurrently.

Impact:

Intervention: In patients taking a bile acid resin, administer fenofibrate at least 1 hour before or 4 to 6 hours after the bile acid resin to avoid impeding its absorption.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with fenofibrate use in pregnant women are insufficient to determine a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, no evidence of embryo-fetal toxicity was observed with oral administration of fenofibrate in rats and rabbits during organogenesis at doses less than or comparable to the maximum recommended clinical dose of 130 mg of fenofibrate daily, based on body surface area (mg/m²). Adverse

reproductive outcomes occurred at higher doses in the presence of maternal toxicity (see Data). Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In pregnant rats given oral dietary doses of 14 mg/kg/day, 127 mg/kg/day, and 361 mg/kg/day from gestation day 6 to 15 during the period of organogenesis, no adverse developmental findings were observed at 14 mg/kg/day (less than the clinical exposure at the maximum recommended human dose [MRHD] of 300 mg fenofibrate daily, comparable to 130 mg fenofibrate daily, based on body surface area comparisons). Increased fetal skeletal malformations were observed at maternally toxic doses (361 mg/kg/day, corresponding to 12 times the clinical exposure at the MRHD) that significantly suppressed maternal body weight gain.

In pregnant rabbits given oral gavage doses of 15 mg/kg/day, 150 mg/kg/day, and 300 mg/kg/day from gestation day 6 to 18 during the period of organogenesis and allowed to deliver, no adverse developmental findings were observed at 15 mg/kg/day (a dose that approximates the clinical exposure at the MRHD, based on body surface area comparisons). Aborted litters were observed at maternally toxic doses (≥ 150 mg/kg/day, corresponding to ≥ 10 times the clinical exposure at the MRHD) that suppressed maternal body weight gain.

In pregnant rats given oral dietary doses of 15 mg/kg/day, 75 mg/kg/day, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), no adverse developmental effects were observed at 15 mg/kg/day (less than the clinical exposure at the MRHD, based on body surface area comparisons), despite maternal toxicity (decreased weight gain). Post-implantation loss was observed at ≥ 75 mg/kg/day (≥ 2 times the clinical exposure at the MRHD) in the presence of maternal toxicity (decreased weight gain). Decreased pup survival was noted at 300 mg/kg/day (10 times the clinical exposure at the MRHD), which was associated with decreased maternal body weight gain/maternal neglect.

8.2 Lactation

Risk Summary

There is no available information on the presence of fenofibrate in human milk, effects of the drug on the breastfed infant, or the effects on milk production. Fenofibrate is present in the milk of rats, and is therefore likely to be present in human milk. Because of the potential for serious adverse reactions in breastfed infants, such as disruption of infant lipid metabolism, women should not breastfeed during treatment with fenofibrate and for 5 days after the final dose [see *Contraindications (4)*].

8.4 Pediatric Use

The safety and effectiveness of fenofibrate have not been established in pediatric patients with severe hypertriglyceridemia or primary hyperlipidemia.

8.5 Geriatric Use

Assess renal function in elderly patients and follow contraindications and dosing recommendations for patients with renal impairment [see *Contraindications (4)*, *Warnings and Precautions (5.3, 5.4)*, and *Use in Specific Populations (8.6)*]. While fenofibric acid exposure is not influenced by age, elderly patients are more likely to have renal impairment, and fenofibric acid is substantially excreted by the kidney [see *Clinical Pharmacology (12.3)*].

Consider monitoring renal function in elderly patients taking fenofibrate.

8.6 Renal Impairment

Fenofibrate is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m²), including those with end-stage renal disease (ESRD) and those receiving dialysis [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)*]. Patients with severe renal impairment have 2.7-fold higher exposure of fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared with healthy volunteers. Renal impairment is a risk factor for myopathy and rhabdomyolysis [see *Warnings and Precautions (5.3, 5.4)*, and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

The use of fenofibrate has not been evaluated in subjects with hepatic impairment. Fenofibrate is contraindicated in patients with active liver disease, including those with unexplained persistent liver function abnormalities [see *Contraindications (4)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In the event of an overdose of fenofibrate, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations. 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 capsules, USP, is a peroxisome proliferator-activated receptor (PPAR) alpha agonist available as capsules for oral administration. Each capsule contains 43 mg or 130 mg of micronized fenofibrate, USP. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, l-methylethyl ester with the following structural formula:



The molecular formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate (micronized), USP is practically insoluble in water, very soluble in methylene chloride, slightly soluble in alcohol. The melting point is 79° to 82° C. Fenofibrate (micronized), USP is a white or almost white crystalline powder.

Inactive Ingredients: Each gelatin capsule contains hypromellose, pregelatinized starch (maize), simethicone emulsion, sodium lauryl sulfate, sodium stearyl fumarate and talc. The gelatin capsules also contain gelatin and titanium dioxide. The imprinting ink contains ferric oxide black, potassium hydroxide, propylene glycol, and shellac.

Meets USP Dissolution Test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of PPAR alpha receptor. Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

12.2 Pharmacodynamics

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, total triglycerides, and triglyceride-rich lipoprotein (VLDL) in treated patients with severe hypertriglyceridemia.

12.3 Pharmacokinetics

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body to fenofibric acid which is the active constituent measurable in the circulation.

Absorption: The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals. However, after fenofibrate is dissolved, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radio-labeled 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 within 4 to 8 hours after administration. There was

less than dose-proportional increase in the systemic exposure of fenofibric acid from 43 mg and 130 mg of fenofibrate under fasting conditions.

Doses of three-capsules of 43 mg fenofibrate given concurrently were dose equivalent to single-capsule doses of 130 mg.

Effect of Food:

The extent of absorption of fenofibric acid was unaffected when fenofibrate was taken either in fasted state or with a low-fat meal. However, the C_{max} of fenofibrate increased in the presence of a low-fat meal. T_{max} was unaffected in the presence of a low-fat meal. In the presence of a high-fat meal, there was a 26% increase in AUC and 108% increase in C_{max} of fenofibric acid from fenofibrate relative to fasting state.

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.

Elimination

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 radio-labelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of 23 hours, allowing once daily dosing.

Specific Populations

Geriatric Patients: In elderly volunteers aged 77 to 87 years, 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 with normal renal function, without increasing accumulation of the drug or metabolites [see *Dosage and Administration (2.4)* and *Use in Special Populations (8.5)*].

Pediatric Patients: Pharmacokinetics of fenofibrate has not been studied in pediatric patients.

Male and Female Patients: No pharmacokinetic difference between males and females has been observed for fenofibrate.

Racial and Ethnic Groups: 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.

Patients with Renal Impairment: 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/1.73m²] 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 mL/min to 80 mL/min or eGFR 30 mL/min/1.73m² to 59 mL/min/1.73m²) 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 is contraindicated in patients with severe renal impairment, including end-stage renal disease (ESRD) or those receiving dialysis. Dose reduction is required in patients having mild to moderate renal impairment [see *Dosage and Administration* (2.4)].

Patients with Hepatic Impairment: No pharmacokinetic studies have been conducted in patients having hepatic impairment.

Drug-Drug Interaction Studies: *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 inhibitor of CYP2C8, CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Table 3 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 4 describes the effects of co-administered fenofibric acid on exposure to other drugs.

Table 3. Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from Fenofibrate or Fenofibrate Administration

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	C _{max}
<i>Lipid-lowering agents</i>				
Atorvastatin	20 mg once daily for 10 days	Fenofibrate 160 mg ¹ once daily for 10 days	↓2%	↓4%
Pravastatin	40 mg as a single dose	Fenofibrate 3 x 67 mg ² as a single dose	↓1%	↓2%
Fluvastatin	40 mg as a single dose	Fenofibrate 160 mg ¹ as a single dose	↓2%	↓10%
<i>Anti-diabetic agents</i>				
Glimepiride	1 mg as a single dose	Fenofibrate 145 mg ¹ once daily for 10 days	↑1%	↓1%
Metformin	850 mg three times daily for 10 days	Fenofibrate 54 mg ¹ three times daily for 10 days	↓9%	↓6%
Rosiglitazone	8 mg once daily for 5 days	Fenofibrate 145 mg ¹ once daily for 14 days	↑10%	↑3%

¹ Fenofibrate oral tablet

² Fenofibrate oral micronized capsule

Table 4. Effects of Fenofibrate Capsule or Fenofibrate on Systemic Exposure of Co-Administered Drugs

Dosage Regimen of Fenofibrate	Dosage Regimen of Co-Administered Drug	Changes in Co-Administered Drug Exposure Analyte	AUC C _{max}	
			AUC	C _{max}
<i>Lipid-lowering agents</i>				
Fenofibrate 160 mg ¹ once daily for 10 days	Atorvastatin, 20 mg once daily for 10 days	Atorvastatin	↓ 17%	0%
Fenofibrate 3 x 67 mg ² as a single dose	Pravastatin, 40 mg as a single dose	Pravastatin	↑ 13%	↑ 13%
		3α-Hydroxyl-iso-pravastatin	↑ 26%	↑ 29%
		3α-Hydroxyl-iso-pravastatin	↑ 39%	↑ 55%
Fenofibrate 160 mg ¹ as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑ 15%	↑ 16%
<i>Anti-diabetic agents</i>				
Fenofibrate 145 mg ¹ once daily for 10 days	Glimepiride, 1 mg once daily as a single dose	Glimepiride	↑ 35%	↑ 18%
Fenofibrate 54 mg ¹ three times daily for 10 days	Metformin, 850 mg three times daily for 10 days	Metformin	↑ 3%	↑ 6%
Fenofibrate 145 mg ¹ once daily for 14 days	Rosiglitazone, 8 mg once daily for 5 days	Rosiglitazone	↑ 6%	↓ 1%

¹ Fenofibrate oral tablet

² Fenofibrate oral micronized capsule

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, Wistar rats were dosed with fenofibrate at 10 mg/kg/day, 45 mg/kg/day, and 200 mg/kg/day, approximately 0.3 times, 1 times, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m²). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed in males at 6 times the MRHD. In a second 24-month study in a different strain of rats (Sprague-Dawley), doses of 10 mg/kg/day and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 mg/kg/day and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, based on mg/m² surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in

males.

In a 21-month study in CF-1 mice, fenofibrate 10 mg/kg/day, 45 mg/kg/day, and 200 mg/kg/day (approximately 0.2 times, 1 times, and 3 times the MRHD on the basis of mg/m² surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at 10 mg/kg/day, 60 mg/kg/day, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

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

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

Impairment of Fertility: In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (approximately 10 times the MRHD, based on mg/m² surface area comparisons).

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The effectiveness of fenofibrate has been established in adults with hypertriglyceridemia or primary hyperlipidemia based on adequate and well-controlled trials of other formulations of fenofibrate, referenced below as “fenofibrate.” Dosages of fenofibrate used in these trials were comparable to fenofibrate 90 mg per day [see *Clinical Pharmacology* (12.3)].

14.2 Clinical Trials in Adults with Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 patients with hypertriglyceridemia. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline TG levels of 500 to 1,500 mg/dL, and the other TG levels of 350 to 499 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate decreased primarily very low-density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with elevated triglycerides often results in an increase of LDL-C (See Table 5).

Table 5. Effects of Fenofibrate in Patients with Hypertriglyceridemia

Study 1	Placebo			Fenofibrate				
	Baseline TG levels 350 to 499 mg/dL	N	Baseline (mean)	Endpoint (mean)	% Change (mean)	N	Baseline (mean)	Endpoint (mean)

Triglycerides	28449	450	-0.5	27432	223	-46.2 *		
VLDL Triglycerides	19367	350	2.7	19350	178	-44.1 *		
Total Cholesterol	28255	261	2.8	27252	227	-9.1 *		
HDL Cholesterol	2835	36	4	2734	40	19.6 *		
LDL Cholesterol	28120	129	1.2	27128	137	14.5		
VLDL Cholesterol	2799	99	5.8	2792	46	-44.7 *		
Study 2	Placebo			Fenofibrate				
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (mean)	Endpoint (mean)	% Change (mean)	N	Baseline (mean)	Endpoint (mean)	% Change (mean)
Triglycerides	44710	750	7.2	48726	308	-54.5 *		
VLDL Triglycerides	29537	571	18.7	33543	205	-50.6 *		
Total Cholesterol	44272	271	0.4	48261	223	-13.8 *		
HDL Cholesterol	4427	28	5	4830	36	22.9 *		
LDL Cholesterol	42100	90	-4.2	45103	131	45*		
VLDL Cholesterol	42137	142	11	45126	54	-49.4 *		

* p < 0.05 vs. placebo

The effect of fenofibrate on serum triglycerides was studied in a double-blind, randomized, 3 arm parallel-group trial of 146 patients. The study population was comprised of 61% male and 39% female patients. Approximately 70% of patients had hypertension and 32% had diabetes. Patients were treated for eight weeks with either a formulation of fenofibrate comparable to 130 mg taken once daily with meals, a formulation of fenofibrate comparable to 130 mg taken once daily between meals, or placebo. Fenofibrate 130 mg, whether taken with meals or between meals, had comparable effects on TG and all lipid parameters (See Table 6).

Table 6. Fenofibrate Treatment in Patients with Hypertriglyceridemia

	Placebo (n = 50)		Fenofibrate with meals (n = 54)		Fenofibrate between meals (n = 42)	
	Baseline mg/dL (mean)	% Change at endpoint (mean)	Baseline mg/dL (mean)	% Change at endpoint (mean)	Baseline mg/dL (mean)	% Change at endpoint (mean)
Triglycerides	479	+0.7	475	-36.7 *	487	-36.6 *
Total Cholesterol	237	-0.8	248	-5.1	241	-3.4
HDL Cholesterol	35	+0.8	36	+13.7 *	36	+14.3 *
Non-HDL Cholesterol	202	-1.1	212	-8.2 **	205	-6.6 **
LDL Cholesterol	115	+3.2	120	+15.4 *	122	+14.5
VLDL Cholesterol	87	-1.6	92	-34.4 *	83	-30.4 *

* p ≤ 0.05 vs placebo

** p ≤ 0.05 vs placebo (log transformed data)

14.3 Clinical Trials in Adults with Primary Hyperlipidemia

The effects of fenofibrate were assessed in four randomized, placebo-controlled, double-blind, parallel group trials in patients with hyperlipidemia and mixed dyslipidemia. Fenofibrate therapy reduced LDL-C, Total-C, and triglycerides, and increased HDL-C (See Table 7).

Table 7. Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Mean baseline lipid values (N = 646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191 mg/dL
All fenofibrate (n = 361)	-18.7% *	-20.6% *	+11% *	-28.9% *
Placebo (n = 285)	-0.4%	-2.2%	+0.7%	+7.7%

† Duration of study treatment was 3 to 6 months.

* p = <0.05 vs. placebo

14.4. Lack of Efficacy in Cardiovascular Outcomes Trials

Fenofibrate did not reduce cardiovascular disease morbidity or mortality in two large, randomized controlled trials of patients with type 2 diabetes mellitus.

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) (NCT00000620) trial was a randomized placebo-controlled trial of 5,518 patients (2,765 assigned to receive fenofibrate) with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean age at baseline was 62 years and 31% were female. Overall, 68% were White, 15% were Black or African American; 7% identified as Hispanic or Latino. The mean duration of follow-up was 4.7 years. The primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death was a HR of 0.92 (95% CI, 0.79 to 1.08) for fenofibrate plus statin combination therapy as compared to statin monotherapy.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a 5-year randomized, placebo-controlled trial of 9,795 patients (4,895 assigned to receive fenofibrate) with type 2 diabetes mellitus treated with fenofibrate. The mean age at baseline was 62 years, 37% were female, and 93% were White. The primary outcome of coronary heart disease events was a HR of 0.89, (95% CI 0.75 to 1.05) with fenofibrate compared to placebo. The HR for total and coronary heart disease mortality, respectively, was 1.11 (95% CI, 0.95 to 1.29) and 1.19 (95% CI, 0.90 to 1.57) with fenofibrate as compared to placebo.

Because of chemical, pharmacological, and clinical similarities between fenofibrate and pemafibrate, findings in a large randomized, placebo-controlled clinical trial with pemafibrate are relevant for fenofibrate.

Pemafibrate did not reduce cardiovascular disease morbidity or mortality in a large, randomized, placebo-controlled trial of patients with type 2 diabetes mellitus on background statin therapy (NCT03071692). The trial was a randomized placebo-controlled trial of 10,497 patients (5,240 assigned to receive pemafibrate) with type 2 diabetes mellitus on background lipid-lowering therapy. The median age at baseline was 64 years and 28% were female. Overall, 86% were White, 5% were Asian, 3% were Black

or African American; 19% identified as Hispanic or Latino. The median duration of follow-up was 3.4 years. The primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal ischemic stroke, coronary revascularization, and death from cardiovascular causes, was a HR of 1.03, (95% CI, 0.91 to 1.15) for pemafibrate plus statin combination therapy as compared to statin monotherapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fenofibrate capsules, USP are supplied as follows:

Strength	Description	NDC	Package Size (capsules per bottle)
43 mg	white to off-white granular powder filled in size '4' white opaque cap and white opaque body hard gelatin capsule imprinted with ' RG78 ' on cap and body in black ink	NDC 63304-443-30	30
		NDC 63304-443-05	500
130 mg	white to off-white granular powder filled in size '0' white opaque cap and white opaque body hard gelatin capsule imprinted with ' RG79 ' on cap and body in black ink	NDC 63304-444-30	30
		NDC 63304-444-90	90
		NDC 63304-444-05	500

Storage

Store at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature] in a tightly closed container.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

Inform patients that fenofibrate capsules may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice [see *Contraindications (4), Warnings and Precautions (5.2)*].

Myopathy and Rhabdomyolysis

Advise patients that fenofibrate capsules may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication and they should discuss all medication, both prescription and over the counter, with

their healthcare provider. Instruct patients to inform other healthcare providers prescribing a new medication or increasing the dosage of an existing medication that they are taking fenofibrate capsules. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever [see *Warnings and Precautions (5.3) and Drug Interactions (7)*].

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as anaphylaxis and angioedema, have been reported with fibrates. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians [see *Warnings and Precautions (5.9)*].

Pregnancy

Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if fenofibrate capsules should be discontinued [see *Use in Specific Populations (8.1)*].

Lactation

Advise patients that breastfeeding during treatment with fenofibrate capsules are not recommended [see *Use in Specific Populations (8.2)*].

Missed Doses

If a dose is missed, advise patients not take an extra dose and to resume treatment with the next dose.

Manufactured by:

Ohm Laboratories Inc.

New Brunswick, NJ 08901

Distributed by:

Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

August 2024

FDA-10

PACKAGE LABEL. PRINCIPAL DISPLAY PANEL

NDC 63304-443-30

FENOFIBRATE CAPSULES, USP

43 mg

Rx only

30's Bottle Label

NDC 63304-444-30

FENOFIBRATE CAPSULES, USP

130 mg

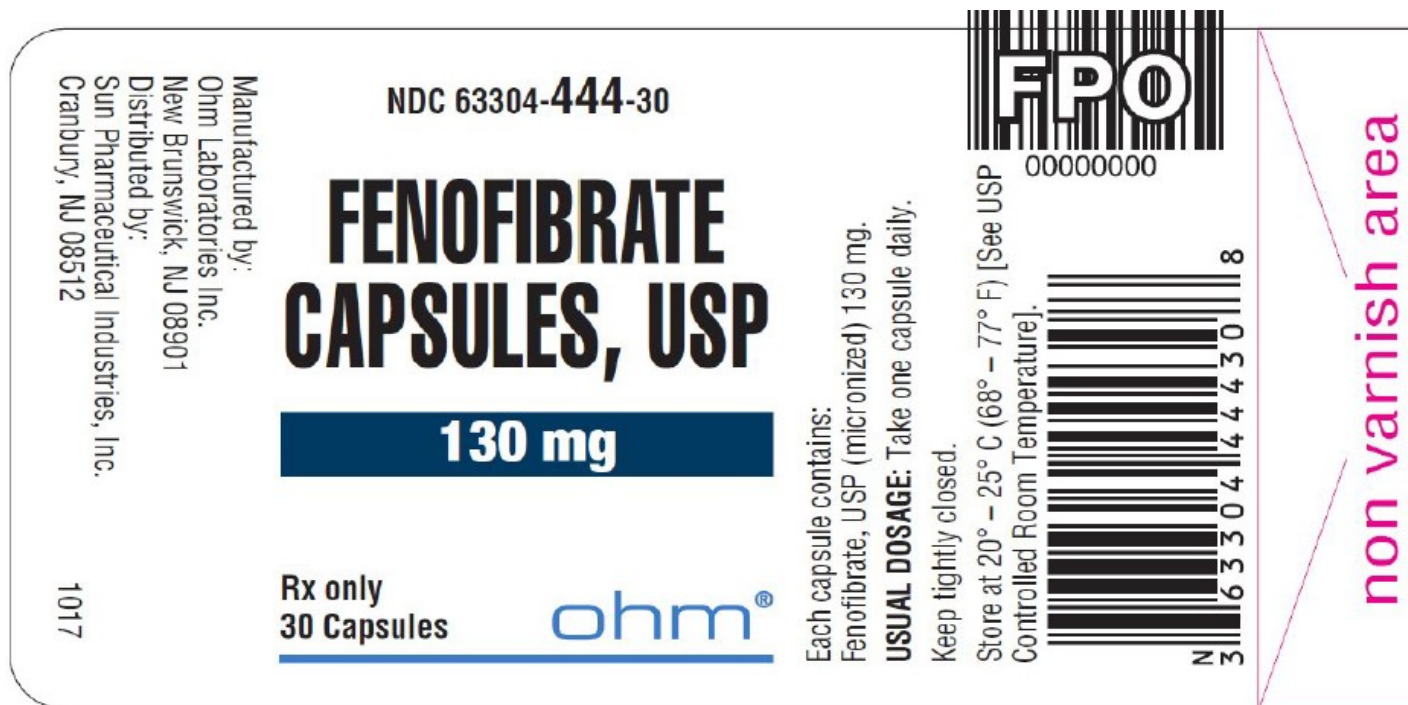
Rx only

30 Capsules ohm®



PACKAGE LABEL. PRINCIPAL DISPLAY PANEL

NDC 63304-444-30
FENOFIBRATE CAPSULES, USP
130 mg
Rx only
30 Capsules ohm®



PACKAGE LABEL. PRINCIPAL DISPLAY PANEL

NDC 63304-444-90
FENOFIBRATE CAPSULES, USP
130 mg
Rx only
90's Bottle Label
FENOFIBRATE
fenofibrate capsule
Product Information
90 Capsules ohm®

Manufactured by:
Ohm Laboratories Inc.
New Brunswick, NJ 08901
Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

NDC 63304-444-90

FENOFIBRATE CAPSULES, USP

130 mg

Rx only
90 Capsules

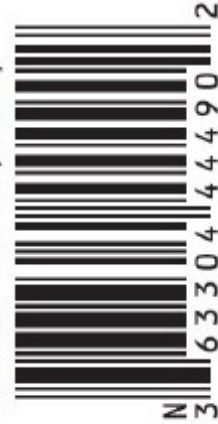
ohm®

Each capsule contains:
Fenofibrate, USP (micronized) 130 mg.
USUAL DOSAGE: Take one capsule daily.
Keep tightly closed.

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



00000000



N 3163304444902

non varnish area

1017

FENOFIBRATE

fenofibrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63304-443
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENOFIBRATE (UNII: U202363UOS) (FENOFIBRIC ACID - UNII: BGF9MN2HU1)	FENOFIBRATE	43 mg

Inactive Ingredients

Ingredient Name	Strength
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
STARCH, CORN (UNII: O8232NY3SJ)	
WATER (UNII: 059QF0KO0R)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

SHELLAC (UNII: 46N107B71O)

POLYSORBATE 65 (UNII: 14BGY2Y3MJ)

METHYLCELLULOSE (400 MPA.S) (UNII: O0GN6F9B2Y)

Product Characteristics

Color	white (white opaque)	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	RG78
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-443-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	
2	NDC:63304-443-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201748	03/02/2015	

FENOFIBRATE

fenofibrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63304-444
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENOFIBRATE (UNII: U202363UOS) (FENOFIBRIC ACID - UNII: BGF9MN2HU1)	FENOFIBRATE	130 mg

Inactive Ingredients

Ingredient Name	Strength
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
STARCH, CORN (UNII: O8232NY3SJ)	
WATER (UNII: 059QF0KO0R)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

SODIUM LAURYL SULFATE (UNII: 368GB5141J)
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)
TALC (UNII: 7SEV7J4R1U)
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)
FERROSFERRIC OXIDE (UNII: XM0M87F357)
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)
SHELLAC (UNII: 46N107B71O)
POLYSORBATE 65 (UNII: 14BGY2Y3MJ)
METHYLCELLULOSE (400 MPA.S) (UNII: O0GN6F9B2Y)

Product Characteristics

Color	white (white opaque)	Score	no score
Shape	CAPSULE	Size	21mm
Flavor		Imprint Code	RG79
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-444-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	
2	NDC:63304-444-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	
3	NDC:63304-444-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201748	03/02/2015	

Labeler - Sun Pharmaceutical Industries, Inc. (146974886)

Registrant - Sun Pharmaceutical Industries, Inc. (146974886)

Establishment

Name	Address	ID/FEI	Business Operations
Ohm Laboratories Inc.		184769029	MANUFACTURE(63304-443, 63304-444)