HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LIPOFEN® (fenofibrate) capsules, for oral use

Initial U.S. Approval: 1993

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	6/2025
Dosage and Administration (2)	6/2025
Warnings and Precautions, Mortality and Coronary Heart Disease Morbidity (5.1)	6/2025

----------INDICATIONS AND USAGE----------

LIPOFEN is a peroxisome proliferator-activated receptor (PPAR) alpha agonist indicated as an adjunct to diet:

- 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:

- Markedly elevated levels of serum TG (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: 50 to 150 mg orally once daily; the dosage should be adjusted according to patient response (2.2)
- Primary hyperlipidemia: 150 mg orally once daily (2.2)
- Administer as a single dose, at any time of day, with food 2.2).
- Assess TG when clinically appropriate, as early as 4 to 8 weeks after initiating TRICOR. Discontinue LIPOFEN in patients who do not have an adequate response after 2 months of treatment (2.2)
- Renal impairment: Initial dosage of 50 mg orally once daily (2.3)
- Geriatric patients: Select the dosage on the basis of renal function (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg and 150 mg (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 LIPOFEN (4)

----------WARNINGS AND PRECAUTIONS----------

- *Hepatotoxicity*: Serious drug-induced liver injury, including liver transplantation and death, has been reported with fenofibrates, including LIPOFEN. 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 fenofibrates. Risks are increased during co-administration with a statin, in geriatric patients and in patients with renal impairment, or hypothyroidism. Discontinue LIPOFEN if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Temporarily discontinue LIPOFEN 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 LIPOFEN dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. (5.3)
- *Increases in Serum Creatinine*: Monitor renal function in patients with renal impairment taking LIPOFEN. Consider monitoring renal function in patients at risk for renal impairment. (5.4)
- *Cholelithiasis*: Fenofibrate may increase cholesterol excretion into the bile, leading to 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 LIPOFEN and treat appropriately if reactions occur. (5.9)

----------ADVERSE REACTIONS----------

Adverse reactions (≥ 2% and greater than placebo): abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact ANI Pharmaceuticals, Inc. at 1-800-308-6755 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------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 LIPOFEN at least 1 hour before or 4 to 6 hours after a bile acid resin to avoid impeding its absorption (7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIPOFEN is 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 TG (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 LIPOFEN

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

2.2 Recommended Dosage and Administration

- Severe hypertriglyceridemia:
  - The recommended dosage of LIPOFEN is 50 mg or 150 mg orally once daily.
  - Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals.
- Primary hyperlipidemia:
  - The recommended dosage of LIPOFEN is 150 mg orally once daily.
- Administer LIPOFEN as a single dose at any time of day, with food.
- Advise patients to swallow LIPOFEN capsules whole. Do not crush, break, dissolve, or chew capsules.
- Assess TG when clinically appropriate, as early as 4 to 8 weeks after initiating LIPOFEN. Discontinue LIPOFEN in patients who do not have an adequate response after 2 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 LIPOFEN 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 LIPOFEN and periodically thereafter *[see Warnings and Precautions (5.4)]*.

- Treatment with LIPOFEN should be initiated at a dosage of 50 mg orally once daily in patients with mild to moderately impaired renal function (eGFR 30 to <60 mL/min/1.73m^2), and increased only after evaluation of the effects on renal function and TG levels at this dosage.
- LIPOFEN is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2), including those with end-stage renal disease (ESRD) and those receiving dialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Recommended Dosage in Geriatric Patients

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

3 DOSAGE FORMS AND STRENGTHS

- 50 mg: Size 3 white opaque gelatin capsule imprinted “G 246” and “50” in black ink.
- 150 mg: Size 1 white opaque gelatin capsule imprinted “G 248” and “150” in green ink.

4 CONTRAINDICATIONS

LIPOFEN is contraindicated in patients with:

- 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 fenofibrate, fenofibric acid, or any of the excipients in LIPOFEN. 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 fenofibrates, including LIPOFEN; pemafibrate; clofibrate; and gemfibrozil; the findings in 5 large randomized, placebo-controlled clinical trials with these other fibrate drugs may also apply to LIPOFEN.

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 1 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.

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 with postmarketing use of fenofibrates, including LIPOFEN. 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 LIPOFEN 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, an intermediate daily dosage or the maximum recommended daily dosage of fenofibrate have been associated with increases in serum AST or ALT. The incidence of increases in transaminases may be dose related *[see Adverse Reactions (6.1)]*.

LIPOFEN is contraindicated in patients with active liver disease, including those with unexplained persistent liver function abnormalities. Monitor patient's liver function, including serum ALT, AST, and total bilirubin, at baseline and periodically for the duration of therapy with LIPOFEN. Discontinue LIPOFEN 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 LIPOFEN in these patients if there is no alternative explanation for the liver injury.

5.3 Myopathy and Rhabdomyolysis

LIPOFEN 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 older, uncontrolled hypothyroidism, renal impairment, and concomitant use with certain other drugs *[see Drug Interactions (7) and Use 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, including fenofibrates, 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), Clinical Pharmacology (12.3),* and *Clinical Studies (14.4)]*.

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

Discontinue LIPOFEN if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if LIPOFEN is discontinued. Temporarily discontinue LIPOFEN 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 LIPOFEN 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 receiving fenofibrates. These increases tend to return to baseline following discontinuation of LIPOFEN. The clinical significance of this finding is unknown. Monitor renal function in patients with renal impairment taking LIPOFEN. Renal monitoring should also be considered

for patients taking LIPOFEN at risk for renal insufficiency, such as geriatric patients and patients with diabetes. LIPOFEN 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), 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. LIPOFEN therapy should be discontinued if gallstones are found. LIPOFEN is contraindicated in patients with pre-existing gallbladder disease.

5.6 Increased Bleeding Risk with Coumarin Anticoagulants

Exercise caution when co-administering anticoagulants with LIPOFEN because of the potentiation of coumarin-type anticoagulant effects in prolonging the prothrombin time/International Normalized Ratio (PT/INR). To prevent bleeding complications, monitor the PT/INR frequently and adjust the dosage of the anticoagulant until the PT/INR has stabilized *[see Drug Interactions (7)]*.

5.7 Pancreatitis

Pancreatitis has been reported in patients taking fenofibrates. 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 therapy with fenofibrates. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with LIPOFEN. Periodic monitoring of red and white blood cell counts is recommended during the first 12 months of LIPOFEN administration.

5.9 Hypersensitivity Reactions

Acute Hypersensitivity

Anaphylaxis and angioedema have been reported with postmarketing use of fenofibrates. 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 LIPOFEN. LIPOFEN is contraindicated in patients with a hypersensitivity to fenofibrate, fenofibric acid, or any of the ingredients in LIPOFEN.

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 with post-marketing use of fenofibrates, occurring days to weeks after treatment initiation. 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 LIPOFEN 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 high-density lipoprotein cholesterol (HDL-C) levels (as low as 2 mg/dL) occurring in patients with and without diabetes initiated on fibrate therapy, including fenofibrate. 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 LIPOFEN. If a severely depressed HDL-C level is detected, discontinue LIPOFEN and monitor HDL-C until it has returned to baseline. LIPOFEN 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)]*
- Hepatoxicity *[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)]*
- Paradoxical Decreases in HDL Cholesterol Levels *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

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

The safety of LIPOFEN 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 LIPOFEN 150 mg per day *[see Clinical Pharmacology (12.3)]*.

Adverse reactions reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during the double-blind, placebo-controlled trials are listed in Table 1 below. 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 either an intermediate or the maximum recommended daily dosage of fenofibrate versus 1.1% of patients treated with placebo. In an 8-week trial, the incidence of ALT or AST elevations ≥ 3 times the upper limit of normal was 13% in patients receiving an intermediate daily dosage or the maximum recommended daily dosage of fenofibrate and was 0% in those receiving the lowest recommended daily dosage of fenofibrate or placebo *[see Warnings and Precautions (5.2)]*.

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: Anemia, white blood cell decreases

Gastrointestinal: Pancreatitis

General: Asthenia

Hepatobiliary: Increased total bilirubin, hepatitis, cirrhosis

Immune System: Anaphylaxis, angioedema

Lipid Disorders: Severely depressed HDL-cholesterol levels

Musculoskeletal: Myalgia, muscle spasms, rhabdomyolysis, arthralgia

Renal and Urinary: Acute renal failure

Respiratory: Interstitial lung disease

Skin and Subcutaneous Tissue: Photosensitivity reactions, days to months after initiation. This may occur in patients who report a prior photosensitivity reaction to ketoprofen.

7 DRUG INTERACTIONS

Table 2 presents clinically important drug interactions with LIPOFEN.

Table 2: Clinically Important Drug Interactions with LIPOFEN

Statins	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with statins.
Intervention:	Consider if the benefit of using LIPOFEN 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 dosage titration of statin therapy.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with fenofibrates.
Intervention:	Consider if the benefit of using colchicine concomitantly with LIPOFEN 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 Impact:	Fibrates may cause potentiation of coumarin-type anticoagulant effects with prolongation of the PT/INR.
Intervention:	Caution should be exercised when coumarin anticoagulants are given in conjunction with LIPOFEN. 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 Impact:	Immunosuppressants such as cyclosporine and tacrolimus can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPOFEN, there is a risk that an interaction will lead to deterioration of renal function.
Intervention:	The benefits and risks of using LIPOFEN 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 Impact:	Bile-acid binding resins may bind other drugs given concurrently.
Intervention:	In patients taking a bile acid resin, administer LIPOFEN 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 dosage of 150 mg daily, based on body surface area (mg/m^2). Adverse reproductive outcomes occurred at higher doses in the presence of maternal toxicity (see Data). LIPOFEN 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 150 mg LIPOFEN 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 LIPOFEN and for 5 days after the final dose

8.3 Pediatric Use

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

8.4 Geriatric Use

Assess renal function in geriatric 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, geriatric 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 geriatric patients taking LIPOFEN.

8.5 Renal Impairment

LIPOFEN is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) including those with end-stage renal disease (ESRD) and those receiving dialysis. Dosage reduction is required in patients with mild to moderate renal impairment *[see Dosage and Administration (2.4) 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)]*.

8.6 Hepatic Impairment

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

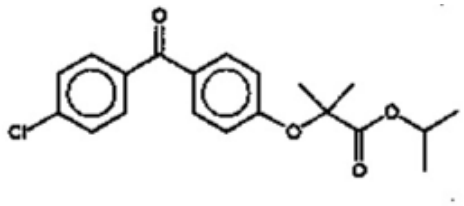
10 OVERDOSAGE

In the event of an overdose of LIPOFEN, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

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

11 DESCRIPTION

LIPOFEN® (fenofibrate capsules, USP), is a peroxisome proliferator-activated receptor (PPAR) alpha agonist available as hard gelatin capsules for oral administration. Each hard gelatin capsule contains 50 or 150 mg of fenofibrate USP. 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 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

LIPOFEN (fenofibrate capsules, USP) meets USP Dissolution Test 2.

Inactive Ingredients: Each hard gelatin capsule contains Gelucire 44/14 (lauroyl macrogol glyceride type 1500), polyethylene glycol 20,000, polyethylene glycol 8000, hydroxypropylcellulose, sodium starch glycolate, gelatin, titanium dioxide, shellac, propylene glycol, may also contain black iron oxide, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, D&C Yellow #10.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active moiety of LIPOFEN 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, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

12.2 Pharmacodynamics

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol (Total-C), 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. In a study of LIPOFEN capsules 200 mg, following single-dose administration, the plasma concentration (AUC) for the parent compound fenofibrate was approximately 40 µg/mL compared to 204 µg/mL for the metabolite, fenofibric acid. In the same study, the half-life was observed to be 0.91 hours for the parent compound versus 16.76 hours for the metabolite.

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. Peak plasma levels of fenofibric acid occur within approximately 5 hours after oral administration.

In a single dose and multiple dose study with LIPOFEN capsules 200 mg, the extent of absorption (AUC) of fenofibric acid, the principal metabolite of fenofibrate, was 42% larger at steady state compared to single-dose administration. The rate of absorption (C_{max}) of fenofibric acid was 73% greater after multiple-dose than after single-dose administration.

The extent of absorption of LIPOFEN in terms of AUC value of fenofibric acid increased in a less than proportional manner while the rate of absorption in terms of C_{max} value of fenofibric acid increased proportionally related to dose.

Effect of Food

The absorption of fenofibrate is increased when administered with food. With LIPOFEN, the extent of absorption is increased by approximately 58% and 25% under high-fat fed and low-fat fed conditions as compared to fasting conditions, respectively.

Distribution

Upon multiple dosing of fenofibrate, fenofibric acid steady state is achieved after 5 days. Plasma concentrations of fenofibric acid at steady state are approximately double of those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Elimination

Fenofibric acid is eliminated with a half-life of approximately 20 hours allowing once daily dosing of LIPOFEN.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; unchanged fenofibrate is detected at low concentrations in plasma compared to fenofibric acid over most of the single dose and multiple dosing periods.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vitro and *in vivo* metabolism data indicate that 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 oral administration of a single dose of radiolabeled fenofibrate in healthy volunteers, approximately 60% of the dose appeared in the urine, primarily as fenofibric acid and its glucuronide conjugate, and 25% was excreted in feces.

Use in Specific Populations

Geriatric Patients

In geriatric volunteers 77 to 87 years of age, the apparent oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an similar dosage regimen can be used in geriatric patients with normal renal function, without increasing accumulation of the drug or metabolites *[see Dosage and Administration (2) and Use in Specific Populations (8)]*.

Pediatric Patients

Pharmacokinetics of LIPOFEN has not been studied in pediatric patients.

Male and Female Patients

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Racial or 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 were examined in patients with mild, moderate and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl ≤30 mL/min] <30 mL/min or estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) showed a 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30 mL/min to 80 mL/min or eGFR 30 to 59 mL/min/1.73m^2) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects.

Patients with Hepatic Impairment

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

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 inhibitors 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 fenofibrate or fenofibric acid on systemic exposure of other drugs.

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

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

* TriCor (fenofibrate) oral tablet
† TriCor (fenofibrate) oral micronized capsule

Table 4: Effects of Fenofibrate on Systemic Exposure of Other Drugs

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

Fenofibrate 145 mg* once daily for 14 days	Rosiglitazone, 8 mg once daily for 5 days	Rosiglitazone	↑6%	↓1%

* TriCor (fenofibrate) oral tablet
† TriCor (fenofibrate) oral micronized capsule

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and 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 time, and 6 times the maximum recommended human dose (MRHD) based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month 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/m^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in CF-1 mice, fenofibrate 10 mg/kg/day, 45 mg/kg/day, and 200 mg/kg/day (approximately 0.2 times, 1 time, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at 10 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 body surface area comparisons).

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The effectiveness of LIPOFEN 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 LIPOFEN 150 mg per day *[see Clinical Pharmacology (12.3)]*.

14.2 Clinical Trials in Adults with Hypertriglyceridemia

The effects of fenofibrate on serum TG were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 patients with hypertriglyceridemia. Patients were treated for 8 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), TG, and VLDL cholesterol (VLDL-C). Treatment of patients with elevated TG often results in an increase of LDL-C (see Table 5).

Table 5: Effects of Fenofibrate in Patients with Hypertriglyceridemia

Trial 1	**Placebo**				**Fenofibrate**			
Baseline TG Levels 350 to 499 mg/dL	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
TG	28	449	450	-0.5	27	432	223	-46.2*
VLDL-TG	19	367	350	2.7	19	350	178	-44.1*
Total-C	28	255	261	2.8	27	252	227	-9.1*
HDL-C	28	35	36	4	27	34	40	19.6*
LDL-C	28	120	129	12	27	128	137	14.5
VLDL-C	27	99	99	5.8	27	92	46	-44.7*
Trial 2	**Placebo**				**Fenofibrate**			
Baseline TG Levels 500 to 1500 mg/dL	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
TG	44	710	750	7.2	48	726	308	-54.5*
VLDL-TG	29	537	571	18.7	33	543	205	-50.6*
Total-C	44	272	271	0.4	48	261	223	-13.8*
HDL-C	44	27	28	5.0	48	30	36	22.9*
LDL-C	42	100	90	-4.2	45	103	131	45.0*
VLDL-C	42	137	142	11.0	45	126	54	-49.4*

* $p<0.05$ vs. Placebo

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 TG, and increased HDL-C (see Table 6).

Table 6: 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	191.0 mg/dL
All fenofibrate (n=361)	-18.7%†	-20.6%†	+11.0%†	-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 ethnicity. 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 LIPOFEN.

Pemafibrate did not reduce cardiovascular disease morbidity or mortality in a large, randomized, placebo-controlled trial of patients with type 2 diabetes mellitus (TG levels of 200 to 499 mg per deciliter and HDL-C levels of 40 mg per deciliter or lower), 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 ethnicity. 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

LIPOFEN® (fenofibrate) capsules is available in two strengths:

Strength	Description	NDC	Package Size (capsules per bottle)
50 mg	Size 3 white opaque/white opaque gelatin capsule, imprinted in black ink with “50” between lines on the body, “G 246” on the cap and containing a white to almost white paste	NDC 62559-305-90	90
150 mg	Size 1 white opaque/white opaque gelatin capsule, imprinted in green ink with “150” between lines on the body, “G 248” on the cap and containing a white to almost white paste	NDC 62559-306-90	90

Storage

Store at 25ºC; Excursions permitted to 15ºC - 30ºC (59ºF - 86ºF). [See USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

Inform patients that LIPOFEN 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) and Warnings and Precautions (5.2)]*.

Myopathy and Rhabdomyolysis

Advise patients that LIPOFEN 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 LIPOFEN. 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)]*.

Increased Bleeding Risk with Coumarin Anticoagulants

Inform patients that the concomitant use of TRICOR with coumarin-type anticoagulants may increase the risk of bleeding. Advise patients if they are taking or planning to take coumarin-type anticoagulants to inform their healthcare providers and that increased monitoring may be necessary *[see Warnings and Precautions (5.6) and Drug Interactions (7)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as anaphylaxis and angioedema, have been reported with fenofibrates. 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 LIPOFEN should be discontinued *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding during treatment with LIPOFEN is 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.

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