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, USP) for oral use
Initial U.S. Approval: 1993

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

Warnings and Precautions (5.9) 05/2018

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

LIPOFEN is a peroxisome proliferator receptor alpha (PPAR α) activator indicated as an adjunct to diet:

- To reduce elevated LDL-C, total-c, TG and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (1.1)
- To reduce triglycerides in adult patients with severe hypertriglyceridemia (1.2)

Important Limitations of Use:

- Fenofibrate at a dose equivalent to 150 mg of LIPOFEN was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus (5.1)

----------DOSAGE AND ADMINISTRATION---------

- Primary hypercholesterolemia or mixed dyslipidemia: 150 mg per day (2.2)
- Severe Hypertriglyceridemia: 50 to 150 mg per day; adjust the dose according to patient response (2.3)
- Renally impaired patients: 50 mg per day; increase the dose according to the effect on renal function and lipid levels (2.4)
- Geriatric patients: select the dose based on renal function (2.5)
- The maximum daily dose is 150 mg per day (2.3)

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

- Oral capsules: 50 mg and 150 mg (3)

----------CONTRAINDICATIONS----------

- Severe renal impairment, including patients receiving dialysis (4, 8.6, 12.3)
- Active liver disease (4, 12.3)
- Gallbladder disease (4, 5.5)
- Known hypersensitivity to fenofibrate or fenofibric acid (4, 5.9)
- Nursing Mothers (4,8.3)

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

- Fibrates increase the risk of myopathy, and rhabdomyolysis has been reported in patients taking fibrates (with a significantly higher rate observed with gemfibrozil); rhabdomyolysis risk is increased in the elderly, patients with diabetes, renal insufficiency or hypothyroidism (5.2)
- Fenofibrate can increase serum transaminases. Monitor liver tests, including ALT, periodically during therapy (5.3)
- Fenofibrate can reversibly increase serum creatinine levels (5.4). Monitor renal function periodically in patients with renal impairment (8.6)
- Fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.5)
- Exercise caution in concomitant treatment with coumarin-type anticoagulants. Adjust dosage of these anticoagulants to maintain the Prothrombin Time/International Normalized Ratio (PT/INR) at the desired level to prevent bleeding complications (5.6, 7.1)
- Acute hypersensitivity reactions, including anaphylaxis and angioedema and delayed hypersensitivity reactions, including severe cutaneous adverse drug reactions have been reported post-marketing. Some cases, were life-threatening and required emergency treatment. Discontinue fenofibrate and treat patients appropriately if reactions occur (5.9).

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

The most common adverse reactions (incidence of > 2% and at least 1% greater than placebo) are abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6).

To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc. at 1 (877) 334-3464 or FDA at 1 (800) 332-1088 or via the web at www.fda.gov/medwatch/index.html for voluntary reporting of adverse reactions.

----------DRUG INTERACTIONS----------

- Coumarin-type anticoagulants (7.1)
- Immunosuppressants (7.2)
- Bile acid binding resins (7.3)
- Colchicine (7.4)

----------USE IN SPECIFIC POPULATIONS-------

- Geriatric Use: Determine dose selection based on renal function (8.5)
- Renal Impairment: Avoid use in patients with severe renal impairment. Dose reduction is required in patients with mild to moderate renal impairment (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Primary Hypercholesterolemia or Mixed Dyslipidemia

LIPOFEN is indicated as adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-c), Triglycerides (TG) and apolopoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

1.2 Severe Hypertriglyceridemia

LIPOFEN is also indicated as adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacologic intervention.

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

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1.3 Important Limitations of Use

Fenofibrate at a dose equivalent to 150 mg of LIPOFEN was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

LIPOFEN capsules should be given with meals thereby optimizing the absorption of the medication.

Patients should be advised to swallow LIPOFEN capsules whole. Do not open, crush, dissolve or chew capsules.

Patients should be placed on an appropriate lipid-lowering diet before receiving LIPOFEN, and should continue this diet during treatment with LIPOFEN.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of LIPOFEN. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 150 mg per day.

Consideration should be given to reducing the dosage of LIPOFEN if lipid levels fall significantly below the targeted range.

2.2 Primary Hypercholesterolemia or Mixed Dyslipidemia: The dose of LIPOFEN is 150 mg once daily.

2.3 Severe Hypertriglyceridemia: The initial dose is 50 to 150 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determination at 4 to 8 week intervals.

The maximum dose of LIPOFEN is 150 mg once daily.

2.4 Impaired Renal Function

In patients with mild-to-moderate renal impairment, treatment with LIPOFEN should be initiated at a dose of 50 mg per day, and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of LIPOFEN should be avoided in patients with severe renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.5 Geriatric Patients

Dose selection for the elderly 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 receiving dialysis *[see Clinical Pharmacology (12.3)]*.
- patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities *[see Warnings and Precautions (5.3)]*.
- patients with preexisting gallbladder disease *[see Warnings and Precautions (5.5)]*.
- patients with known hypersensitivity to fenofibrate or fenofibric acid *[see Warnings and Precautions (5.9)]*.
- nursing mothers *[see Use in Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Coronary Heart Disease Morbidity and Mortality

The effect of LIPOFEN on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p=0.18) and 19% (HR 1.19 [0.90, 1.57], p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.[1]

Because of chemical, pharmacological, and clinical similarities between fenofibrate, clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to LIPOFEN.

In the Coronary Drug Project, a large study of post myocardial infarction patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from the WHO study (RR=1.29).

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05).

5.2 Skeletal Muscle

Fibrates increase the risk for myopathy and have been associated with rhabdomyolysis. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal insufficiency, or hypothyroidism.

Data from observational studies indicate that the risk for rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are co-administered with an HMG-CoA reductase inhibitor (statin). The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination *[see Clinical Pharmacology (12.3)]*.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase (CPK) levels.

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

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

5.3 Liver Function

Fenofibrate at doses equivalent to 100 mg to 150 mg LIPOFEN per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials of fenofibrate, increases to > 3 times the upper limit of normal of ALT occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. The incidence of increases in transaminases observed with fenofibrate therapy may be dose related. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed.

Chronic active hepatocellular and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Baseline and regular monitoring of liver tests, including ALT should be performed for the duration of therapy with LIPOFEN, and therapy discontinued if enzyme levels persist above three times the normal limit.

5.4 Serum Creatinine

Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. Monitor renal function in patients with renal impairment taking LIPOFEN. Renal monitoring should also be considered for patients taking LIPOFEN and are at risk for renal insufficiency, such as the elderly and patients with diabetes.

5.5 Cholelithiasis

Fenofibrate, like clofibrate and gemfibrozil, 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.

5.6 Coumarin Anticoagulants

Caution should be exercised when LIPOFEN is given in conjunction with coumarin anticoagulants. LIPOFEN may potentiate the anticoagulant effects of these agents resulting in prolongation of the Prothrombin Time/International Normalized Ratio (PT/INR). To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the anticoagulant are recommended until PT/INR has stabilized *[see Drug Interactions (7.1)]*.

5.7 Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. 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 decreases in hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. 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 LIPOFEN administration.

5.9 Hypersensitivity Reactions

Acute Hypersensitivity

Anaphylaxis and angioedema have been reported post-marketing 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.

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 post-marketing, 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 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, 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group (p = 0.074); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group (p = 0.022).

In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis than the placebo group (5.2% vs. 3.3% at 5 years; p<0.01).

5.11 Paradoxical Decreases in HDL Cholesterol Levels

There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical 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 rate observed in clinical practice.

Adverse reactions reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during the double-blind, placebo-controlled trials, regardless of causality, are listed in Table 1 below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver 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

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
DIGESTIVE		
Abnormal Liver Function Tests	**7.5%****	**1.4%**
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
Increased ALT	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
Increased AST	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

***** Dosage equivalent to 150 mg LIPOFEN

** Significantly different from placebo

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.

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: myalgia, rhabdomyolysis, pancreatitis, acute renal failure, muscle spasm, hepatitis, cirrhosis, anemia, arthralgia, decreases in hemoglobin, decreases in hematocrit, white blood cell decreases, asthenia, and severely depressed HDL cholesterol levels. Photosensitivity reactions have occurred days to months after initiation; in some of these cases, patients reported a prior photosensitivity reaction to ketoprofen.

7 DRUG INTERACTIONS

7.1 Coumarin Anticoagulants

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

Caution should be exercised when LIPOFEN is given in conjunction with coumarin anticoagulants. LIPOFEN may potentiate the anticoagulant effect of these agents resulting in prolongation of the PT/INR. To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the oral anticoagulant as recommended until the PT/INR has stabilized *[see Warnings and Precautions (5.6)]*.

7.2 Immunosuppressants

Immunosuppressant agents such as cyclosporine and tacrolimus can impair renal function 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. When immunosuppressants and other potentially nephrotoxic agents are co-administered with LIPOFEN, the lowest effective dose of LIPOFEN should be employed and renal function should be monitored.

7.3 Bile-Acid Binding Resins

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

7.4 Colchicine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the maximum recommended human dose (MRHD), based on body surface area comparisons; mg/m^2.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

8.3 Nursing Mothers

Fenofibrate should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Fenofibrate is substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, the dose selection for the elderly should be made on the basis of renal function *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*. Fenofibrate exposure is not influenced by age. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking LIPOFEN.

8.6 Renal Impairment

The use of LIPOFEN should be avoided in patients who have severe renal impairment [*see Contraindication (4)*]. Dose reduction is required in patients with mild to moderate renal impairment [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. Monitoring renal function in patients with renal impairment is recommended.

8.7 Hepatic Impairment

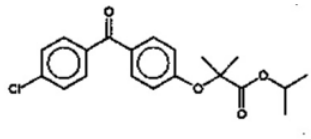
The use of LIPOFEN has not been evaluated in patients with hepatic impairment *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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. The usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION

LIPOFEN® (fenofibrate capsules, USP), is a lipid regulating agent 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 $C_{20}H_{21}O_4C1$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82ºC. 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 extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, 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). The resulting decrease in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apolipoproteins AI, AII and HDL cholesterol.

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

12.2 Pharmacodynamics

Elevated levels of total-c, LDL-C, and apo B and decreased levels of HDL-C and its transport complex, Apo AI and Apo AII, are risk factors for atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-c, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

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

12.3 Pharmacokinetics

The extent and rate of absorption of fenofibric acid after administration of 150 mg LIPOFEN capsules are equivalent under low-fat and high-fat fed conditions to 160 mg TriCor® tablets.

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 bioavailability study with 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 hrs for the parent compound versus 16.76 hrs 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. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled 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 occur within approximately 5 hours after oral administration.

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.

In a single dose and multiple dose bioavailability 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.

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

Metabolism: Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; 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.

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

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

Geriatrics: In elderly 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 equivalent dose of LIPOFEN can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites *[see Dosage and Administration (2.5) and Use in Specific Populations (8.5)]*.

Pediatrics: Pharmacokinetics of LIPOFEN has not been studied in pediatric patients.

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

Race: The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability.

Renal Impairment: The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate and severe renal impairment. Patients with mild (estimated glomerular filtration rate eGFR 60-89 ml/min/1.73m^2) to moderate (eGFR 30-59 mL/min/1.73m^2) renal impairment had similar exposure but an increase in the half-life for fenofibric acid was observed as compared to that of healthy subjects. Patients with severe renal impairment (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. In patients with mild to moderate renal impairment, treatment with LIPOFEN should be

initiated at a dose of 50 mg per day, and increased only after evaluation of the effects on renal function and lipid levels at this dose. Based on these findings, the use of LIPOFEN should be avoided in patients who have severe renal impairment.

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

Drug-Drug Interactions: *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome P450 (CYP) 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 2 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 3 describes the effects of fenofibrate on co-administered drugs.

Table 2. 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 agents				
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%
Anti-diabetic agents				
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] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

Table 3. Effects of Fenofibrate on Systemic Exposure of Co-Administered Drugs

Dosage Regimen of Fenofibrate	Dosage Regimen of Co-Administered Drug	Change in Co-Administered Drug Exposure		
		Analyte	AUC	C_{max}
Lipid-lowering agents				
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%
Fenofibrate 160 mg[1] as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑15%	↑16%
Anti-diabetic agents				
Fenofibrate 145 mg[1] once daily for 10 days	Glimepiride, 1 mg as a single dose	Glimepiride	↑35%	↑18%
Fenofibrate 54 mg[1] 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] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

13 NON-CLINICAL 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, 45 and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface are comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times 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 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 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg; 2 times the human dose), and gemfibrozil (250 mg/kg; 2 times the human dose, based on mg/m^2 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, 45 and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at 10, 60 and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male 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/m^2 surface area comparisons).

14 CLINICAL STUDIES

Clinical trials have not been conducted with LIPOFEN.

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

The effects of fenofibrate at a dose equivalent to 150 mg per day of LIPOFEN were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-c 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, total-c, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 4).

Table 4. Mean Percent Change in Lipid Parameters at End of Treatment[+]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	* -28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C >160 mg/dL and TG <150 mg/dL				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C >160 mg/dL and TG ≥150 mg/dL				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

[+] Duration of study treatment was 3 to 6 months.
* p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

14.2 Severe Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline TG levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 150 mg LIPOFEN per day decreased primarily very low density lipoprotein (VLDL), triglycerides and VLDL cholesterol. Treatment of some with elevated triglycerides often results in an increase of LDL-C (see Table 5).

Table 5. Effects in Patients With Severe 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)**	**% Change (Mean)**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*

Study 2	Placebo				Fenofibrate			
Baseline TG Levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = P<0.05 vs. Placebo

The effect of LIPOFEN on cardiovascular morbidity and mortality has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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, available in bottles of 30 (NDC 66869-137-20) and 90 (NDC 66869-137-30).

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, available in bottles of 30 (NDC 66869-147-20) and 90 (NDC 66869-147-30).

Store at USP controlled room temperature 20-25ºC (68-77º F); Excursions permitted to 15ºC - 30ºC (59ºF - 86ºF). Keep out of the reach of children. Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

- of the potential benefits and risks of LIPOFEN.
- not to use LIPOFEN if there is a known hypersensitivity to fenofibrate or fenofibric acid.
- of medications that should not be taken in combination with LIPOFEN.
- that if they are taking coumarin anticoagulants, LIPOFEN may increase their anti-coagulant effect, and increased monitoring may be necessary.
- to inform their physician of all medications, supplements, and herbal preparations they are taking and any change in their medical condition.
- to inform a physician prescribing a new medication, that they are taking LIPOFEN.
- to continue to follow an appropriate lipid-modifying diet while taking LIPOFEN.
- to take LIPOFEN once daily at the prescribed dose, swallowing each capsule whole.
- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms.
- to return to their physician’s office for routine monitoring.

Product of Israel

Manufactured for:
Kowa Pharmaceuticals America, Inc.
Montgomery, AL 36117