PRODUCT MONOGRAPH

[Pr]APO-FENO-MICRO
Fenofibrate Capsules Apotex Standard
67 mg and 200 mg

[Pr]APO-FENOFIBRATE
Fenofibrate Capsules Apotex Standard
100 mg

Lipid Metabolism Regulator

APOTEX INC.
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Control No.: 169773

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THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Fenofibrate lowers elevated serum lipids by decreasing the low-density lipoprotein (LDL) fraction rich in cholesterol and the very low density lipoprotein (VLDL) fraction rich in triglycerides. In addition, fenofibrate increases the high density lipoprotein (HDL) cholesterol fraction.

Fenofibrate appears to have a greater depressant effect on the VLDL than on the low density lipoproteins (LDL). Therapeutic doses of fenofibrate produce elevations of HDL cholesterol, a reduction in the content of the low density lipoproteins cholesterol, and a substantial reduction in the triglyceride content of VLDL.

The mechanism of action of fenofibrate has not been definitively established. Work carried out to date suggests that fenofibrate:

- enhances the liver elimination of cholesterol as bile salts;
- inhibits the biosynthesis of triglycerides and enhances the catabolism of VLDL by increasing the activity of lipoprotein lipase;
- has an inhibitory effect on the biosynthesis of cholesterol by modulating the activity of HMG-CoA reductase.

Metabolism and Excretion
After oral administration with food, fenofibrate is rapidly hydrolyzed to fenofibric acid, the active metabolite.

In man it is mainly excreted through the kidney. Half-life is about 20 hours. In patients with severe renal failure, significant accumulation was observed with a large increase in half-life. Therefore, the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance.

Distribution

Fenofibric acid is extensively bound (> 99 %) to plasma albumin. This binding is not saturable.

Absorption

Fenofibrate's absorption is low and variable when the product is administered under fasting conditions. Fenofibrate's absorption is increased when the compound is given with food. The APO-FENO-MICRO formulation of fenofibrate offers in the order of 33% greater bioavailability than the APO-FENOFIBRATE formulation of fenofibrate. Thus, a 200 mg capsule of the APO-FENO-MICRO formulation of fenofibrate achieves equivalent plasma levels to a single dose of three 100 mg capsules of the APO-FENOFIBRATE formulation and a 67 mg capsule of the APO-FENO-MICRO formulation of fenofibrate achieves equivalent plasma levels to a 100 mg capsule of APO-FENOFIBRATE. In comparison with the APO-FENOFIBRATE formulation, the absorption of APO-FENO-MICRO is less influenced by fat content of the diet.

COMPARATIVE BIOAVAILABILITY

A randomized, two-way crossover, single dose bioavailability study was conducted in fed, healthy, adult male subjects. The bioavailability of APO-FENO-MICRO Capsules, 200 mg, relative to Lipidil Micro® Capsules, 200 mg, was determined following a single dose of 200 mg (1×200 mg capsule). The average values of the pharmacokinetic parameters determined for each of the formulations are listed in the following table for the 16 subjects completing the study.

Summary Table of the Comparative Bioavailability Data
Fenofibrate (Dose: 1x200 mg capsule) (from measured data)

Parameter	Geometric Mean Arithmetic Mean (C.V.)		Ratio of Geometric Means(%)
	APO-FENO-MICRO	Lipidil Micro®*	
AUC_{0-72} (µg·hr/mL)	133.6 139.2 (29)	140.7 146.2 (27)	95
AUC_I (µg·hr/mL)	140.6 147.1 (30)	147.8 154.1 (28)	95
C_{max} (µg/mL)	8.866 9.102 (24)	10.014 10.248 (23)	89
T_{max}** (hr)	6.66 (45)	6.31 (41)	--
$T_{1/2}$** (hr)	14.98 (34)	14.93 (29)	--

* Lipidil Micro® is manufactured by Laboratories Fournier S.C.A., France and distributed by Jouveinal Inc., and was purchased in Canada.

**The arithmetic means (CV) are presented for T_{max} and $T_{1/2}$.

INDICATIONS AND CLINICAL USE

APO-FENOFIBRATE (fenofibrate) and APO-FENO-MICRO (fenofibrate) are indicated as an adjunct to diet and other therapeutic measures for:

1) Treatment of patients with hypercholesterolemia, Fredrickson classification Types IIa and IIb mixed hyperlipidemias, to regulate lipid levels (reduce serum triglycerides and LDL cholesterol levels and increase HDL cholesterol).

2) Treatment of adult patients with very high serum triglyceride levels, Fredrickson classification Type IV and Type V hyperlipidemias, who are at a high risk of sequelae and complications (i.e., pancreatitis) from their hyperlipidemia.

APO-FENOFIBRATE and APO-FENO-MICRO alone may not be adequate therapy in some patients with familial combined hyperlipidemia with Type IIb and Type IV hyperlipoproteinemia.

Initial therapy for hyperlipidemia should include a specific diet (at least equivalent to the American Heart Association (AHA) Step I diet), weight reduction, and an exercise program; and for patients with diabetes mellitus, good diabetic control.

CONTRAINDICATIONS

- Hepatic insufficiency (including primary biliary cirrhosis and unexplained persistent liver function abnormality).
- Pre-existing gallbladder disease (see WARNINGS).
- Severe renal dysfunction.
- Chronic or acute pancreatitis.
- Hypersensitivity to fenofibrate, any component of this medication, or other drugs of the fibrate class.
- The drug should not be used during pregnancy and breastfeeding.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- APO-FENOFIBRATE (fenofibrate) and APO-FENO-MICRO (fenofibrate) are not indicated for the treatment of Type I hyperlipoproteinemia.
- Should not be co-administered with HMG-CoA reductase inhibitors (statins) in patients with pre-disposing factors for myopathy.
- Under 18 years of age.

WARNINGS

Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)
The concomitant administration of fenofibrate and statins should be avoided unless the benefit for further alteration in lipid levels is likely to outweigh the increased risk of this combination.
The concomitant administration of fenofibrate with Pravastatin (40 mg) once daily for 10 days, in healthy adults, increased the mean Cmax and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with Pravastatin also increased the mean Cmax and AUC of the major metabolites, 3-alpha-hydroxy-

isopravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively.
The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic action, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading to a high proportion of cases to acute renal failure.
This combination therapy must not be used in patients with predisposing factors for myopathy (pre-existing myopathy, age >70 years, renal impairment, hepatic impairment, severe infection, surgery and trauma, frailty, hypothyroidism or electrolyte imbalance, personal or family history of hereditary muscular disorders, previous history of muscle toxicity with another HMG-CoA reductase inhibitor, concomitant use of a fibrate, niacin or ezetimibe, alcohol abuse, excessive physical exercise, diabetes with hepatic fatty change situations where an increase in plasma levels of active ingredient may occur).
For information on a specific HMG-CoA reductase inhibitor, consult a respective Product Monograph.
The use of fibrates alone, including fenofibrate, may occasionally be associated with myositis, myopathy or rhabdomyolysis. Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy and or myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

Liver Function
Abnormal liver function tests have been observed occasionally during fenofibrate administration, including elevations of transaminases, and decreases or, rarely, increases in alkaline phosphatase. From 5 placebo-controlled trials of 2 to 6 months' duration, increases up to >3 times the upper limit of normal occurred in 2.9% (14/477) of patients taking fenofibrate versus 0.5% (2/386) of those treated with placebo. In the DAIS study (3 years duration), increases up to 3 times the upper limit of normal occurred in 1.9% (4/207) of patients taking fenofibrate versus 0% of those treated with placebo (0/211). Follow-up measurements, performed either at the end of treatment or during continued treatment, showed that transaminase values generally returned to normal limits. Therefore regular periodic liver function tests (AST, ALT and GGT) in addition to other baseline tests are recommended every 3 months for the first 12 months and at least yearly thereafter. APO-FENO-MICRO should be discontinued if abnormalities persist and/ or AST and ALT levels increase to more than 3 times the upper limit of normal.

Cholelithiasis
Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. APO-FENO-MICRO therapy should be discontinued if gallstones are found.

Haematologic changes

Mild hemoglobin, haematocrit and white blood cell decreases have been observed occasionally in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

PRECAUTIONS

Initial Therapy

Before instituting fenofibrate therapy, laboratory tests should be conducted to ensure that lipid levels are consistently abnormal. Attempts should be made to control serum lipids with appropriate diet, exercise and weight loss in obese patients. Secondary causes of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment and excessive alcohol intake should be adequately treated before fenofibrate therapy is initiated. In patients at high risk, consideration should be given to the control of other risk factors such as smoking, use of preparations containing estrogen and inadequately controlled hypertension.

Long-term Therapy

Because long-term administration of fenofibrate is recommended, the potential risks and benefits should be carefully weighed. Adequate pretreatment laboratory studies should be performed to ensure that patients have elevated serum cholesterol and/or triglycerides or low HDL-cholesterol levels. Response to therapy should be monitored by determination of serum lipid values (e.g. total cholesterol, LDL-C, triglycerides). If a significant serum lipid response is not obtained in 3 months, APO-FENO-MICRO should be discontinued.

Skeletal muscle

Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis or myositis, usually in patients with impaired renal function and in cases of hypoalbuminaemia. Myopathy should be considered in any patient with diffuse myalgias, myositis, muscle cramps, tenderness or weakness, and/or marked elevation of creatinine phosphokinase levels.

Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels (5 times the upper limit of normal) occur or myopathy is diagnosed.
Patient with pre-disposing factors for myopathy may be at an increased risk of developing rhabdomyolysis (see WARNINGS). For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed.
The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease (see WARNINGS). Consequently, the co-administration of fenofibrate with a HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease or other pre-disposing factors for myopathy (see WARNINGS) and with a close monitoring of potential muscle toxicity.

Reproductive studies

Standard tests for teratology, fertility and peri- and post-natal effects in animals have shown a relative absence of risk; however, embryo-toxicity has occurred in animals at maternally toxic doses.

Use in pregnancy
Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and in rabbits when given in doses 9 times the MRHD (on the basis of mg/m2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should not be used during pregnancy. (See CONTRAINDICATIONS).

Nursing mothers
It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore APO-FENO-MICRO and APO-FENOFIBRATE should not be used during breast-feeding.

Carcinogenicity

In long-term animal toxicity and carcinogenicity studies fenofibrate has been shown to be tumorigenic for the liver in male rats at 12 times the human dose. At this dose level in male rats there was also an increase in benign Leydig cell tumors. Pancreatic acinar cell tumors were increased in male rats at 9 and 40 times the human dose. However, mice and female rats were unaffected at similar doses. Florid hepato-cellular peroxisome proliferation has been observed following fenofibrate administration to rats. Such changes have not been found in the human liver after up to 3.5 years of fenofibrate administration.

Hepatobiliary disease
APO-FENO-MICRO and APO-FENOFIBRATE is not recommended for use in patients with hepatic impairment due to the lack of data.
Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis.

Renal Function
APO-FENO-MICRO should not be used in patients with severe renal dysfunction including patients on dialysis. In patients with hypoalbuminemia, e.g., nephrotic syndrome, and in patients with renal insufficiency, the dosage of fibrates must be reduced and renal function should be monitored regularly (see PRECAUTIONS, Skeletal muscle and DOSAGE AND ADMINISTRATION).
Treatment should be interrupted in case of an increase in creatinine levels > 50% upper limit of normal. It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.

Pancreatitis
In common with some other fibrates, pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary

tract stone or sludge formation with obstruction of the common bile duct. In patients with severe hypertriglyceridemia, cases of acute pancreatitis have been reported.

Geriatric Population

Fenofibrate is excreted by the kidney. Therefore, the risk of adverse reactions to APO-FENO-MICRO may be greater in the elderly patients with impaired renal function. Since elderly patients are more likely to have a decreased renal function, dose should be carefully selected (see DOSAGE AND ADMINISTRATION).

Pediatric Population

The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data for fenofibrate micronized formulation are available. Therefore the use of APO- FENOFIBRATE and APO-FENO-MICRO is not recommended in pediatric subjects under 18 years.

Drug Interactions

General

Fenofibrate is highly protein bound (>99%), mainly to albumin. Consideration should be given to the potential for displacement drug interactions with other highly protein-bound drugs.

Statins
No drug-drug interaction studies with fenofibrate and statins have been conducted in patients. Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying disease and use of concomitant medications (See WARNINGS).

Pravastatin
Concomitant administration in 23 healthy adults of fenofibrate with pravastatin, 40 mg once daily for 10 days, has been shown to increase the mean Cmax and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with pravastatin also increased the mean Cmax and AUC of the major metabolite, 3-alpha-hydroxy-iso-pravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively.

Atorvastatin
Concomitant administration of fenofibrate with atorvastatin (20 mg) once daily for 10 days resulted in a 14% decrease in the mean atorvastatin AUC value (range: from a 67% decrease to a 44% increase) in 22 healthy males. There was a 0% change in the atorvastatin mean Cmax value (range: from a 60% decrease to a 136% increase). No significant pharmacokinetic interaction was observed in the mean fenofibric acid AUC (2.3% decrease, range: from a 39% decrease to a

40 % increase) or in the mean Cmax (3.8% decrease, range: from a 29% decrease to a 42% increase) when fenofibrate was co-administered with multiple doses of atorvastatin.

Simvastatin
In a 10-day trial, fenofibrate was taken once daily. On day 10, simvastatin 40 mg was added to the fenofibrate regimen. The mean AUC of simvastatin acid, the main active metabolite, decreased by 42% (range: from a 77% decrease to a 50% increase) in the presence of fenofibrate. Fenofibrate had no impact (0%) on the mean simvastatin acid Cmax (range: from a 67% decrease to a 92% increase). The mean fenofibric acid Cmin plasma levels increased by 14% (range: from a 7% decrease to a 48% increase) following the co-administration of simvastatin, indicating that fenofibric acid concentrations are not significantly affected by the addition of a 40 mg dose of simvastatin.

Rosuvastatin
Co-administration of fenofibrate (67 mg three times daily) and rosuvastatin (10 mg once daily) for seven days did not lead to a clinically significant change in the plasma concentrations of either drug.

Ezetimibe
The safety and effectiveness of ezetimibe and fibrate combination therapy have not been established, therefore co-administration is not recommended until use in patients has been studied.

Oral anticoagulants
Caution should be exercised when oral anticoagulants are given in conjunction with APO-FENOFIBRATE (fenofibrate) or APO-FENO-MICRO (fenofibrate). The dosage of oral anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Careful monitoring of prothrombin time is therefore recommended until it has been definitely determined that the prothrombin level has been stabilized.

Statins and cyclosporine
Severe myositis and rhabdomyolisis have occurred when a statin or cyclosporine was administered in combination therapy with a fibrate. Therefore, the benefits and risks of using fenofibrate concomitantly with these drugs should be carefully considered.
Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with APO-FENO-MICRO stopped in the case of severe alteration of laboratory parameters.

Bile Acid Sequestrants
When a fibrate is used concurrently with cholestyramine or any other resin, an interval of at least 2 hours should be maintained between the administration of the two drugs, since the absorption of fibrates are impaired by cholestyramine.
Estrogens

Estrogens may lead to a rise in lipid levels.Prescribing APO-FENO-MICRO in patients taking estrogens or estrogen-containing contraceptives must be considered clinically on an individual basis.

Rosiglitazone

Some epidemiologic studies and case reports suggest that markedly decreased HDL-C in some patients involve the interaction of rosiglitazone with fenofibrate or bezafibrate.

Laboratory findings in some published case reports demonstrated that, in some cases, it is the combination of rosiglitazone and fenofibrate, and neither agent alone, that lowers HDL-C.

ADVERSE REACTIONS

In five placebo-controlled clinical trials, conducted in the U.S. and Europe, a total of 477 patients on fenofibrate and 386 patients on placebo were evaluated for adverse effects during 2 to 6 months of treatment.

Adverse events led to the withdrawal of treatment in 5.5% of patients (26/477) treated with fenofibrate, the most common symptoms being abnormal elevation in transaminases, skin reactions and digestive disorders. Of the placebo-treated patients, 2.6% (10/386) were discontinued due to adverse effects.

The most frequently reported adverse events include: gastrointestinal (epigastric distress, flatulence, abdominal pain, nausea, diarrhea, constipation), dermatologic (erythema, pruritus, urticaria), musculoskeletal (muscle pain and weakness, arthralgia), central nervous system (headache, dizziness, insomnia), miscellaneous (decreased libido, hair loss, weight loss).

Adverse events, regardless of their causality, reported in more than 1% of patients are shown in Table 1.

Table 1: Number (%) of Patients Reporting Adverse Events

	Fenofibrate N=477	Placebo N=386
Body as a whole	68 (14.3%)	51 (13.2%)
Abdominal pain	12 (2.5%)	8 (2.1%)
Asthenia	14 (2.9%)	7 (1.8%)
Headache	15 (3.1%)	11 (2.8%)
Cardiovascular system	15 (3.1%)	13 (3.4%)
Digestive system	63 (13.2%)	47 (12.2%)
Diarrhoea	10 (2.1%)	13 (3.4%)
Nausea	12 (2.5%)	7 (1.8%)
Constipation	6 (1.3%)	3 (0.8%)
Dyspepsia	5 (1.0%)	6 (1.6%)
Flatulence	10 (2.1%)	10 (2.6%)
Endocrine system	1 (0.2%)	1 (0.3%)
Haemic & lymphatic system	3 (0.6%)	1 (0.3%)
Metabolic & nutritional disorders	18 (3.8%)	14 (3.6%)
	12 (2.5%)	4 (1.0%)
ALT increase	8 (1.7%)	1 (0.3%)
AST increase	9 (4.9%)	0
ALT/AST increase	1 (0.2%)	5 (1.3%)

CPK increase Creatinine increase	8 (1.7%)	1 (0.3%)
Musculo-skeletal system Arthralgia Myalgia	31 (6.5%) 11 (2.3%) 3 (0.6%)	21 (5.4%) 11 (2.8%) 4 (1.0%)
Nervous system Dizziness	31 (6.5%) 5 (1.0%)	11 (2.8%) 4 (1.0%)
Respiratory system Rhinitis	34 (7.1%) 10 (2.1%)	25 (6.5%) 4 (1.0%)
Skin and appendages Rash Pruritus	24 (5.0%) 11 (2.3%) 10 (2.1%)	12 (3.1%) 3 (0.8%) 3 (0.8%)
Special senses	14 (2.9%)	10 (2.6%)
Urogenital system	14 (2.9%)	9 (2.3%)

Safety was monitored for 3 years during the placebo-controlled DAIS study (See Clinical Studies) for both adverse events and laboratory anomalies. Fenofibrate was used safely in type 2 diabetic patients, as the overall incidence and severity of adverse events were comparable in fenofibrate and placebo groups. Table 2 below summarizes the incidence of adverse events, by body system, observed in both treatment groups.

Table 2 DAIS study: Incidence of adverse events (AEs) by system, experienced by type 2 diabetic patients during treatment with fenofibrate or placebo (ITT population)

Body System	**Fenofibrate (N=207)**		**Placebo (N=211)**	
Total # pts. with at least 1 AE	AEs	Patients	AEs	Patients
	Total AEs: 1710	201(97%)	Total AEs: 1759	202(95.7%)
Body as a whole	371 (21.7%)	136 (65.7%)	362 (20.6%)	146 (69.2%)
Cardiovascular	183 (10.7%)	84 (40.6%)	220 (12.5%)	96 (45.5%)
Digestive	196 (11.5%)	86 (41.6%)	194 (11.0%)	87 (41.2%)
Endocrine	11 (0.6%)	10 (4.8%)	19 (1.1%)	11 (5.2%)
Haemic/lymphatic	31 (1.8%)	19 (9.2%)	23 (1.3%)	15 (7.1%)
Metabolic/ nutritional	50 (2.9%)	32 (15.5%)	70 (4.9%)	41 (19.4%)
Musculo-skeletal	155 (9, 1%)	84 (40.6%)	180 (10.2%)	84 (39.8%)
CNS	103 (6.0%)	59 (28.5%)	98 (5.6%)	58 (27.5%)
Respiratory	301 (17.6%)	108 (52.2%)	279 (15.9%)	105 (49.8%)
Skin/appendage	107 (6.3%)	58 (28.0%)	107 (6.1%)	48 (22.8%)
Special senses	73 (4.3%)	44 (21.3%)	90 (5.1%)	50 (23.7%)
Urogenital	118 (6.9%)	55 (26.6%)	103 (5.9%)	46 (21.8%)
Other	11 (0.6%)	9 (4.4%)	14 (0.8%)	11 (5.2%)

In two open, non- controlled clinical studies conducted in Canada and Germany, a total of 375 patients on fenofibrate, microcoated formulation, were evaluated for adverse events. Listed in Table 3 are the adverse events possibly or probably related to fenofibrate, microcoated formulation and reported by more than 0.5% of the patients.

Table 3: Number (%) of patients reporting adverse events possibly or probably related to fenofibrate	
Canadian and German multicenter studies (12-week treatment)	
Adverse Events	**microcoated fenofibrate (n = 375)**
Digestive system	
Gastrointestinal disorder	4 (1.1%)
Nausea	3 (0.8%)
Flatulence	2 (0.5%)
Diarrhea	2 (0.5%)
Liver function tests abnormal	2 (0.5%)
Dyspepsia	2 (0.5%)
Gastritis	2 (0.5%)
Constipation	2 (0.5%)
Body as a whole	
Abdominal pain	4 (1.1%)
Headache	2 (0.5%)
Asthenia	2 (0.5%)
Lab test abnormal	2 (0.5%)
Metabolic and Nutritional Disorders	
ALT increased (> 3 x UNL)	3 (0.8%)
AST increased (> 3 x UNL)	4 (1.1%)
Creatine kinase increased (> 5 x UNL)	1 (0.3%)
Nervous system	
Dizziness	2 (0.5%)
Libido decreased	2 (0.5%)

Some epidemiological studies and case reports support paradoxical HDL-C lowering with fenofibrate.

Other adverse events include commonly reported cases of vomiting. Uncommonly reported cases of pancreatitis and venous thromboembolism (pulmonary embolism and deep vein thrombosis). Rarely reported cases of alopecia, sexual asthenia, myositis and muscular cramps. Very rarely reported cases of, rhabdomyolysis and interstitial pneumopathies. Episodes of hepatitis have been reported. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued (see **WARNINGS**).

Photosensitivity reactions, development of gallstones and cutaneous hypersensitivity with erythema and vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light in individual cases (even after many months of uncomplicated use) have also been reported.

Post-Marketing:

In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during post-marketing use:

Hepatobiliary Disorders: jaundice, complications of cholelithiasis (e.g., cholecystitis, cholangitis, biliary colic, etc.)

Skin and Subcutaneous Tissue Disorders: severe cutaneous reactions (e.g erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)

Laboratory Tests:
In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of AST and ALT elevations was variable; in the clinical trials conducted in Canada and Germany elevations above three times the upper limit of normal were observed in 2.0 % of the patients (7/375) treated with fenofibrate, microcoated formulation. In two dose-ranging studies, the incidence of increases in transaminases (>3 x ULN) due to fenofibrate therapy appears to be dose related; 0.6% (1/157) (80mg tablet), 1.9% (3/158) (160mg tablet) and 4.0% (6/149) (240mg tablet). Values usually return to normal without interruption of treatment (see **PRECAUTIONS**). Reductions in alkaline phosphatase levels have also been observed.

Mild decreases in hemoglobin, hematocrit and white blood cell counts have been observed occasionally in patients following initiation of fenofibrate therapy but these observations were without clinical significance. However, these levels stabilize during long-term administration. In addition, a decrease in haptoglobin concentration has been observed in some patients with Type IV hyperlipidemia during long-term use of fenofibrate. However, this decrease in haptoglobin was not associated with any other sign of blood dyscrasia and/or hemolysis.

The mean plasma levels of urea and creatinine showed increases, particularly during long-term fenofibrate treatment, most of them remaining within the limits of normal values.

Fenofibrate also has the potential to provoke CK elevations and changes in hematologic parameters which generally subside when the drug is discontinued (see PRECAUTIONS). In the clinical studies conducted in Canada and Germany, the reported frequency of CK elevations above five times the upper limit of normal was approximately 0.3% (2/375) of the patients treated with fenofibrate, microcoated formulation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

While there has been no reported case of overdosage, symptomatic and supportive measures should be taken. Fenofibrate is not dialysable because the main metabolite (fenofibric acid) is highly bound to plasma proteins.

For management of a suspected drug overdose, contact your Regional Poison Centre immediately

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving APO-FENO-MICRO (fenofibrate) and should continue on this diet during treatment with APO-FENO-MICRO (fenofibrate). If appropriate, a program of weight control and physical exercise should be implemented.
Prior to initiating therapy with APO-FENO-MICRO (fenofibrate), secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.
If a significant serum lipid response is not obtained in three months, APO-FENO-MICRO (fenofibrate) should be discontinued.
The recommended dose for APO-FENO-MICRO (fenofibrate) in adults is 200 mg daily administered as one 200 mg capsule taken with the main meal or, three 67 mg capsules in two or three divided doses taken with meals. The maximum recommended total daily dose is 200 mg.

The recommended dose of APO -FENOFIBRATE (fenofibrate) is 300 mg daily administered in three divided doses (three 100 mg capsules) to be taken with meals. The maximum recommended total daily dose is 400 mg.

In patients with renal insufficiency (creatinine clearance between 20 and 85 ml/min in women and between 20 and 95 ml/min in men), APO-FENO-MICRO treatment should be initiated at the dose of 67 mg/day and increased progressively after evaluation of the tolerance and effects on the lipid parameters. No fenofibrate, regardless of formulation, should be used when the creatinine clearance is lower than 20 mL/min.

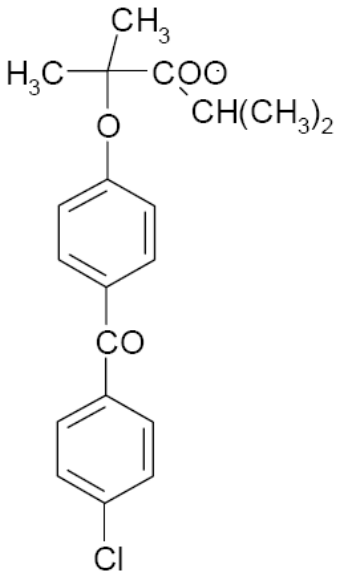
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Fenofibrate

Chemical Name:
1) Isopropyl 2-[*p*-(*p*-chlorobenzoyl)phenoxy]-2-methylpropionate.
2) 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-propanoic acid 1-methylethyl ester.

Structural Formula:



Molecular Formula: $C_{20}H_{21}ClO_4$
Molecular Weight: 360.84
Description:
Fenofibrate is a crystalline, white to off-white odourless powder. It has a melting point range of 79° to 82°C. It is practically insoluble in water, sparingly soluble in methanol, and freely soluble in acetone, chlorophorm and ether

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-FENOFIBRATE (fenofibrate) 100 mg: Each opaque, white, #2 hard gelatin capsule imprinted "100" contains 100 mg of fenofibrate. Available in bottles of 100, 250, 500 and 1000 Capsules and in blister packs of 100 Capsules.

APO-FENO-MICRO (fenofibrate) 67 mg: Each yellow, hard gelatin capsule imprinted "67" contains 67 mg of fenofibrate. Available in bottles of 100 and 500 Capsules and unit dose blister packages of 30 and 100 Capsules.

APO-FENO-MICRO (fenofibrate) 200 mg: Each orange, hard gelatin capsule imprinted "200" contains 200 mg of fenofibrate. Available in bottles of 100, 250, 500 and 1000 Capsules and blister packages of 30 Capsules.

APO-FENOFIBRATE (fenofibrate) Capsules contain the following non-medicinal ingredients: lactose monohydrate spray-dried, starch (corn), stearic acid.

The capsule shell contains the following non-medicinal ingredients: titanium dioxide, gelatin.

The edible black ink on the capsule shells contain the following non-medicinal ingredients: pharmaceutical glaze, black iron oxide, ethylene glycol monoethyl ether 5DA-3A alcohol, lecithin, dimethyl polysiloxane.

APO-FENO-MICRO (fenofibrate) Capsules contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate (spray-dried), stearic acid. The capsule shells contain the following non-medicinal ingredients: FD&C Red No. 40, D&C Red No. 28 (200 mg only), FD&C Yellow No. 6, FD&C Blue No. 1 (200 mg only), D&C Yellow #10 (67 mg only), titanium dioxide, gelatin.

The edible black ink on the capsule shells contain the following non-medicinal ingredients: pharmaceutical glaze, synthetic black iron oxide, n-butyl alcohol, propylene glycol, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake.

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature (15° C -25°C). Avoid excessive humidity.

INFORMATION FOR THE CONSUMER

Full prescribing information is available to doctors and pharmacists on request.

APO-FENOFIBRATE and APO-FENO-MICRO reduce blood cholesterol, in particular cholesterol associated with low and very low density lipoproteins (LDL and VLDL-cholesterol). Fenofibrate also reduces high triglyceride levels associated with hypercholesterolemia. Blood uric acid levels are also reduced by fenofibrate treatment. The mechanism of action of fenofibrate is not fully established.

APO-FENOFIBRATE and APO-FENO-MICRO are only available on prescription. These medicines should only be used to supplement an appropriate diet recommended and followed up by your doctor for the long-term treatment of raised lipid levels; prescription of this medicine in no way replaces dietary treatment. In addition, depending on the situation, your doctor may recommend further physical exercise, weight loss or other measures.

Take exactly as instructed by your doctor. Do not change the dose without your doctor's advice. Consult your doctor before stopping treatment since to do so may result in an increase in your blood lipid levels.

DO NOT USE APO-FENO-MICRO IF:

- you have liver or kidney problems;
- you have gallbladder problems;
- you have pancreatitis (an inflamed pancreas which causes abdominal pain);
- you are allergic to fenofibrate or similar drug or if you are allergic to any of the ingredients in APO-FENO-MICRO capsules (see WHAT DOES APO-FENO-MICRO CONTAIN ?*)*
- you are pregnant, think you may be pregnant or are planning to have a baby; in the event of pregnancy during treatment, your doctor should be informed and APO-FENO-MICRO should be discontinued;
- you are breast-feeding or planning to breast-feed your baby.
- you have a photoallergy (skin sensitivity to sunlight or UV light) when taking a fibrate (a class of drugs used for lowering cholesterol, which includes APO-FENO-MICRO and gemfibrozol) or an anti-inflammatory drug called ketoprofen.
- you are taking statins and have muscle problems or have potential risks of developing muscle problems.
- you are under 18 years of age.

BEFORE STARTING TREATMENT WITH THIS MEDICINE:

Before starting treatment with this medicine, your doctor must know:

- if you have had an allergic reaction (or poorly tolerated) APO-FENO-MICRO, any of its ingredients(see WHAT DOES APO-FENO-MICRO CONTAIN?)or any other lipid treatment ;
- if you suffer from liver or kidney problems;
- if you have an inflamed liver (hepatitis) - signs include yellowing of the skin and the whites of the eyes (jaundice) and an increase in liver enzymes (shown in blood tests);
- if you have pancreas problems;
- if you have a gall bladder or gallstone problem;
- if you have an under-active thyroid gland (hypo-thyroidism);
- if you are pregnant, or intend to become pregnant, or are breast-feeding, or intend to breast-feed;
- if you are taking any other medicines , prescription or not. Of particular concern are:
  - Statins (a class of drugs, which includes atorvastatin, pravastatin, simvastatin, etc., used to lower cholesterol). Taking a statin at the same time as APO-FENO-MICRO may increase the risk of muscle problems
  - Ezetimibe (another type of cholesterol lowering agent)
  - Oral anticoagulants (blood thinning agents such as warfarin)
  - Cyclosporine (a drug which may be taken following an organ transplant)
  - Cholestyramine or similar drug (another type of cholesterol lowering agent)
  - Estrogens (hormones which may be found in oral contraceptives or hormone replacement therapy)
  - a particular class of medicines to treat diabetes (such as rosiglitazone or pioglitazone)

Your doctor will ask you to have regular medical check-ups and appropriate laboratory tests. It is

important to respect the dates proposed for these tests: we strongly recommend that you keep these appointments faithfully so that any abnormalities that may occur can be identified promptly. These problems can include muscle inflammation and breakdown, which can cause kidney damage or even death. The risk of muscle breakdown is higher in some patients. Tell your doctor if:

- you are over 70 years old;
- you have kidney problems;
- you have thyroid problems;
- you or a close family member has muscle problem which runs in the family;
- you drink large amounts of alcohol;
- you are taking medicines called statins to lower cholesterol such as simvastatin, atorvastatin, pravastatin, rosuvastatin or fluvastatin;
- you have ever had muscle problems during treatment with fibrates such as fenofibrate, bezafibrate or gemfibrozil.

PROPER USE OF THE MEDICINE:

- APO-FENOFIBRATE and APO-FENO-MICRO should be taken with meals, as directed by your doctor.
- It is particularly important to follow this advice because fenofibrate is less well absorbed and hence, less effective when not taken with food.
- The usual recommended dose for APO-FENO-MICRO (fenofibrate) in adults is 200 mg daily administered as one 200 mg capsule or three 67 mg capsules in two or three divided
- The recommended dose of APO -FENOFIBRATE (fenofibrate) is 300 mg daily administered in three divided doses (three 100 mg capsules)
- Never change the dose unless directed by your doctor.
- APO-FENO-MICRO is not recommended for use in children.
- The safety of using fenofibrate in combination with a statin has not been extensively studied in patients. Therefore, the combined use of fenofibrate with a statin should be avoided unless recommended by your doctor.
- Tell your doctor of any health problem that occurs while you are taking APO-FENOFIBRATE or APO-FENO-MICRO as well as any prescription or non-prescription medicine. If you need other medical treatment, let the doctor know that you are taking APO-FENOFIBRATE or APO-FENO-MICRO.

If you forget a dose, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

SIDE EFFECTS:

In addition to its intended action, any medicine may cause unwanted effects.
Tell your doctor if you feel in any way unwell while taking APO-FENOFIBRATE or APO-FENO-MICRO .Some common side effects may include abdominal pains, constipation, diarrhea, flatulence, nausea, vomiting, headache, dizziness, skin reactions, fatigue, raised levels of liver enzymes in the blood.

This is not a complete list of side effects. If you experience any unexpected symptoms while taking APO-FENOFIBRATE or APO-FENO-MICRO, contact your doctor or pharmacist.

Stop taking APO-FENOFIBRATE or APO-FENO-MICRO and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

- allergic reaction - the signs may include swelling of the face, lips, tongue or throat, which may cause difficulty in breathing
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis)
- chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis)
- yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis).

Muscle pain or cramps, or muscle weakness, may indicate rare, but more serious, side effects. If you suffer any unexplained muscle pain, stop the drug and contact your doctor immediately.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

WHAT DO APO-FENOFIBRATE AND APO-FENO-MICRO CONTAIN?

APO-FENOFIBRATE Capsules contain the following non-medicinal ingredients: lactose monohydrate spray-dried, starch (corn), stearic acid; the capsule shell contains the following non-medicinal ingredients: titanium dioxide, gelatin; the edible black ink on the capsule shells contain the following non-medicinal ingredients: pharmaceutical glaze, black iron oxide, ethylene glycol monoethyl ether 5DA-3A alcohol, lecithin, dimethyl polysiloxane.

APO-FENO-MICRO (fenofibrate) Capsules contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate (spray-dried), stearic acid. The capsule shells contain the following non-medicinal ingredients: FD&C Red No. 40, D&C Red No. 28 (200 mg only), FD&C Yellow No. 6, FD&C Blue No. 1 (200 mg only), D&C Yellow #10 (67 mg only), titanium dioxide, gelatin; the edible black ink on the capsule shells contain the following non-medicinal ingredients: pharmaceutical glaze, synthetic black iron oxide, n-butyl alcohol, propylene glycol, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake.

THIS MEDICINE IS PRESCRIBED FOR A PARTICULAR HEALTH PROBLEM AND FOR YOUR PERSONAL USE. DO NOT GIVE IT TO OTHER PERSONS.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

IF YOU WANT FURTHER INFORMATION, ASK YOUR DOCTOR OR PHARMACIST.

Last revised:

PHARMACOLOGY

Animal Pharmacology

The antilipidemic activity of fenofibrate was investigated in normal and hyperlipidemic rats. Fenofibrate significantly lowers total lipids, LDL and VLDL-cholesterol, and triglyceride levels. At the same time it has been found to variably increase HDL-cholesterol concentrations. Its effect is more pronounced in hyperlipidemic rats and those fed high-fat diets than in normal rats and those fed standard diets. Studies comparing fenofibrate with clofibrate have found that fenofibrate is a potent cholesterol-lowering drug.

The pronounced hypolipidemic effect in hyperlipidemic animals suggests that fenofibrate reduces cholesterol by enhancing the rate of cholesterol elimination. In normocholesterolemic rats, the main effect of fenofibrate is an inhibition of cholesterol biosynthesis.

Fenofibrate has no anti-inflammatory, cardiovascular, respiratory, CNS, autonomic nervous system, or other basal metabolism activities.

PHARMACOKINETICS AND CLINICAL PHARMACOLOGY

Pharmacokinetics

In rats, dogs and man, fenofibrate is poorly absorbed from the gastrointestinal tract. This absorption is increased when the compound is administered in oil with food.
In man, a dose of 300 mg of non-micronized fenofibrate per day produced mean steady-state plasma drug concentrations ranging between 10 and 15 μg/mL after 5 days of administration.

Fenofibrate is metabolized by hydrolysis to its active form, fenofibric acid. In man, fenofibric acid is eliminated as conjugated with glucuronic acid. In rats this glucuroconjugation is very low and in dogs, practically non-existent. In these two species the main metabolic pathway is carbonyl reduction. The excretion in rats is principally a biliary excretion. In man, within 7 days after oral administration of fenofibrate with food, about 60% is excreted in the urine and 25% in the feces.

The elimination half-life of fenofibric acid is about 7 - 8 hours in rats and 24 hours in dogs. In man, the elimination half-life of fenofibric acid is about 20 - 24 hours. This value is not modified after multiple dosing. Very minor changes of pharmacokinetic parameters were observed in elderly subjects, but in patients with severe renal failure, significant accumulation was observed with a large increase of the half-life.

No sex related differences in pharmacokinetics and metabolism were observed in any species.

Fenofibric acid is extensively bound (>99%) to plasma proteins. This binding is not saturable.

Five specific pharmacokinetic studies were performed with a formulation of fenofibrate that APO-FENO-MICRO was shown to be bioequivalent to.

A first single dose study in 18 healthy volunteers (9M, 9F) demonstrated that one capsule of the 200 mg/capsule formulation of fenofibrate was bioequivalent to one capsule containing 300 mg of the original formulation of fenofibrate. In this balanced crossover study, the two formulations were administered immediately after a high-fat meal. The mean results are presented in the following table:

	AUC ($mg.L^{-1}.h$)	**C_{max} ($mg.L^{-1}$)**	**T_{max} (h)**	**$t_{½}$ (h)**
Fenofibrate (200 mg capsule)	176.7	11.0	5.9	15.4
Original Formulation Fenofibrate (300 mg capsule)	171.3	10.7	5.6	17.9
95% Confidence Interval (Westlake)	14.1%	15%		

A second single dose study in 18 healthy male volunteers demonstrated that one 200 mg capsule of fenofibrate was bioequivalent to three 100 mg capsules of original formulation fenofibrate taken simultaneously.

The two formulations were administered immediately after a high-fat meal according to a balanced crossover design. The mean results are presented in the following table:

	AUC ($mg.L^{-1}.h$)	**C_{max} ($mg.L^{-1}$)**	**T_{max} (h)**	**$t_{½}$ (h)**
Fenofibrate (200 mg capsule)	178.2	8.9	6	22.9
3 x Original Formulation Fenofibrate (100 mg capsules)	180.0	10.2	6	22.0
95% Confidence Interval (Westlake)	12.9%	31.4%		12.4%

In a third cross-over study, 18 healthy volunteers (8F, 10M) received either one 200 mg capsule or three original formulation 100 mg capsules once daily, during a low fat, low calorie meal, for 10 days.

The comparison of the pharmacokinetic parameters obtained at steady-state (Day 10) with the two formulations shows that the amount of fenofibrate absorbed is slightly higher with one 200 mg capsule than with three original formulation 100 mg capsules but also that the better absorption of the 200 mg/capsule formulation of fenofibrate leads to a better homogeneity of the fenofibric acid plasma concentrations. This lower inter-subject variability with the 200 mg/capsule formulation of fenofibrate is shown by the decrease of the coefficients of variation of AUC_{0-24}, C_{max} as well as C_{min} obtained on Day 10. The mean values obtained on Day 10 and their coefficients of variation (CV%) are presented in the following table:

	AUC_{0-24} ($mg.L^{-1}.h$)	**C_{max} ($mg.L^{-1}$)**	**C_{min} ($mg.L^{-1}$)**	**T_{max} (h)**	**$t_{½}$ (h)**
Fenofibrate (200 mg capsule)	154.1 (19%)	10.8 (23%)	3.9 (24%)	4.6 (20%)	26.1 (50%)
3 × Original Formulation Fenofibrate (100 mg capsules)	119.4 (45%)	8.6 (46%)	3.2 (54%)	5.6 (34%)	23.5 (40%)

In a fourth cross-over study, 5 healthy adult volunteers (male) received either one 200 mg capsule or three original formulation 100 mg capsules once daily, during a standard supper containing 40% lipids, for 10 days.

The comparison of the pharmacokinetic parameters obtained at steady-state (Day 10) with the two formulations shows that the amount of fenofibrate absorbed is slightly higher with three original formulation 100 mg capsules than with one 200 mg capsule. The mean values of pharmacokinetic parameters measured at Day 10 (CV%) are presented in the following table:

	AUC_{0-24} (mg.L^{-1}.h)	C_{max} (mg.L^{-1})	T_{max} (h)	$t_{½}$ (h)
Fenofibrate (200 mg capsule)	335.5 (34%)	20.1 (25%)	9.2 (4%)	15.1 (59%)
3 × Original Formulation Fenofibrate (100 mg capsules)	409.0 (31%)	25.5 (23%)	7.0 (36%)	15.3 (34%)

The apparent discrepancy of the results of the two multiple-dose studies can be explained by the difference in fat content of the meals used in these studies and by the difference of particle size of fenofibrate in the two formulations.

The larger sized particles of fenofibrate contained in the original formulation fenofibrate are indeed poorly absorbed in the presence of a low-fat meal whereas the smaller particles of the 200 mg/capsule formulation of fenofibrate are already well absorbed.

Fenofibrate dissolves more easily in the presence of a larger amount of fat and food, this seems to affect the absorption of original formulation fenofibrate more than that of 200 mg/capsule formulation of fenofibrate.

The fifth specific pharmacokinetic study was performed with the 67 mg/capsule formulation of fenofibrate: 24 healthy male volunteers took part and completed this two-way, open randomized, cross-over study. Each volunteer received a single oral dose of each formulation with a standard breakfast and with a one week interval between doses.

Values obtained for the two formulations were as follows:

		C_{max} (mg.L^{-1})	T_{max} (h)	AUC (mg.L^{-1})	$t_{½}$ (h)	MRT (h)
Fenofibrate (capsules 67 mg)	Mean	3.7	4.0*	62.1	19.7	25.2
	sd	0.5	(2.0-7.0)	19.0	6.1	6.0
Original Formulation Fenofibrate (100 mg capsules)						
	Mean	4.0	4.0*	59.6	19.0	26.5
	sd	0.9	(2.0-6.0)	21.8	5.8	6.3

*: Median (range); sd: Standard deviation

In summary, under the conditions of the studies, the data show that biological equivalence was achieved between the two formulations of fenofibrate.

Clinical Pharmacology

Action on Lipid Parameters:

The oral administration of 300 mg/day of fenofibrate for one week significantly reduced the plasma cholesterol and triglyceride levels in normolipidemic subjects. However, no change in HDL cholesterol levels was observed.

The effects of fenofibrate 300 mg/day, clofibrate 1500 mg/day and placebo on plasma lipoprotein and biliary lipid composition were compared in a double-blind study involving 12 normolipidemic subjects. Each treatment lasted two weeks. Fenofibrate lowered plasma cholesterol by 17%, triglycerides by 9% and LDL cholesterol by 16%.

Fenofibrate 400 mg/day was administered for one month to 18 patients with hyperlipoproteinemia who failed to achieve normal lipid levels with a lipid-lowering diet. Fenofibrate treatment significantly reduced the total plasma cholesterol concentrations by 14%, plasma triglycerides by 49% and VLDL triglycerides by 62%. No significant change was observed in HDL cholesterol concentration. LDL-cholesterol was reduced in patients with Type IIa and IIb hyperlipoproteinemia and increased in Types IV and V. Lipoprotein-lipase activity was significantly increased.

In a double-blind study, two parallel groups of hyperlipidemic patients were treated with either 400 mg/day of fenofibrate (15 patients) or placebo (8 patients) for one month. Significant decreases in total cholesterol, triglycerides and Apo-B were observed in the fenofibrate treated group, along with a significant increase in HDL-cholesterol.

Uricosuric action:
Fenofibrate decreased the plasma uric acid levels in normal as well as hyperuricemic subjects. In a study involving 10 normal male volunteers, single doses of 300 mg of fenofibrate were compared to benzbromarone. A uricosuric action was observed with both drugs. During a 14-day study in hyperlipidemic patients, a 28% decrease in plasma uric acid concentration was observed less than four days after the onset of treatment with 300 mg/day of fenofibrate. This effect remained constant until the end of the study. An additional study conducted in healthy volunteers confirmed the rapid onset of the fenofibrate induced hypouricemic effect and demonstrated the increased capability of the kidneys under these conditions to eliminate uric acid without damage to the proximal tubules.

Effect on lithogenic index:
By virtue of structural similarity to other fibrates, fenofibrate might be suspected to increase the risk of gallstones as a result of increased cholesterol excretion via the bile.

Thus, five investigators have studied the biliary lithogenic index in fenofibrate-treated patients. In most studies, the lithogenic index was shown to be increased but the effect of fenofibrate was not marked and the degree of significance varied from one study to another. The relative proportions of bile lipids were also affected by fenofibrate treatment.

It is not known how fenofibrate treatment modifies the lipid composition of the bile.

Human liver biopsies:

Two specific studies have been conducted in hyperlipidemic patients to evaluate the potential hepatocellular toxicity of fenofibrate. Examination of biopsies from liver samples of 38 patients including 28 receiving non-micronized fenofibrate over a mean period of approximately 2 years did not show any difference between treated and untreated patients. Peroxisomes were relatively rare, and macroscopic light and electron-microscopic observations revealed no sign of treatment-associated cellular abnormality. A similar study, taking biopsies from 10 patients who had, on average, received fenofibrate for 9 months, and comparing these with tissue from 13 hyperlipidemic patients who had only received dietary treatment did not show any morphological difference between the two groups or any significant difference in the number or in the size of peroxisomes.

Clinical Experience

The activity of fenofibrate has been evaluated in more than 150 clinical trials performed in the U.S., Canada and Europe. The majority of these were conducted with the original formulation of fenofibrate at a daily dose of 300 mg.

U.S. Studies:

Two multicenter, double-blind, placebo-controlled studies were conducted in the U.S., one in patients with Type II hyperlipoproteinemia, and the other in Type IV/V patients.

Type II Study:

Two hundred and twenty-seven (227) hypercholesterolemic patients (181 Type IIa and 46 Type IIb) were enrolled during 6 months. After the double-blind phase, the study became open and all patients were given fenofibrate for the ensuing 6 month period.

One hundred and sixteen (116) patients received fenofibrate (100 mg t.i.d.) and one hundred and eleven (111) received placebo. At the end of this first period, ninety-eight (98) of the one hundred and sixteen (116) who were given fenofibrate and ninety-four (94) of the one hundred and eleven (111) patients who were given placebo, entered the second 6 month open phase of fenofibrate treatment.

Fenofibrate reduced the mean plasma concentrations of total cholesterol and VLDL-cholesterol in both Type IIa and IIb patients. LDL-cholesterol concentration was substantially decreased in all Type IIa patients, whereas there was little change in the Type IIb patients in whom the pre-treatment LDL-cholesterol levels were relatively normal. The mean concentrations of HDL-cholesterol were increased in both types of patients. Plasma triglyceride levels were decreased in the hypertriglyceridemic Type IIb patients. These effects were observed in the double-blind and open phases of the study (Table 5).

Table 5
Effect of Fenofibrate on Percent Change of Lipoprotein Lipids from Baseline

	Type IIa		Type IIb	
Plasma Lipid Parameter	**Double-Blind Phase n=92**	**Open Phase n=73**	**Double-Blind Phase n=24**	**Open Phase n=21**
Total cholesterol	-16%	-18%	-15%	-24%
LDL-cholesterol	-20%	-22%	-3%	-20%
VLDL-cholesterol	-34%	-38%	-53%	-64%
Total triglyceride	-34%	-30%	-41%	-51%
HDL-cholesterol	+12%	+8%	+14%	+11%
LDL/HDL-cholesterol	-27%	-25%	-14%	-26%

N.B.: p-values <0.01 for differences between fenofibrate and placebo groups for all parameters except LDL-cholesterol in Type IIb. Inversely, placebo treatment induced no statistically significant changes in the lipid parameters.

Type IV/V Study:
One hundred forty-seven (147) patients entered the study and all were stabilized on a low-fat diet. Following a placebo baseline period, patients were stratified according to plasma triglyceride (TG) levels (Group A, 350-499 mg/dL; Group B, 500-1,500 mg/dL) and randomly assigned to treatment with either 100 mg fenofibrate or one placebo capsule three times a day with meals. Demographically, the treatment groups were similar. A dramatic reduction in total TG levels occurred in the fenofibrate-treated patients but not in the placebo-treated patients. This effect, seen in both Group A (46%) and Group B (55%) patients, reached near maximum reduction in only 2 weeks of treatment, and continued throughout the 8-week treatment period. In both groups, fenofibrate treatment also decreased very low-density lipoprotein (VLDL) TG, total cholesterol and VLDL cholesterol, and increased high-density lipoprotein (HDL) levels (Table 6).

Table 6
Percent Change in Lipid/Lipoprotein Values (mg/dL) from Baseline to End-point

	Group A		Group B	
	Fenofibrate	**Placebo**	**Fenofibrate**	**Placebo**
Total TG	-46%	-1%	-55%	+7%
VLDL-TG	-44%	+3%	-51%	+19%
Cholesterol				
Total	-9%	+3%	-14%	0%
HDL	+20%	+4%	+23%	+5%
VLDL	-45%	+6%	-49%	+11%
LDL	+15%*	+12%	+45%	-4%

Mean values rounded to nearest whole number.
*Not significantly different from placebo at p<0.05. All other changes with fenofibrate were significantly different from placebo at p ranging from 0.05 to <0.001.

LDL cholesterol levels increased 45% from baseline in Group B but not in Group A. It should be noted that baseline LDL cholesterol levels were considerably depressed in Group B as compared with Group A patients.

Canadian Study:
Seventeen (17) patients with hypercholesterolemia were included in this six-month open study. The dosage of fenofibrate was 100 mg t.i.d. Twelve (12) patients had familial hypercholesterolemia with tendon xanthomas (FHX) and five (5) patients were suffering from various types of hyperlipidemia including two cases of mixed familial hyperlipidemia, one case of Type IV hyperlipidemia and two cases of familial dysbetalipoproteinemia (Type III). Ten (10) patients showed serum cholesterol levels greater than 400 mg/dL; severe atherosclerosis was present in four other patients.

Plasma cholesterol and triglyceride concentrations were measured monthly and VLDL-C, LDL-C and HDL-C concentrations were measured every three months. These results were compared to the values obtained during a period of diet control. In the 12 patients suffering from familial hypercholesterolemia with tendon xanthomas, fenofibrate was very effective in lowering both cholesterol (mean decrease 19.8%) and LDL-C (mean decrease of 20.4%) ($p<0.0001$ in both cases). However, the drug had no effect on HDL-C. Ten of the 12 patients showed a response characterized by a significant decrease in serum cholesterol of 15% or more. A marked and significant effect was observed in three of the other five patients. This effect, apparent on both cholesterol (decreases ranging from 33.6 to 38.2%) and triglycerides (decreases ranging from 36.3 to 77.8%), was accompanied by a corresponding effect on VLDL-C and a significant increase in HDL-C. One case of mixed familial hyperlipidemia proved resistant to treatment and the treatment in one Type III patient had to be interrupted after 3 months because of deterioration of lipoprotein profile and digestive problems.

In nine hundred and seventy-one (971) patients with hypercholesterolemia (Type IIa), fenofibrate decreased the levels of total cholesterol (-16 to -30%), LDL-cholesterol (-20 to -33%) and apoprotein B (-14 to -37%). HDL-cholesterol levels were variably affected depending on initial levels (-15 to +28%). In eight hundred and fifty-four (854) patients with mixed hyperlipidemia (Type IIb), more variable decreases were observed in total (-3 to -36%) and LDL-cholesterol levels (-11 to -29%), as well as substantial decreases in triglyceride levels (-19 to -67%). In five hundred and seven (507) patients with hypertriglyceridemia (Type IV), marked decreases of triglycerides (-30 to -70%) and VLDL-triglycerides (-47 to -70%) were obtained following fenofibrate treatment. Results observed in short-term trials were maintained over long-term treatment periods.

European Studies:
Non-micronized formulation of Fenofibrate: Thirty-one (31) short-term studies of up to twelve (12) months duration and six (6) long-term trials of up to six (6) years duration were conducted in Europe, involving two thousand four hundred and forty-nine (2,449) patients. In most studies, the recommended fenofibrate dose of 300 mg daily, administered in three equally divided doses, was used; occasionally, this dose was increased to 400 mg or 600 mg, or reduced to 200 mg daily depending on patient response.

Micronized Formulation of Fenofibrate: Specific clinical studies were performed with the 200 mg/capsule formulation of fenofibrate.

The first clinical trial, a double-blind comparative trial with the 200 mg/capsule formulation of fenofibrate (one 200 mg capsule per day), the original formulation of fenofibrate (100 mg three times daily) and matched placebo, of 3 months treatment duration, demonstrated comparable clinical response on all lipidic parameters with both the intent-to-treat and efficacy analysis.

The results of this study indicate that the fenofibrate treatments, 3 × 100 mg or 1 × 200 mg micronized, are significantly more active than the placebo on lipid parameters: cholesterol, triglycerides, LDL-cholesterol fraction and apolipoprotein B. The two treatments did not present any noticeable activity on the HDL-cholesterol or apolipoprotein A1 concentrations when they were subnormal at T0.

In the intent-to-treat analysis, the two treatments showed equivalent success levels of 73.4% for 3 × 100 mg fenofibrate and 71.9% for 1 × 200 mg micronized fenofibrate and significantly greater than that observed in the placebo group (14.8%).

In the analysis of efficacy, the two treatments decreased the mean cholesterol concentrations by more than 15% versus the placebo group in this difference was significant ($p<0.0001$).

Concerning triglycerides, the difference between the means for each of the fenofibrate groups and the placebo group is greater than the comparison value (30% of placebo).

The second clinical trial conducted in Germany was established to evaluate the general acceptability associated with efficacy on lipid parameters of the 200 mg/capsule formulation of fenofibrate. From patients evaluated for efficacy, there were 45.1% patients with type IIa and 69.6% patients with type IIb classified as good responders on total cholesterol at T_3. The total number of good responders for triglycerides (patients type IIb and IV) was 71.4% at T_3 and 77.7% at T_{12}. The treatment effect was consistent throughout the 12 months of the study.

After 3 months of treatment, the mean value of total cholesterol was lowered in patients with type IIa from 311.4 mg/dL to 258.3 mg/dL with a mean decrease of 17%. In patients with type IIb the mean value of total cholesterol lowered from 328.0 mg/dL to 266.5 mg/dL with a mean decrease of 18.6%.

After 3 months of treatment, the mean value of triglycerides was lowered in patients with type IIb from 254.8 mg/dL to 165.7 mg/dL with a mean decrease of 34.4%. In patients with type IV, the mean value of triglycerides was lowered from 383.8 mg/dL to 231.1 mg/dL with a mean decrease of 37.9% after 3 months of treatment.

TOXICOLOGY

Acute toxicity

Results from studies in mice, rats, hamsters and dogs indicate a low toxicity for fenofibrate with the highest administered doses (3200 to 24000 mg/kg), resulting in no deaths over the 7-day observation period. Autopsy findings were negative.

Chronic toxicity studies
Rats with normal or high cholesterol diet were treated for 7 days by gavage with fenofibrate at 0, 3, 10, 30, 100 and 300 mg/kg/day or clofibrate at 20, 60, 200 and 600 mg/kg/day. SGOT levels were raised in treated rats but SGPT levels remained within the normal range for rats on normal diet and were only slightly elevated in rats on the high cholesterol diet. Dose-related hepatomegaly and proliferation of peroxisomes occurred, at doses above 30 mg/kg/day. In a second but similar study of drug-metabolizing enzymes, rats were treated daily by gavage for 7 days with fenofibrate at 0, or 100 mg/kg or clofibrate 200 mg/kg. The absence of significant change in the parameters measured suggests that the mechanisms resulting in hepatomegaly caused by both fibrates had little effect on cell organelles involved in drug metabolism and protein synthesis. In a third study in rats, oral doses of fenofibrate (0 to 1000 mg/kg) were given for 3 months. Depression of blood lipids was seen at all dose levels. SGOT and SGPT values were increased at 500 and 1000 mg/kg. Hepatomegaly was a consistent finding at all dose levels, reaching a maximum of 78% increase in weight compared to controls but appeared to regress rapidly. There were no other significant findings in the histological examination.

A 7-month study in dogs with 50 and 100 mg/kg/day and a 24-month study with 25 mg/kg/day were carried out. None of the dogs died but there was substantial weight loss associated with cholelithiasis and some interstitial nephritis. No important changes were observed in the biological parameters. Livers were apparently normal.

Fenofibrate (0, 12, 50 or 500 mg/kg) or clofibrate (200 mg/kg) was administered via a banana preparation, during 12 months to Rhesus monkeys. No fenofibrate-related effect with regard to toxicity was noted in any of the test groups during the study. No evidence of compound-related histomorphologic alterations were present in the animals sacrificed. The Rhesus monkey resembles man where biopsy studies show no signs of peroxisome proliferation during up to 2 years of fenofibrate treatment.

Carcinogenity studies
Five rodent feeding studies have shown that target organs for tumorigenic effects of fenofibrate are liver, pancreas and testis.
Mice showed increased liver weight with intra-hepatic cholestasis and some degenerative changes but not liver tumours with 50 mg/kg/day for 22 months.

Dose-related increases in liver and kidney weight were seen in mice treated with 10 to 200 mg/kg/day of fenofibrate for 80 weeks.

Gross hepatomegaly associated with cholestasis was seen at the high dose level and in clofibrate (200 mg/kg/day) treated mice with occasional cholangitis and periportal fibrosis. Neoplastic lesions were confined to the liver with significant increases in hepatocellular carcinoma at the high dose of fenofibrate in both sexes. Hepatocellular adenomas were also increased in males. In clofibrate-treated mice there was an excess of hepatic adenomas in females but not in males.

Both fenofibrate and clofibrate were found to be associated with an increased incidence of hepatocellular hypertrophy, lobular dysplasia and Kupffer cell pigmentation in another long-term toxicity study (93 weeks) on mice. In both sexes the incidence of total hepatic neoplasms and carcinomas was significantly increased by the high dose of fenofibrate (200 mg/kg). At the intermediate dose (60 mg/kg) the combined tumour incidence was almost significant in males but not in females, while incidence of carcinomas was not significantly increased in males and absent in females. Also, clofibrate (400 mg/kg) significantly increased the total tumour incidence but not carcinomas in males; females were unaffected.

Rats which received fenofibrate (0, 10, 45 or 200 mg/kg/day) or clofibrate (200 mg/kg/day) mixed with their diet for a 2-year period showed no significant differences in mortality over the study period. Significant increases in incidences of hepatocellular carcinoma were found in the high-dose fenofibrate group of animals of both sexes, in mid-dose fenofibrate males, and in clofibrate-treated males. Mid-dose fenofibrate males and clofibrate-treated males and females also showed significantly increased incidence of hepatocellular adenomas. Well-differentiated pancreatic acinar cell carcinomas and adenomas were increased in a dose-related manner in the fenofibrate-treated males, and higher incidences were also evident in the clofibrate males.

The chronic toxicity and carcinogenicity of fenofibrate was further studied in rats (0, 10 and 60 mg/kg/day) in order to compare treatment-related responses with those produced by clofibrate (400 mg/kg/day) and gemfibrozil (250 mg/kg/day) during 117 weeks of treatments. The absolute and relative weights of the liver were increased in all treatment groups except with 10 mg/kg fenofibrate. Although comparatively low, the incidence of hepatocellular carcinoma was observed in gemfibrozil-treated rats and neoplastic nodules were also found in the livers of 50% of the males which survived up to the termination of the study. Fewer neoplastic nodules were seen in the clofibrate-treated rats but these animals had a high incidence of hepatocellular carcinoma at termination. A significantly increased incidence of pancreatic acinar cell adenoma was seen in the 60 mg/kg fenofibrate males, while this increase in females was not significant. A significant increase in acinar adenoma and a slight increase in acinar carcinoma occurred with clofibrate (400 mg/kg) and some adenomas were seen in gemfibrozil-treated rats. There was some excess of benign interstitial cell tumours of the testis in all treatment groups except the group that received 10 mg/kg of fenofibrate.

Reproduction and teratology studies
There was no evidence of any increase in malformation frequency in mice, rabbits and rats after administration of fenofibrate compared to that seen in controls. Examination of offspring from fenofibrate-treated dams and those having received clofibrate did not disclose any significant abnormalities when compared to offspring from the controls.

With the highest dose levels at which the mothers were adversely affected, there was evidence of embryotoxicity in rats and rabbits.

Genetic toxicity studies
Gene Mutations: *In vitro* tests for mutagenicity with either fenofibrate or fenofibric acid in the presence or absence of activating rat or human microsomal enzyme preparations, have all given

negative results. Thus, fenofibric acid was without effect on gene mutation frequency in bacteria (Ames), yeast and mouse lymphoma cells in culture.

In a second mouse lymphoma cell comparative study, there was no response to clofibric acid while some increased response to fenofibric acid at the highest concentration used was discounted due to poor relative growth. Similar activity was seen with gemfibrozil at toxic concentrations in the absence of metabolic activation. In conclusion, all three fibrates were found to be non-mutagenic on the protocol criteria, both in the absence and presence of metabolic activation.

Chromosome aberrations: Some trace of an increased but not significant incidence of aberrations was seen in an *in vitro* mouse lymphoma cell multiple end-point assay.

Chromosome aberrations as such were not seen in a more recent comparative *in vitro* study with CHO cells when testing clofibric acid and gemfibrozil as well as fenofibric acid. However, clofibric acid did have a marginal effect in increasing sister chromatid exchange frequency.

The absence of excision repair in human originated HeLa cells incubated with a wide range of concentrations of fenofibric acid with or without S9, reaffirmed the essentially non-genotoxic nature of the product.

Direct effects on DNA: The ability to bind covalently to target organ DNA is a property common to chemical substances which act by direct initiation of the carcinogenic process at the nuclear level. This type of genotoxic activity can be studied *in vivo* by DNA assay in rodents treated with the radiolabelled drug.

Although binding of fenofibric and clofibric acids to proteins was readily observed, no binding to DNA was demonstrated after oral administration of ^{14}C-labelled fenofibric or clofibric acid. The data therefore exclude somatic mutations as responsible for the known hepatocarcinogenic activity of these fibrates in rodents.

In a second *in vivo* test the effects of fenofibric acid were compared with those of clofibric acid and gemfibrozil on DNA synthesis in mouse testicular tissue, as measured by the incorporation of ^{3}H-thymidine. Any response is representative of changes in DNA synthesis in any testicular cells such as germ, Sertoli, Leydig or interstitial cells undergoing scheduled or unscheduled synthesis.

Both fenofibric acid and gemfibrozil caused modest increases in thymidine incorporation above control values. Clofibrate caused some inhibition of the incorporation of thymidine into DNA at the two lowest doses with a small increase at the highest. No positive control substance was used but it would be assumed that, for example, genotoxic alkylating agents might cause a decrease in incorporation due to an inhibition of DNA synthesis. Such inhibition or cell cycle delay is well known for such agents.

The increase in DNA synthesis as observed in mouse testicular tissue with fenofibric acid and gemfibrozil is difficult to evaluate in the absence of a positive control or historical data for this

recently-developed test, nevertheless such an effect might be anticipated of such agents which are known to cause peroxisome proliferation and which produce increased cell turnover. The occurrence of increased cell turnover would be in keeping with a non-genotoxic but promoting mode of such compounds in mice.

In a rat primary hepatocyte unscheduled DNA synthesis (UDS) assay *in vitro*, gemfibrozil, clofibric acid and fenofibric acid showed a negative response. None caused nuclear labelling significantly different from the control and no dose-related trends were evident.

Cell Growth or Malignant Transformation *In Vitro*:Fenofibric acid was without effect on growth or malignant transformation of cultured mammalian cell lines.

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