PRODUCT MONOGRAPH

APO-FENO-MICRO
Fenofibrate Capsules
67 mg and 200 mg

APO-FENOFIBRATE
Fenofibrate Capsules
100 mg

Lipid Metabolism Regulator

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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 very low density lipoproteins (VLDL) than on the low density lipoproteins (LDL). Therapeutic doses of fenofibrate produce variable elevations of HDL cholesterol, a reduction in the content of the total low density lipoproteins cholesterol, and a substantial reduction in the triglyceride content of very low density lipoproteins.

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.

After oral administration with food, fenofibrate is rapidly hydrolyzed into fenofibric acid, the active metabolite.

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. 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.

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 adjuncts 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 an 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

1) Hepatic or severe renal dysfunction (creatinine clearance <20 mL/min), including primary biliary cirrhosis.

2) Pre-existing gallbladder disease (see WARNINGS).

3) Hypersensitivity to fenofibrate, or other drugs of the fibrate class.

4) The drug should not be used in pregnant or lactating patients.

5) APO-FENOFIBRATE (fenofibrate) and APO-FENO-MICRO (fenofibrate) are not indicated for the treatment of Type I hyperlipoproteinemia.

WARNINGS

DRUG INTERACTIONS

Concomitant 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 rhabdomyolysis have occurred when a statin or cyclosporine was administered in combined therapy with a fibrate. Therefore, the benefits and risks of using fenofibrate concomitantly with these drugs should be carefully considered.

MAO-Inhibitors: MAO-inhibitors with hepatotoxic potential must not be administered together with fibrates such as fenofibrate as they may increase the risk of hepatotoxicity.

Sulphonylureas and Insulin*:* It has been previously reported that the fibrates may potentiate the effects of these classes of drug. This effect has not yet been documented in the case of fenofibrate. No case of hypoglycemia or hypoglycemic reaction has been reported to date.

PEDIATRIC USE

Limited experience is available in children and adolescents, at the dose of 5 mg/kg/day, non-micronized formulation. However, safety and effectiveness has not been established in this sub-population.

USE IN PREGNANCY

Strict birth control procedures must be exercised by women of childbearing potential. If pregnancy occurs despite birth control procedures, APO-FENOFIBRATE or APO-FENO-MICRO should be discontinued. Women who are planning pregnancy should discontinue fenofibrate products several months prior to conception.

NURSING MOTHERS

In the absence of information concerning the presence of fenofibrate in human breast milk, APO-FENOFIBRATE or APO-FENO-MICRO should not be used by nursing mothers.

CHOLELITHIASIS

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

OTHER

Fenofibrate clinically and pharmacologically shows similarities with clofibrate. Physicians prescribing fenofibrate products should also be familiar with the risks and benefits of clofibrate.

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 tumours. Pancreatic acinar cell tumours were increased in male rats at 9 and 40 times the human dose. However, mice and female rats were unaffected at similar doses. Florid hepatocellular 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.

Since a relationship between reduction of mortality from coronary artery disease and total mortality has not been established, APO-FENOFIBRATE and APO-FENO-MICRO should be administered only to those patients described in INDICATIONS AND CLINICAL USE. If a significant serum lipid response is not obtained in three months, fenofibrate products should be discontinued. If APO-FENOFIBRATE or APO-FENO-MICRO is chosen for treatment, the prescribing physician should discuss the proposed therapy and inform the patient of the expected benefits and potential risks which may be associated with long-term administration (see PRECAUTIONS).

PRECAUTIONS

INITIAL THERAPY

Before instituting fenofibrate therapy, attempts should be made to control serum lipids with appropriate diet, exercise and weight loss in obese patients. Other medical problems, such as diabetes mellitus and hypothyroidism, should also be controlled. In patients at high risk, consideration should be given to the control of other risk factors such as smoking, excessive alcohol intake, hormonal contraceptive use, 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. Periodic determination of serum lipids, fasting glucose, creatinine and ALT (SGPT) should be considered during fenofibrate treatment, particularly during the first months of therapy.

REPRODUCTION STUDIES

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

HEMATOLOGIC CHANGES

Mild hemoglobin, hematocrit 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.

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. However, these abnormalities disappear when therapy with fenofibrate is discontinued. Therefore, periodic liver function tests (AST [SGOT], ALT [SGPT] and GGT [if originally elevated]) in addition to other baseline tests are recommended after 3 to 6 months and at least yearly thereafter. APO-FENOFIBRATE (fenofibrate) and APO-FENO-MICRO (fenofibrate) therapy should be terminated if abnormalities persist. Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis.

HEPATOBILIARY DISEASE

In patients with a past history of jaundice or hepatic disorder, fenofibrate should be used with caution.

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. Myopathy should be

considered in any patient with diffuse myalgias, muscle 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 (10 times the upper limit of normal) occur or myopathy is diagnosed.

DRUG INTERACTIONS (see also WARNINGS)

Resins: 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: Since estrogens may lead to a rise in lipid levels, the prescribing of fibrates in patients taking estrogens or estrogen-containing contraceptives must be critically considered on an individual basis.

RENAL FUNCTION

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). Fenofibrate is not removed by hemodialysis and should not be used in dialysis patients.

ADVERSE REACTIONS

Clinical adverse effects of fenofibrate therapy have been reported at an incidence between 2 and 15% with a mean of 6.3% in European trials of less than 12 months duration. In longer term studies, the incidence was between 7 and 14% with a mean of 11.3%. 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.

In two separate controlled clinical studies conducted in the U.S., a total of 191 patients on non-micronized fenofibrate (116 Type II and 75 Type IV/V patients) were evaluated for adverse effects versus 183 patients on placebo (111 Type II and 72 Type IV/V patients). Listed in Table 1 are the adverse reactions considered by the investigators to be possibly or probably related to treatment, and reported by more than 1% of the patients receiving fenofibrate in these trials.

Table 1
Number (%) of Patients Reporting Adverse Reactions

U.S. Multicentre Studies
Type II study (6-month treatment)
Type IV/V study (2-month treatment)

Adverse Reactions	Fenofibrate (n=191)	Placebo (n=183)
GASTROINTESTINAL		
Dyspepsia	6 (3.1)	8 (4.4)
Flatulence	6 (3.1)	5 (2.7)
Nausea	4 (2.1)	3 (1.6)
Abdominal pain	4 (2.1)*	2 (1.1)
Constipation	3 (1.6)	1 (0.5)
SKIN AND APPENDAGES		
Pruritus	6 (3.1)*	1 (0.5)
Rash	6 (3.1)	1 (0.5)
Hives	3 (1.6)	--
BODY AS A WHOLE		
Fatigue	4 (2.1)	2 (1.1)
MUSCULOSKELETAL		
Arthralgia	3 (1.6)*	--

*One patient reported multiple adverse effects

In these studies, the difference between the numbers of fenofibrate and placebo patients reporting these adverse reactions was not statistically significant ($p>0.05$). While the nature of the reported adverse reactions was similar in both studies, these reactions were observed in most cases at a higher frequency in the longer term, six-month trial in Type II patients.

Adverse reactions for the APO-FENO-MICRO formulation of fenofibrate at recommended therapeutic doses in clinical trials have shown a comparable profile with those described for the APO-FENOFIBRATE formulation of fenofibrate.

Surveillance in countries in which fenofibrate has been marketed for up to 20 years such as France, Germany and the United Kingdom, indicates that clinical adverse effects reported include gastrointestinal complaints, painful muscles, skin disorders typically classified as pruritus, urticaria or erythema, loss of weight, impotence, diverse nervous complaints, hair loss, gallstones, pancreatitis and hepatitis.

LABORATORY TESTS

In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of SGOT and SGPT elevations was variable; in the U.S. clinical trials, elevations above twice the upper limit of normal were observed in 6.8% of the patients treated with fenofibrate, versus 1.6% of the patients on placebo. Values usually return to normal without interruption of treatment. On some occasions, more severe elevations of transaminases (above twice the upper limit of normal values) were noted; such rises subside when fenofibrate therapy is discontinued (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. 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 CPK elevations and changes in hematologic parameters which generally subside when the drug is discontinued (see PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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 267 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 100 mL/min), 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. Fenofibrate is not removed by hemodialysis and should not be used when the creatinine clearance is lower than 20 mL/min.

PHARMACEUTICAL INFORMATION

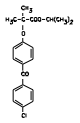
DRUG SUBSTANCE

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 and ether. It is very soluble in chloroform.

COMPOSITION

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: sodium lauryl sulphate, methyl and propyl parabens, 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°-25°C). Avoid excessive humidity.

AVAILABILITY OF DOSAGE FORMS

APO-FENOFIBRATE (fenofibrate) 100 mg: Each opaque, white, #2 hard gelatin capsule imprinted "APO 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 "APO 67" contains 67 mg of fenofibrate. Available in bottles of 100 and 500 capsules, unit dose blister packages of 30 and 100, and Apotex Long-Term Care unit dose packages (APO-LTC packs) of 620 and 700 capsules.

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

INFORMATION FOR THE PATIENT

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.

Comply exactly to the terms of the prescription. 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.

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

- if you have taken fenofibrate or any other lipid treatment before and if it caused an allergy or was otherwise poorly tolerated;
- if you suffer from liver or kidney problems;
- if you have a gall bladder or gallstone problem;
- if you are pregnant, or intend to become pregnant, or are breast-feeding, or intend to breast-feed;
- if you are taking other medicines, in particular an oral anticoagulant such as warfarin (Warfilone®).

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.

Your doctor will ask you to have regular medical check-ups and laboratory tests. It is important to respect the dates proposed: we strongly recommend that you keep faithfully these appointments.

Inform your doctor of any health problem that occurs while you are taking APO-FENOFIBRATE or APO-FENO-MICRO as well as any prescription or nonprescription medicine. If you need other medical treatment, let the doctor know that you are taking APO-FENOFIBRATE or APO-FENO-MICRO.

Tell your doctor if you feel in any way unwell while taking APO-FENOFIBRATE or APO-FENO-MICRO (see UNWANTED EFFECTS).

Safety of use in children and young adolescents has not been established with fenofibrate.

The effects of fenofibrate in preventing heart attacks, atherosclerosis or heart disease are not yet known.

APO-FENOFIBRATE and APO-FENO-MICRO are contraindicated during pregnancy. In the event of pregnancy during treatment, APO-FENOFIBRATE or APO-FENO-MICRO should be discontinued and the physician should be informed.

It is not recommended to take APO-FENOFIBRATE or APO-FENO-MICRO while breast-feeding.

UNWANTED EFFECTS:

In addition to its intended action, any medicine may cause unwanted effects.

Unwanted effects may occur in certain patients. They may appear and disappear without involving any particular risk, but if any unwanted effects persist or become bothersome, you must let your doctor know without delay. Such unwanted effects may consist of abdominal pains, constipation, diarrhea, nausea, headache, dizziness, skin reactions, muscular pain or cramps and fatigue.

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.

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 humans, a dose of 300 mg 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 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 urine and 25% in the feces.

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 little 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 EXPERIENCES

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 multicentre, 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 2).

Table 2
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 3).

Table 3
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:

Original 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.

200 mg/capsule 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 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.

CARCINOGENICITY 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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