PRODUCT MONOGRAPH

[Pr]phl-FENOFIBRATE SUPRA

fenofibrate

microcoated formulation

film-coated tablets

100 mg, 160 mg tablets

Lipid Metabolism Regulator

PHARMEL INC.
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100 mg and 160 mg

PHARMACOLOGICAL CLASSIFICATION

Lipid metabolism regulator

ACTIONS AND CLINICAL PHARMACOLOGY

phl-FENOFIBRATE SUPRA (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 elevations of HDL cholesterol, a reduction in the content of the low density lipoproteins cholesterol, and a substantial reduction in the triglyceride content of very low density lipoproteins.

Recent findings suggest that the lipid modulating effects of fenofibrate are mediated by the activation of a specific nuclear receptor called peroxisome proliferator activated receptor alpha (PPARα) which produces:

- a reduction in apo C-III, and therefore a reduction in the level of dense atherogenic LDL particles;
- a stimulation of mitochondrial beta-oxidation, and therefore a reduction in triglyceride secretion;
- a rise in lipoprotein lipase production, and therefore an acceleration of triglyceride rich lipoprotein breakdown;
- a rise in apo A-I and apo A-II production, and a corresponding rise in HDL.

After oral administration, fenofibrate is rapidly hydrolysed to 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.

INDICATIONS AND CLINICAL USE

phl-FENOFIBRATE SUPRA (fenofibrate, microcoated formulation) is indicated as an adjunct to diet, at least equivalent to the Adults Treatment Panel III (ATP III) and Therapeutic lifestyle changes (TLC diet), and other therapeutic measures when the response to diet and other measures has been inadequate for:

1. Treatment of patients, including patients with type 2 diabetes (non-insulin dependent), with dyslipoproteinemia (hypercholesterolemia, Fredrickson classification Types IIa and IIb mixed hyperlipidemia), to regulate lipid levels by reducing serum triglycerides and LDL cholesterol levels and increasing HDL cholesterol.

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

   phl-FENOFIBRATE SUPRA (fenofibrate, microcoated formulation) alone may not be adequate therapy in some patients with familial combined hyperlipidemia with Type IIb and Type IV hyperlipoproteinemia.

   phl-FENOFIBRATE SUPRA is not indicated for the treatment of Type I hyperlipoproteinemia.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction (creatinine clearance <20 ml/min), including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to fenofibrate, any component of this medication or other drugs of the fibrate class.
4. The drug should not be used during pregnancy and breast-feeding.
5. Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.

WARNINGS

1. **Pediatric use:** Limited experience is available in children and adolescents, at the dose of 5 mg/kg/day fenofibrate non-micronized formulation. However, safety and effectiveness have not been established in this sub-population (see selected bibliography).

2. **Use in pregnancy:** Strict birth control procedures must be exercised by women of childbearing potential. If pregnancy occurs despite birth control procedures, phl-FENOFIBRATE SUPRA (fenofibrate) should be discontinued. Women who are planning pregnancy should discontinue phl-FENOFIBRATE SUPRA several months prior to conception.

3. **Nursing mothers:** In the absence of information concerning the presence of fenofibrate in human breast milk, phl-FENOFIBRATE SUPRA should not be used by nursing mothers.

4. **Cholelithiasis:** Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. phl-FENOFIBRATE SUPRA therapy should be discontinued if gallstones are found.

5. **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.

6. **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, ALT and GGT [if originally elevated]) in addition to other baseline tests are recommended after 3 to 6 months and at least yearly thereafter. phl-FENOFIBRATE SUPRA (fenofibrate, microcoated formulation) should be terminated if abnormalities persist.

7. **Skeletal muscle**: Treatment with drugs of the fibrate class has been associated on rare occasions with myositis or rhabdomyolysis, 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 creatine phosphokinase levels.

   Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CK levels should be assessed in patients reporting these

symptoms, and fenofibrate therapy should be discontinued if markedly elevated CK levels (10 times the upper limit of normal) occur or myopathy is diagnosed.

8. **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.

PRECAUTIONS

1. **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.

2. **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 should be considered during fenofibrate treatment, particularly during the first months of therapy.

3. **Reproduction 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.

4. **Hepatobiliary disease**: In patients with a past history of jaundice or hepatic disorder, fenofibrate should be used with caution.
   Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis.

5. **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 should not be used in dialysis patients.

6. **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.

7. **Drug Interactions:**

Concomitant oral anticoagulants: Caution should be exercised when oral anticoagulants are given in conjunction with phl-FENOFIBRATE SUPRA (fenofibrate, microcoated formulation). 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.

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 is 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.

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 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 1 are the adverse events possibly or probably related to fenofibrate, microcoated formulation and reported by more than 0.5% of the patients.

Table 1: 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%)

Adverse reactions for fenofibrate, microcoated formulation, at recommended therapeutic doses in clinical trials have shown a comparable profile with those described for the micronized formulation.

Surveillance in countries in which fenofibrate has been marketed for more than 25 years in Europe, indicates that clinical adverse effects reported include gastrointestinal disorders (abdominal pain, nausea, vomiting, diarrhea and flatulence), painful muscles (diffuse myalgia, myositis, cramps, weakness, rhabdomyolysis), skin reactions such as rashes, pruritus, urticaria, erythema or photosensitivity reactions (with or without erythema, vesiculation or nodulation), loss of weight, impotence, sexual asthenia (rare), diverse nervous complaints, alopecia (rare), interstitial pneumopathies (very rare), gallstones, pancreatitis and hepatitis (jaundice).

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 studies conducted in Canada and Germany elevations above three times the upper limit of normal were observed in 2.0% of the patients treated with fenofibrate, microcoated formulation. In two dose-ranging studies, the incidence of increases in transaminases (>3 x UNL) due to fenofibrate therapy appears to be dose related; 0.6% (80mg tablet), 1.9% (160mg tablet) and 4.0% (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, haematocrit, 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 haemolysis.

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 haematologic 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% 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.

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 phl-FENOFIBRATE SUPRA (fenofibrate, microcoated formulation), and should continue on this diet during treatment with phl-FENOFIBRATE SUPRA. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with phl-FENOFIBRATE SUPRA, 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, phl-FENOFIBRATE SUPRA should be discontinued.

The usual recommended dose for phl-FENOFIBRATE SUPRA in adults is one 160 mg tablet daily taken with the main meal. The maximum recommended total daily dose of phl-FENOFIBRATE SUPRA is 200 mg.

In patients with renal insufficiency (creatinine clearance between 20 and 100 ml/min), phl-FENOFIBRATE SUPRA treatment should be initiated at the dose of 100 mg per day and increased only after evaluation of the tolerance and effects on the lipid parameters. phl-FENOFIBRATE SUPRA should not be used when the creatinine clearance is lower than 20 ml/min.

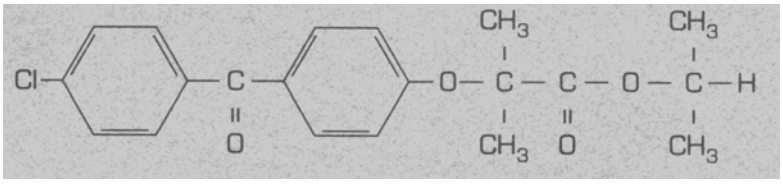
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: Fenofibrate

Chemical name: 2-(4-(4-chlorobenzoyl) phenoxy)-2-methyl-propanoic acid 1-methylethyl ester.

Structural formula:



Molecular formula: $C_{20}\ H_{21}\ O_4\ Cl$

Molecular weight: 360.83

Description: Fenofibrate is a crystalline, cream-colored, odourless and tasteless powder.

Melting point: 79 to 82°C.

Solubilities: Fenofibrate is practically insoluble in water, soluble in ethanol, freely soluble in acetone and chloroform.

COMPOSITION

phl-FENOFIBRATE SUPRA contains, in addition to fenofibrate, the following excipients (in alphabetical order): colloidal silicon dioxide, crospovidone, lactose monohydrate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium stearyl fumerate and Opadry (coating agent containing: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin and xanthan gum).

STABILITY AND STORAGE RECOMMENDATIONS

Store at 15-30°C. Protect from light and moisture.

AVAILABILITY OF DOSAGE FORMS

phl-FENOFIBRATE SUPRA 100 (100 mg tablets): each white, oblong, film-coated tablet contains 100 mg microcoated fenofibrate, and is embossed with the “P” logo on one side and “100" on the other. phl-FENOFIBRATE SUPRA 100 is available in blister packs of 30 tablets and HDPE bottles of 100 tablets.

phl-FENOFIBRATE SUPRA 160 (160 mg tablets): each white, oblong, film-coated tablet contains 160 mg microcoated fenofibrate, and is embossed with the “P” logo on one side and “160" on the other. phl-FENOFIBRATE SUPRA 160 is available in blister packs of 30 tablets and HDPE bottles of 100 tablets.

INFORMATION FOR THE CONSUMER

[Pr]phl-FENOFIBRATE SUPRA

(fenofibrate)

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

phl-FENOFIBRATE SUPRA (fenofibrate) reduces blood cholesterol, in particular cholesterol associated with low and very low density lipoproteins (bad cholesterol). phl-FENOFIBRATE SUPRA reduces high triglyceride levels associated with hypercholesterolemia (excess of cholesterol in the blood) and increases the high density lipoprotein (HDL) cholesterol fraction (good cholesterol). Because of the effects on these parameters, phl-FENOFIBRATE SUPRA is indicated for the treatment of dyslipoproteinemia (abnormal lipoproteins in the blood) in adult patients with type 2 diabetes. Blood uric acid levels are also reduced by phl-FENOFIBRATE SUPRA treatment.

phl-FENOFIBRATE SUPRA is only available on prescription. This medicine 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 with 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 had an allergic reaction to (or poorly tolerated) phl-FENOFIBRATE SUPRA, **any of its ingredients**, or any other lipid treatment (**See What Does phl-FENOFIBRATE SUPRA Contain**).
- 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.

1. ***PROPER USE OF THE MEDICINE***

- phl-FENOFIBRATE SUPRA 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 phl-FENOFIBRATE SUPRA as well as any prescription or non-prescription medicine. If you need other medical treatment let the doctor know that you are taking phl-FENOFIBRATE SUPRA.
- Tell your doctor if you feel in any way unwell while taking phl-FENOFIBRATE SUPRA (see **UNWANTED EFFECTS**).
- Contact your doctor promptly if you suffer any unexplained muscle pain, tenderness or weakness.
- Safety of use in children and young adolescents has not been established with phl-FENOFIBRATE SUPRA.
- The effects of phl-FENOFIBRATE SUPRA in preventing heart attacks, atherosclerosis or heart disease are not yet known.
- phl-FENOFIBRATE SUPRA is not recommended during pregnancy. In the event of pregnancy during treatment, phl-FENOFIBRATE SUPRA should be discontinued and your doctor should be informed.
- It is not recommended to take phl-FENOFIBRATE SUPRA 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, fatigue.

WHAT DOES PHL-FENOFIBRATE SUPRA CONTAIN

phl-FENOFIBRATE SUPRA contains, in addition to fenofibrate, the following nonmedicinal ingredients (in alphabetical order): colloidal silicon dioxide, crospovidone, lactose monohydrate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium stearyl fumerate and Opadry (coating agent containing: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin and xanthan gum).

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

Fenofibrate is metabolized by hydrolysis to its active form, fenofibric acid. In man, fenofibric acid is eliminated conjugated with glucuronic acid.

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.

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

In a two-way, randomized, crossover bioavailability study, 200 mg fenofibrate, micronized formulation, was compared to 160 mg fenofibrate, microcoated formulation, (Fenofibrate) in 24 healthy male volunteers. Each volunteer received a single oral dose of each formulation with a standard breakfast and with a one week interval between doses.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

A SINGLE DOSE STUDY

(Blood levels measured as fenofibric acid)

Bioavailability Parameters	fenofibrate, microcoated - Tablet 160 mg - mean (CV%)	fenofibrate, micronized - Capsule 200 mg - mean (CV%)	Ratio of Means	90% Confidence Interval Limits (%)	
				Lower	Upper
AUC_T (mcg.h/mL)	138.7 (26) arith. 134.0 (27) geom	152.0 (24) arith. 147.8 (24) geom	0.91 arith. 0.91 geom	88 88	94 arith. 94 geom
AUC∞ (mcg.h/mL)	141.5 (27) arith. 136.5 (28) geom	155.3 (25) arith. 150.8 (25) geom	0.91 arith. 0.91 geom	88 88	95 arith. 94 geom
C_{MAX} (mcg/mL)	7.98 (13) arith. 7.92 (13) geom	8.9 (17) arith. 8.8 (17) geom	0.89 arith. 0.90 geom	85 86	94 arith. 95 geom
T_{MAX} (h)	3.9 (24) arith.	4.4 (15) arith.	0.88 arith.		
$t_{1/2}$ (h)	20.1 (21) arith.	19.4 (21) arith.	1.03 arith.		

These data show that biological equivalence was achieved between fenofibrate microcoated tablets and fenofibrate, micronized formulation. During the bioavailability study, three subjects reported gastrointestinal irritation after the administration of fenofibrate microcoated tablets; none were reported after fenofibrate, micronized formulation. The causality of these events in relation to fenofibrate has not been established.

Clinical Studies

The effects of fenofibrate on total mortality, and cardiovascular mortality and morbidity have not been established.

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 fenofibrate, micronized formulation, at a daily dose of 200 mg.

Specific clinical studies were performed with fenofibrate, micronized formulation.

The first clinical trial followed a double-blind, parallel group versus placebo design. One hundred and eighty-nine patients (Type IIa; 120 and Type IIb; 69) were randomized in three groups: placebo, 200 mg micronized fenofibrate and 3 x 100 mg non micronized fenofibrate. The ages of the patients ranged from 18 to 75 years. The intent-to-treat analysis indicated an efficacy level after 3 months (as assessed by the number of patients who experienced a cholesterol reduction > 15%) which was significantly greater in the micronized fenofibrate

group (71.9%) than in the placebo group (14.8%). Micronized fenofibrate treatment was significantly more active than placebo in reducing total cholesterol (-18%), LDL-cholesterol (-22%), triglycerides (-19%) and apolipoprotein B (-24%).

The second clinical trial evaluated the effectiveness of micronized fenofibrate on lipid parameters. Of 131 eligible patients, 94 (31 Type IIa, 23 Type IIb and 40 Type IV) were evaluated for efficacy. Of those with Type IIa and Type IIb, 45.1% and 69.6%, respectively, were classified as good responders for total cholesterol. Of patients with Type IIb and IV, 71.4% and 77.7%, respectively, were considered good responders for triglycerides. 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 was lowered from 328.0 mg/dl to 266.5 mg/dl, with a mean decrease of 18.6 %. 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 %.

A placebo-controlled, double-blind study was also performed in 418 patients with type 2 diabetes: The Diabetes Atherosclerosis Intervention Study (DAIS). The patients were randomized to either fenofibrate 200 mg once daily or to placebo for an average of 38 months. The main objectives were to determine the safety of 200 mg fenofibrate, micronized formulation, in a population of type 2 diabetic patients and to measure angiographic responses by quantitative coronary angiography (QCA). Male (73%) and female patients were included in the study. They presented with adequate glycemic control, total cholesterol/high density lipoprotein cholesterol ratio $\geq$4, and either low density lipoprotein cholesterol (LDL-C) from 3.5 to 4.5 mmol/l with triglycerides (TG) $\leq$5.2 mmol/l, or TG from 1.7 to 5.2 mmol/l with LDL-C $\leq$4.5 mmol/l. An adequate QCA with previous CABG or PTCA or at least one coronary segment with a minimal detectable stenosis was also required.

The primary efficacy parameter was the mean segment parameter, averaged per patient, to test a null hypothesis of no difference between fenofibrate- and placebo-treated patients. Additional secondary angiographic efficacy parameters were also analyzed.

The angiographic results showed that the primary endpoint (mean segment diameter per patient) did not reach statistical significance and the change from baseline was not clinically meaningful (see following table). The change in mean segment diameter was minimal in both groups over the treatment period, with no statistical difference between groups.

DAIS study: Mean coronary angiogram values (± S.D.) averaged per patient and per segment at baseline and at the end of study (ITT population)

	Fenofibrate	Placebo	p-value*
Per patient analysis	N=207	N=211	
- **Mean segment diameter (mm)**			
Baseline	2.70 (0.45)	2.67 (0.45)	0.494
Final	2.62 (0.49)	2.56 (0.50)	0.173
- **Minimum segment diameter (mm)**			
Baseline	2.14 (0.44)	2.10 (0.44)	0.457
Final	2.05 (0.46)	1.98 (0.48)	0.028
- **Percent diameter stenosis (%)**			
Baseline	21.8 (7.8)	21.8 (7.4)	0.958
Final	24.1 (9.8)	25.7 (10.8)	0.02
Per segment analysis	N=1884	N=1993	
-Mean diameter (mm)			
Baseline	2.76 (0.84)	2.72 (0.83)	0.145
Final	2.68 (0.87)	2.62 (0.87)	0.037
-Minimum diameter (mm)			
Baseline	2.20 (0.82)	2.16 (0.81)	0.077
Final	2.11 (0.84)	2.03 (0.83)	0.541
% stenosis			
Baseline	21.0 (13.1)	21.4 (12.8)	0.309
Final	23.0 (15.9)	24.9 (17.2)	0.059

*p-values for Student's t test and for covariance analysis to compare treatment groups, respectively, at baseline and at the end of the study (last available value on treatment). Statistical significance was established at 0.025.

The changes in lipid levels were also monitored in the type 2 diabetic patients included in the DAIS study. The major lipid values at baseline and at the end of the study are shown in the following table for both the fenofibrate- and placebo-treated groups.

DAIS study: Mean major lipid values (±S.D.) at baseline and at the end of the study (ITT population)

	Fenofibrate	Placebo	p-values*
-Total cholesterol (mmol/L)			
Baseline	5.56 (0.80)	5.58 (0.72)	0.751
Final	4.93 (0.83)	5.42 (0.79)	< 0.001
- Total triglycerides (mmol/L)			
Baseline	2.56 (1.23)	2.52 (1.22)	0.706
Final	1.65 (0.90)	2.16 (1.20)	< 0.001
- HDL-C (mmol/L)			
Baseline	1.00 (0.19)	1.04 (0.21)	0.045
End of study	1.06 (0.26)	1.06 (0.24)	0.045
-Calc. LDL-C (mmol/L)			
Baseline	3.36 (0.71)	3.39 (0.72)	0.532
Final	3.12 (0.69)	3.38 (0.73)	0.042
TC / HDL-C			
Baseline	5.63 (1.08)	5.51 (1.10)	0.115
Final	4.87 (1.27)	5.35 (1.25)	< 0.001
Apo AI (g/L)			
Baseline	1.24 (0.18)	1.26 (0.277)	0.277
Final	1.33 (0.22)	1.29 (0.20)	0.02

*p-values for Student's t test and for covariance analysis to compare treatment groups at baseline and at the end of the study (last available value on treatment)

Safety was closely monitored in the DAIS study 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 for the two treatment groups. The table below summarizes the incidence of adverse events, by body system, observed in the fenofibrate and placebo treatment groups.

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)**	
	AEs	Patients	AEs	Patients
Total # pts. with at least 1 AE	Total AEs: 1710	201 (97.1%)	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%)
Hemic/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%)

Clinical Pharmacology

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, non-micronized formulation, 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, non-micronized formulation. 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 of increasing the risk of gallstones as a result of increased cholesterol excretion via the bile.

The biliary lithogenic index in fenofibrate-treated patients was evaluated. 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 fenofibrate, non-micronized formulation, 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, non-micronized formulation, 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.

TOXICOLOGY

All toxicology studies were performed using fenofibrate, non-micronized formulation.

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. AST levels were raised in treated rats but ALT 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 metabolising 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. AST and ALT 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/day) or clofibrate (200 mg/kg/day) was administered in the food of Rhesus monkeys for 12 months. 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 was 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 studies have shown that target organs for tumorigenic effects of fenofibrate are liver, pancreas and testis.

Mice showed increased liver weight with intrahepatic cholestasis and some degenerative changes but not liver tumors 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.

When given at a dose of 200 mg/kg/day, both fenofibrate and clofibrate produced gross hepatomegaly associated with cholestasis and 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 tumor 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 tumor 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, an 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 tumors 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 radiolabeled drug.

Although binding of fenofibric and clofibric acids to proteins was readily observed, no binding to DNA was demonstrated after oral administration of C^{14}-labeled 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.

SELECTED BIBLIOGRAPHY

1. Blane GF. Reviews of European clinical experience with fenofibrate. Cardiology 1989; 76 (suppl. 1): 1-13.

2. Hunninghake DB. Treatment of hypertriglyceridemia with fenofibrate. Practical Cardiology 1989; 15 (2): 38-39.

3. Schneider AG, Ditschuneit HH, Stange EF, Ditschuneit H. Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase in freshly isolated human mononuclear cells by fenofibrate. 41st Meeting of the European Atherosclerosis Group, Stockholm June 2-3, 1984, ed by : L.A. CARLSON, A.G. OLSSON in : Treatment of hyperlipoproteinemia, Raven Press, New-York 1984: 181-184.

4. Desager JP, Hulhoven R, Harvengt C. Uricosuric effect of fenofibrate in healthy volunteers. J Clin Pharmacol 1980; 20 (10): 560-564.

5. Blumke S, Schwartzkopff W, Lobeck H, Edmonson NA, Prentice DE, Blane GF. Influence of Fenofibrate on Cellular and Subcellular Liver Structure in Hyperlipidemic Patients. Atherosclerosis 1983; 46: 105-116.

6. Gariot P, Barrat TE, Mejean L, Pointel JP, Drouin P, Debry G. Fenofibrate and human liver. Lack of proliferation of peroxisomes. Arch Toxicol 1983; 53 (2): 151-163.

7. Blane GF, Bogaievsky Y, Bonnefous F. Fenofibrate : influence on circulating lipids and side-effects in medium and long-term clinical use. Pharmacological control of hyperlipidaemia, ed. JR. Prous Science Publishers 1986; 187-216.

8. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. Am J Med 1987; 83 (suppl 5B.): 26- 36.

9. Knopp RH, Brown WV, Dujovne CA, Farquhar JW, Feldman EB, Goldberg AC, Grundy SM, Lasser NL, Mellies MJ, Palmer RH, Samuel P, Schonfeld G, Superko HR. Effects of fenofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. Am J Med 1987; 83 (suppl. 5B): 50-59.

10. Knopp RH. Review of the effects of fenofibrate on lipoproteins, apoproteins and bile saturation : US studies. Cardiology 1989; 76 (suppl. 1): 14-22 and 29-32.

11. Seidehamel RJ. Fenofibrate in type IV and type V hyperlipoproteinemia. Cardiology 1989; 76 (suppl. 1): 23-32.

12. Gurrieri J, Le Lous M, Renson FJ, Tourne C, Voegelin H, Majoie B, Wulfert E. Experimental study of a new potent hypolipidemic drug, is opropyl-[4'-) p-chlorobenzoyl-2-phenoxy-2-methyl]-propionate (LF178) Arzneimmittelforschung 1976; 26 (5): 889-894.

13. Desager JP, Harvengt C. Clinical pharmacokinetic study of procetofen, a new hypolipidemic drug, in volunteers. Int J Clin Pharmacol Res 1978; 16: 570-574.

14. Podda M, Zuin M. Effects of fenofibrate on biliary lipids and bile acid pool size in patients type IV hyperlipoprotenemia. Atherosclerosis 1985; 55: 135-142.

15. Brunova E, Valek J, Vondra K, Slabochova Z, Grafnetter D, Bruna J. Treatment of Hyperlipoproteinemia with Procetofen. Curr Ther Res 1982; 31 (1): 37-44.

16. Harvengt C, Heller F, Desager JP. Hypolipidemic and Hypouricemic Action of Fenofibrate in Various Types of Hyperlipoproteinemias. Artery 1980; 7 (1): 73-82.

17. Lethonen A and Viikari J. Fenofibrate and Cholestyramine in type II hyperlipoproteinemia. Artery 1982; 10 (5): 353-367.

18. Avogaro P, Bittolo Bon G, Belussi F, Pontoglio E, Cassolato G. Variations in Lipids and Proteins of lipoproteins by Fenofibrate in some hyperlipoproteinaemic states. Atherosclerosis 1983; 47: 95-100.

19. Chanu B, Bakir R, Goy-Loeper J, Bouthillier D, Rouffy J. Intérêt de l'évaluation d'un indice achilléen pour la surveillance thérapeutique des hyperlipoprotéinémies avec xanthomatose tendineuse (on the Evaluation of an Achilles Tendon Index for the Therapeutic Surveillance of Hyperlipoproteinemia with Tendinous Xanthomata). Gaz Méd France, numéro spécial du 3ème Colloque Intern. «Lipides et Athérosclérose" 13-14 mars 1982: 96-99.

20. Rouffy J, Sauvanet JP, Chanu B, Bakir R, Goy-Loeper J, Saya C, Pinaroli F. Evaluation à long terme de l'activité hypolipidémiante et de la tolérance du fénofibrate. Effet à court terme du médicament sur les taux de lipides des lipoprotéines (HDL, LDL, VLDL) et apoprotéines B. (Fenofibrate : Hypolipidemic Activity

and Safety in Long term Treatment. Effects of HDL, LDL, VLDL and Apoprotein B in Short-term Treatment). Nouv Presse Méd 1980; 9 (49): 3747-3751.

21. Drouin P. Two-year Treatment with Procetofen (Fenofibrate) in Patients with Primary Type II Hyperlipoproteinemia. Effect on Lipoprotein Lipids and Biochemical Tolerance. Clin Ter Cardiovasc 1982; 2: 165-170.

22. Fromantin M, Gautier D, Quatre JM, Bon R. Efficacité et tolérance du fénofibrate au cours de traitements à long terme. Thérapie 1981; 36: 473-476.

23. Farnier M, Bonnefous F, Debbas N, Irvine A. Comparative Efficacy and Safety of Micronized Fenofibrate and Simvastatin in Patients With Primary Type IIa or IIb Hyperlipidemia. Arch Intern Med 1994; 154: 441-449.

24. Chicaud P., Demange J., Debry G. Long-term (18 months) effects of fenofibrate in young hypercholesterolemic subjects. Presse Med., 1984,13: 417-419.

25. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomized study. Lancet, 2001; 357: 905-910.

26. Guichard JP, Blouquin P, Qing Y. A new formulation of fenofibrate: suprabioavailable tablets. Curr Med Res Opin. 2000;16(2): 134-138.

27. Kirchgassler KU, Schmitz H, Bach G. Effectiveness and tolerability of 12-week treatment with micronized fenofibrate 200mg in a drug-monitoring programme involving 9884 patients with dyslipidaemia. Clin Drug Invest., 1998; 15: 197-204.

28. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. CMAJ. 2000;162: 1441-1447.

29. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002, 106: 3143-3421.

30. Product Monograph LIPIDIL SUPRA (fenofibrate microcoated formulation film-coated tablets), Current Submission: July 2002