

PRODUCT MONOGRAPH

**Pr LIPIDIL EZ®**  
**(fenofibrate tablets)**

**48 mg and 145 mg**

**Lipid Metabolism Regulator**

**NanoCrystal® Formulation**

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Date of Preparation:  
July 12, 2005

Date of Previous Revision:  
October 1, 2007

Date of Revision:  
July 15, 2011

Submission Control No: 147053

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### **THERAPEUTIC CLASSIFICATION**

Lipid Metabolism Regulator

### **ACTIONS AND CLINICAL PHARMACOLOGY**

LIPIDIL EZ<sup>®</sup> (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 lipoprotein 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 (PPAR $\alpha$ ), 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. In man, fenofibric acid is eliminated as the glucuronic acid conjugate and is mainly excreted through the kidney. In man, the elimination half-life of fenofibric acid is about 20-24 hours, a value that is not modified after multiple dosing.

In healthy elderly patients (77 to 87 years of age), the terminal half-life is prolonged, but no dose adjustment is required due to unchanged clearance.

#### Concomitant administration with ezetimibe

Administration of fenofibrate with ezetimibe is effective in improving serum total-C, LDL-C, Apo-B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

Clinical studies have demonstrated that elevated levels of total-C, low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B; the major protein constituent of LDL), promote atherosclerosis in humans. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and remnants, can also promote atherosclerosis. **The effects of fenofibrate given with ezetimibe on cardiovascular morbidity and mortality have not been established.**

#### Pediatrics

Safety and effectiveness have not been established in pediatric patients.

#### Renal Insufficiency

In patients with severe renal impairment the rate of clearance of fenofibric acid is greatly reduced, and the compound accumulates during chronic dosage.

In patients having moderate renal impairment (creatinine clearance of 50 to 90 mL per min.), the oral clearance and oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/H and 30 L, respectively).. Therefore, the dosage of LIPIDIL EZ should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

#### Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

No gender-related differences in pharmacokinetics and metabolism have been observed.

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

Absorption of a micronized fenofibrate formulation (LIPIDIL Micro 200 mg capsules) is low and variable when administered under fasting conditions and increases when given with food. Fenofibrate, given in a micro-coated formulation (LIPIDIL Supra 160 mg tablets), requires lower doses (160 mg) to achieve equivalent plasma levels to the micronized (200 mg) formulation. Nanocrystallization of fenofibrate allows for further

reduction in the dose (LIPIDIL EZ 145 mg tablets), and LIPIDIL EZ may be taken without regard to meals, because of optimized product absorption.

In a single-dose three-way randomized crossover bioavailability study in 72 healthy male and female volunteers, under low fat fed conditions, one 145 mg LIPIDIL EZ or three 48 mg LIPIDIL EZ tablets were compared to one 200 mg micronized capsule (LIPIDIL Micro 200 mg). Each subject received a single oral dose of each formulation with a low fat breakfast (30% fat, approx. 400 Kcal), with a two-week interval between doses.

**TABLE 1: Summary Table of the Comparative Bioavailability Data:  
A Single Dose Study (LIPIDIL EZ 145 mg tablet vs. LIPIDIL Micro 200 mg capsule)**

Analyte: Fenofibric Acid				
From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test : LIPIDIL EZ 145 mg	Reference : LIPIDIL Micro 200 mg	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (µg.h/mL)	148.47 153.5 (27%)	170.49 174.2 (25%)	87.1%	85.2-89.0%
AUC <sub>I</sub> (µg.h/mL)	151.69 157.4 (28%)	176.03 180.4 (27%)	86.2%	84.3-88.1%
C <sub>MAX</sub> (µg/mL)	8.646 8.80 (19%)	8.582 8.87 (26%)	100.8%	96.8-104.9%
T <sub>MAX</sub> (h)	3.5 (35%)	4.4 (38%)		
T <sub>½</sub> (h)	20.7 (24%)	22.0 (34%)		

\*expressed as arithmetic mean (CV%) only

**TABLE 2: Summary Table of the Comparative Bioavailability Data :  
A Single Dose Study (LIPIDIL EZ 3 x 48 mg tablet vs. LIPIDIL Micro 200 mg capsule)**

Analyte: Fenofibric Acid				
From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test : LIPIDIL EZ 3 x 48 mg	Reference : LIPIDIL Micro 200 mg	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (µg.h/mL)	148.29 153.3 (27%)	170.49 174.2 (25%)	87.0%	85.1-88.9%
AUC <sub>I</sub> (µg.h/mL)	151.34 157.0 (29%)	176.03 180.4 (27%)	86.0%	84.3-88.1%
C <sub>MAX</sub> (µg/mL)	8.399 8.54 (19%)	8.582 8.87 (26%)	97.9%	94.0-101.9%
T <sub>MAX</sub> (h)	3.6 (35%)	4.4 (38%)		
T <sub>½</sub> (h)	20.1 (23%)	22.0 (34%)		

\* expressed as arithmetic mean (CV%) only.

These data demonstrate that comparable bioavailability was achieved between LIPIDIL EZ, 145 mg or 3x48 mg tablets, and LIPIDIL Micro 200 mg capsules.

In a single-dose two-way randomized crossover bioavailability study in 40 healthy male volunteers, under low fat fed conditions, one 145 mg LIPIDIL EZ tablet was compared to

one 160 mg LIPIDIL Supra tablet. Each subject received a single oral dose of each formulation with a low fat breakfast (30% fat, approx. 400 Kcal), with a two-week interval between doses.

**TABLE 3 : Summary Table of the Comparative Bioavailability Data :  
A Single Dose Study (LIPIDIL EZ 145 mg tablet vs. LIPIDIL Supra 160 mg tablet)**

<b>Analyte: Fenofibric Acid</b>				
<b>From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)</b>				
Parameter	Test LIPIDIL EZ 145 mg tablet	Reference LIPIDIL Supra 160 mg tablet	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (µg.h/mL)	103.52 107.99 (29%)	103.93 108.96 (29%)	99.6%	96.2-103.1%
AUC <sub>I</sub> (µg.h/mL)	105.00 109.53 (29%)	105.80 110.86 (29%)	99.2%	96.0-102.6%
C <sub>MAX</sub> (µg/mL)	8.02 8.14 (17%)	6.73 6.91 (23%)	119.2%	111.5-127.4%
T <sub>MAX</sub> <sup>*</sup> (h)	2.88 (42%)	3.72 (31%)		
T <sub>½</sub> <sup>*</sup> (h)	17.15 (20%)	18.74 (20%)		

\* expressed as arithmetic mean (CV %) only.

These data demonstrate that comparable bioavailability was achieved between, 145 mg LIPIDIL EZ tablets and LIPIDIL Supra 160 mg tablets.

A study to examine the effect of food on the absorption of nanocrystallized fenofibrate was performed as a single-dose three-way randomized cross-over bioavailability study in 45 healthy male and female volunteers. Each subject received a single dose of 145 mg LIPIDIL EZ with either a high fat breakfast [50% fat, approx. 1000 Kcal, High Fat Fed (HFF)], a low fat breakfast [30% fat, approx. 400 Kcal; Low Fat Fed (LFF)] or no breakfast (fasted state), with a two-week interval between study arms.

**TABLE 4: Summary Table of the Comparative Bioavailability Data:  
A Single Dose Study (LIPIDIL EZ 145 mg tablets (High Fat Fed vs. Fasted Conditions))**

<b>Analyte: Fenofibric Acid</b>				
<b>From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test : 145 mg high fat fed</b>	<b>Reference : 145 mg fasted</b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>T</sub> (µg.h/mL)	123.0 127.9 (27.7%)	116.5 121.6 (28.1%)	105.4%	102.0-109.0%
AUC <sub>I</sub> (µg.h/mL)	124.8 129.9 (28.0%)	118.5 123.8 (28.8%)	105.2%	101.8-108.8%
C <sub>MAX</sub> (µg/mL)	7.82 7.96 (18.5)	7.77 7.94 (20.1%)	100.7%	96.3-105.4%
T <sub>MAX</sub> <sup>*</sup> (h)	4.27 (45.5%)	2.33 (31.4%)		
T <sub>½</sub> <sup>*</sup> (h)	17.8 (23.3%)	18.9 (24.9%)		

\* expressed as arithmetic mean (CV %) only.

**TABLE 5: Summary Table of the Comparative Bioavailability Data:  
A Single Dose Study (LIPIDIL EZ 145 mg tablets (Low Fat Fed vs. Fasted Conditions))**

<b>Analyte: Fenofibric Acid</b>				
<b>From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test : 145 mg low fat fed</b>	<b>Reference : 145 mg fasted</b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>T</sub> (µg.h/mL)	118.1 123.2 (28.4%)	116.5 121.6 (28.1%)	101.3%	98.1-104.7%
AUC <sub>I</sub> (µg.h/mL)	119.8 125.1 (28.7%)	118.5 123.8 (28.8%)	101.2%	97.8-104.6%
C <sub>MAX</sub> (µg/mL)	7.84 7.96 (17.9%)	7.77 7.94 (20.1%)	100.9%	96.4-105.5%
T <sub>MAX</sub> <sup>*</sup> (h)	3.56 (33.1%)	2.33 (31.4%)		
T <sub>½</sub> <sup>*</sup> (h)	18.7 (19.5%)	18.9 (24.9%)		

\* expressed as arithmetic mean (CV %) only.

These data demonstrate that LIPIDIL EZ can be administered with or without food, as there was no effect of food on the bioavailability of the nanocrystallized fenofibrate tablets when compared to the bioavailability under the fasted state.

## INDICATIONS AND CLINICAL USE

LIPIDIL EZ 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.

LIPIDIL EZ, administered in combination with ezetimibe, is indicated for the reduction of elevated total-C, LDL-C, Apo B, and non HDL-C in patients with mixed hyperlipidemia.

LIPIDIL EZ alone may not be adequate therapy in some patients with familial combined hyperlipidemia with Type IIb and Type IV hyperlipoproteinemia.

LIPIDIL EZ (fenofibrate) is not indicated for the treatment of Type I hyperlipoproteinemia.

## CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction (creatinine clearance <20 mL per min), including primary biliary cirrhosis.
2. Pre-existing gallbladder disease (**see WARNINGS**).
3. Hypersensitivity to fenofibrate, any component of this medication or other drugs of the fibrate class.
4. Should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions.
5. The drug should not be used during pregnancy and breast-feeding.
6. Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
7. When LIPIDIL EZ is to be administered with ezetimibe, the contraindications to ezetimibe should be reviewed before starting concomitant therapy.

## WARNINGS

1. General: When LIPIDIL EZ is to be administered with ezetimibe, the ezetimibe Product Monograph should be consulted.
2. **Fenofibrate and HMG-CoA Reductase Inhibitors (Statins): The concomitant administration of fenofibrate and statins should be avoided unless the benefit for further alteration in lipid levels is likely to outweigh the increased risk of this combination.**

**The concomitant administration of fenofibrate (equivalent to 145 mg LIPIDIL EZ) with Pravastatin (40 mg) once daily for 10 days, in healthy adults, increased the mean C<sub>max</sub> and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with Pravastatin also increased the mean C<sub>max</sub> and AUC of the major metabolites, 3-alpha-hydroxy-isopravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively.**

**The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic action, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading to a high proportion of cases to acute renal failure.**

**This combination therapy must not be used in patients with predisposing factors for myopathy (pre-existing myopathy, age >70 years, renal impairment, hepatic impairment, severe infection, surgery and trauma, frailty, hypothyroidism or electrolyte imbalance, personal or family history of hereditary muscular disorders, previous history of muscle toxicity with another HMG-CoA reductase inhibitor, concomitant use of a fibrate, niacin or ezetimibe, alcohol abuse, excessive physical exercise, diabetes with hepatic fatty change situations where an increase in plasma levels of active ingredient may occur).**

**For information on a specific HMG-CoA reductase inhibitor, consult a respective Product Monograph.**

**The use of fibrates alone, including LIPIDIL EZ, may occasionally be associated with myositis, myopathy or rhabdomyolysis. Patients receiving LIPIDIL EZ and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy and or myositis is suspected or diagnosed, LIPIDIL EZ therapy should be stopped.**

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

Concomitant administration with ezetimibe:

When ezetimibe is initiated in a patient already taking LIPIDIL EZ, liver function tests should be considered at initiation of ezetimibe therapy and then as indicated. When ezetimibe is initiated at the same time as LIPIDIL EZ, liver function tests should be performed at initiation of therapy according to the above recommendations (see **ADVERSE REACTIONS**).

- Cholelithiasis:** Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIDIL EZ therapy should be discontinued if gallstones are found.
- Haematologic changes:** Mild hemoglobin, haematocrit and white blood cell decreases have been observed occasionally in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

## PRECAUTIONS

1. **General:** When LIPIDIL EZ is to be administered with ezetimibe, the ezetimibe Product Monograph should also be consulted.
2. **Initial therapy:** Before instituting fenofibrate therapy, laboratory tests should be conducted to ensure that lipid levels are consistently abnormal. Attempts should be made to control serum lipids with appropriate diet, exercise and weight loss in obese patients. Secondary causes of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment and excessive alcohol intake should be adequately treated before fenofibrate therapy is initiated. In patients at high risk, consideration should be given to the control of other risk factors such as smoking, use of preparations containing estrogen and inadequately controlled hypertension.
3. **Long-term therapy:** Because long-term administration of fenofibrate is recommended, the potential risks and benefits should be carefully weighed. Adequate pretreatment laboratory studies should be performed to ensure that patients have elevated serum cholesterol and/or triglycerides or low HDL-cholesterol levels.

Response to therapy should be monitored by determination of serum lipid values (e.g. total cholesterol, LDL-C, triglycerides). If a significant serum lipid response is not obtained in three months, LIPIDIL EZ should be discontinued.

4. **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 and in cases of hypoalbuminemia. Myopathy should be considered in any patient with diffuse myalgias, myositis, muscle cramps, 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 (5 times the upper limit of normal) occur or myopathy is diagnosed.

Patients with pre-disposing factors for myopathy may be at an increased risk of developing rhabdomyolysis (**see WARNINGS**). For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed.

### Concomitant administration with ezetimibe:

Post marketing reports of adverse events have included rare cases of myopathy/rhabdomyolysis occurring in patients taking ezetimibe. Myopathy/rhabdomyolysis should be considered in patients presenting with muscle pain

during treatment with ezetimibe and LIPIDIL EZ, and consideration given to discontinuation of the drugs. Most cases of myopathy/rhabdomyolysis resolved when drugs were discontinued.

5. **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.
6. **Use in pregnancy:** Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and in rabbits when given in doses 9 times the MRHD (on the basis of mg/m<sup>2</sup> surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should not be used during pregnancy. (see **CONTRAINDICATIONS**).
7. **Nursing mothers:** In the absence of information concerning the presence of fenofibrate in human breast milk, LIPIDIL EZ should not be used by nursing mothers.
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.
9. **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.

Concomitant administration with ezetimibe:

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of ezetimibe and fibrates other than fenofibrate is not recommended (see **DRUG INTERACTIONS**, and Product Monograph for ezetimibe).

If cholelithiasis is suspected in a patient receiving ezetimibe and LIPIDIL EZ, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (See **ADVERSE REACTIONS**).

10. **Renal function:** In patients with hypoalbuminemia, e.g., nephrotic syndrome, and in patients with renal insufficiency, the dosage of fenofibrate must be reduced and

renal function should be monitored regularly (**see WARNINGS, Skeletal muscle and DOSAGE AND ADMINISTRATION**). Fenofibrate should not be used in dialysis patients.

Treatment should be interrupted in case of an increase in creatinine level > 50% upper limit of normal. It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.

11. **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.
12. **Use in Elderly:** Fenofibrate is excreted by the kidney. Therefore, the risk of adverse reactions to LIPIDIL EZ may be greater in the elderly patients with impaired renal function. Since elderly patients are more likely to have a decreased renal function, dose should be carefully selected (**see DOSAGE AND ADMINISTRATION**).

### 13. Drug Interactions:

#### **General**

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

#### **Statins**

No drug-drug interaction studies with fenofibrate and statins have been conducted in patients.

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying disease and use of concomitant medications (**see WARNINGS**).

#### **Pravastatin**

Concomitant administration in 23 healthy adults of fenofibrate (equivalent to 145 mg LIPIDIL EZ) with pravastatin, 40 mg once daily for 10 days, has been shown to increase the mean C<sub>max</sub> and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with pravastatin also increased the mean C<sub>max</sub> and AUC of the major metabolite, 3- $\alpha$ -hydroxy-iso-pravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively.

### Atorvastatin

Concomitant administration of fenofibrate (equivalent to 145 mg LIPIDIL EZ) with atorvastatin (20 mg) once daily for 10 days resulted in a 14% decrease in the mean atorvastatin AUC value (range: from a 67% decrease to a 44% increase) in 22 healthy males. There was a 0% change in the atorvastatin mean C<sub>max</sub> value (range: from a 60% decrease to a 136% increase). No significant pharmacokinetic interaction was observed in the mean fenofibric acid AUC (2.3% decrease, range: from a 39% decrease to a 40 % increase) or in the mean C<sub>max</sub> (3.8% decrease, range: from a 29% decrease to a 42% increase) when fenofibrate was co-administered with multiple doses of atorvastatin.

### Simvastatin

In a 10-day trial, fenofibrate (equivalent to 145 mg LIPIDIL EZ) was taken once daily. On day 10, simvastatin 40 mg was added to the fenofibrate regimen. The mean AUC of simvastatin acid, the main active metabolite, decreased by 42% (range: from a 77% decrease to a 50% increase) in the presence of fenofibrate. Fenofibrate had no impact (0%) on the mean simvastatin acid C<sub>max</sub> (range: from a 67% decrease to a 92% increase). The mean fenofibric acid C<sub>min</sub> plasma levels increased by 14% (range: from a 7% decrease to a 48% increase) following the co-administration of simvastatin, indicating that fenofibric acid concentrations are not significantly affected by the addition of a 40 mg dose of simvastatin.

### Rosuvastatin

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

### Ezetimibe

The safety and effectiveness of fenofibrate co-administered with ezetimibe have been evaluated in a clinical study (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and CLINICAL TRIALS**). Co-administration of ezetimibe with other fibrates has not been studied (see ezetimibe Product Monograph). Co-administration of ezetimibe with fibrates other than fenofibrate is not recommended until use in patients is studied.

In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

### Oral Anticoagulants

Caution should be exercised when oral anticoagulants are given in conjunction with LIPIDIL EZ (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 combination therapy with a fibrate. Therefore, the benefits and risks of using fenofibrate concomitantly with these drugs should be carefully considered.

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporine. The renal function of these patients must therefore be closely monitored and treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

### **Bile Acid Sequestrants**

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

### **Estrogens**

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

### **Rosiglitazone**

Some epidemiologic studies and case reports suggest that markedly decreased HDL-C in some patients involve the interaction of rosiglitazone with fenofibrate or bezafibrate. Laboratory findings in some published case reports demonstrated that, in some cases, it is the combination of rosiglitazone and fenofibrate, and neither agent alone, that lowers HDL-C.

## ADVERSE REACTIONS

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

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

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

Adverse events, regardless of their causality, reported in more than 1% of patients are shown in Table 6.

<b>TABLE 6: Number (%) of Patients Reporting Adverse Events</b>		
	<b>Fenofibrate N= 477</b>	<b>Placebo N= 386</b>
<b>Body as a whole</b>	68 (14.3%)	51 (13.2%)
Abdominal pain	12 (2.5%)	8 (2.1%)
Asthenia	14 (2.9%)	7 (1.8%)
Headache	15 (3.1%)	11 (2.8%)
<b>Cardiovascular system</b>	15 (3.1%)	13 (3.4%)
<b>Digestive system</b>	63 (13.2%)	47 (12.2%)
Diarrhea	10 (2.1%)	13 (3.4%)
Nausea	12 (2.5%)	7 (1.8%)
Constipation	6 (1.3%)	3 (0.8%)
Dyspepsia	5 (1.0%)	6 (1.6%)
Flatulence	10 (2.1%)	10 (2.6%)
<b>Endocrine system</b>	1 (0.2%)	1 (0.3%)
<b>Haemic &amp; lymphatic system</b>	3 (0.6%)	1 (0.3%)
<b>Metabolic &amp; nutritional disorders</b>	18 (3.8%)	14 (3.6%)
ALT increase	12 (2.5%)	4 (1.0%)
AST increase	8 (1.7%)	1 (0.3%)
ALT/AST increase	9 (4.9%)	0
CPK increase	1 (0.2%)	5 (1.3%)
Creatinine increase	8 (1.7%)	1 (0.3%)
<b>Musculo-skeletal system</b>	31 (6.5%)	21 (5.4%)
Arthralgia	11 (2.3%)	11 (2.8%)
Myalgia	3 (0.6%)	4 (1.0%)
<b>Nervous system</b>	31 (6.5%)	11 (2.8%)
Dizziness	5 (1.0%)	4 (1.0%)
<b>Respiratory system</b>	34 (7.1%)	25 (6.5%)
Rhinitis	10 (2.1%)	4 (1.0%)
<b>Skin and appendages</b>	24 (5.0%)	12 (3.1%)
Rash	11 (2.3%)	3 (0.8%)
Pruritus	10 (2.1%)	3 (0.8%)
<b>Special senses</b>	14 (2.9%)	10 (2.6%)
<b>Urogenital system</b>	14 (2.9%)	9 (2.3%)

Safety was monitored for 3 years during the placebo-controlled DAIS study (see **CLINICAL STUDIES**) for both adverse events and laboratory anomalies. Fenofibrate was used safely in type 2 diabetic patients, as the overall incidence and severity of adverse events were comparable in fenofibrate and placebo groups. Table 7 below summarizes the incidence of adverse events, by body system, observed in both treatment groups.

**TABLE 7 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%)
Haemic/lymphatic	31 (1.8%)	19 (9.2%)	23 (1.3%)	15 (7.1%)
Metabolic/ nutritional	50 (2.9%)	32 (15.5%)	70 (4.9%)	41 (19.4%)
Musculo-skeletal	155 (9, 1%)	84 (40.6%)	180 (10.2%)	84 (39.8%)
CNS	103 (6.0%)	59 (28.5%)	98 (5.6%)	58 (27.5%)
Respiratory	301 (17.6%)	108 (52.2%)	279 (15.9%)	105 (49.8%)
Skin/appendage	107 (6.3%)	58 (28.0%)	107 (6.1%)	48 (22.8%)
Special senses	73 (4.3%)	44 (21.3%)	90 (5.1%)	50 (23.7%)
Urogenital	118 (6.9%)	55 (26.6%)	103 (5.9%)	46 (21.8%)
Other	11 (0.6%)	9 (4.4%)	14 (0.8%)	11 (5.2%)

In two open, non-controlled clinical studies conducted in Canada and Germany, a total of 375 patients on fenofibrate, microcoated formulation, were evaluated for adverse events. Listed in Table 8 are the adverse events possibly or probably related to fenofibrate, microcoated formulation and reported by more than 0.5% of the patients.

**TABLE 8: 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)
<b>Digestive system</b>	
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%)
<b>Body as a whole</b>	
Abdominal pain	4 (1.1%)
Headache	2 (0.5%)
Asthenia	2 (0.5%)
Lab test abnormal	2 (0.5%)
<b>Metabolic and Nutritional Disorders</b>	
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%)
<b>Nervous system</b>	
Dizziness	2 (0.5%)
Libido decreased	2 (0.5%)

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

Other adverse events include commonly reported cases of vomiting. Uncommonly reported cases of pancreatitis and venous thromboembolism (pulmonary embolism and deep vein thrombosis). Rarely reported cases of alopecia, sexual asthenia, myositis and muscular cramps. Very rarely reported cases of, rhabdomyolysis and interstitial pneumopathies. Episodes of hepatitis have been reported. When symptoms (e.g. jaundice) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable (see **WARNINGS**). Photosensitivity reactions, development of gallstones and cutaneous hypersensitivity with erythema and vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light in individual cases (even after many months of uncomplicated use) have also been reported.

#### Combination with ezetimibe:

When LIPIDIL EZ is to be administered with ezetimibe, the ezetimibe Product Monograph should also be consulted.

In a clinical study involving 625 patients treated for up to 12 weeks and 576 patients treated for up to 1 year, co-administration of fenofibrate and ezetimibe was well tolerated. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (>3 ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 0.4) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively (**see WARNINGS, PRECAUTIONS, DRUG INTERACTIONS**). There were no CPK elevations > 10X ULN in either treatment group in this study. No cases of myopathy, rhabdomyolysis, or pancreatitis were reported in this 12 weeks study.

#### **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 (7/375) treated with fenofibrate, microcoated formulation. In two dose-ranging studies, the incidence of increases in transaminases (>3 x ULN) due to fenofibrate therapy appears to be dose related; 0.6% (1/157) (80mg tablet), 1.9% (3/158) (160mg tablet) and 4.0% (6/149) (240mg tablet). Values usually return to normal without interruption of treatment (**see PRECAUTIONS**). Reductions in alkaline phosphatase levels have also been observed.

Mild decreases in hemoglobin, 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 heptoglobin 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% (2/375) of the patients treated with fenofibrate, microcoated formulation (LIPIDIL Supra).

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

While there has been no reported case of overdose, 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 LIPIDIL EZ (fenofibrate), and should continue on this diet during treatment with LIPIDIL EZ. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with LIPIDIL EZ, 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, LIPIDIL EZ should be discontinued.

The usual recommended dose for LIPIDIL EZ in adults, is one 145 mg tablet daily, taken any time with or without food. In the elderly, the initial dose should be limited to 48 mg per day. The dose should be individualized according to patient response and should be adjusted if necessary following repeat lipid determinations.

The maximum recommended daily dose of LIPIDIL EZ is 145 mg.

In patients having impaired renal function, treatment with LIPIDIL EZ should be initiated at a dose of 48 mg per day and increased only after evaluation of the effects on renal function and lipid levels at this dose.

### Concomitant administration with ezetimibe:

The recommended dose of ezetimibe is 10 mg once daily orally in combination with LIPIDIL EZ. LIPIDIL EZ in combination with ezetimibe, may be taken with or without food, preferably at the same time each day.

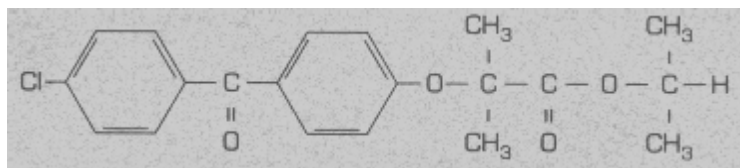
## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

**Proper name:** fenofibrate

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

**Structural formula:**



**Molecular formula:** C<sub>20</sub> H<sub>21</sub> O<sub>4</sub> Cl

**Molecular weight:** 360.83

**Description:** Fenofibrate is a crystalline, whitish powder.

**Melting point:** 79 to 82°C.

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

### COMPOSITION

LIPIDIL EZ contains, in addition to fenofibrate, the following excipients: crospovidone, docusate sodium, hypromellose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose, sodium lauryl sulfate, sucrose,

The tablet coating for the 145 mg tablets contains polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

The tablet coating for the 48 mg tablets contains polyvinyl alcohol, titanium dioxide, talc, lecithin, D&C Yellow #10 Aluminum Lake, D&C yellow #6/sunset yellow FCF Aluminum Lake, D&C Blue #2/Indigo carmine FCF Aluminum Lake.

### STABILITY AND STORAGE RECOMMENDATIONS

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

## **AVAILABILITY OF DOSAGE FORMS**

LIPIDIL EZ 145 mg tablets: each white, oblong, film-coated tablet (NanoCrystal<sup>®</sup> formulation) contains 145 mg and is embossed with the Fournier logo on one side and 145 on the other. Available in blister packs of 30 tablets.

LIPIDIL EZ 48 mg tablets: each yellow, oblong, film-coated tablet (NanoCrystal<sup>®</sup> formulation) contains 48 mg, and is embossed with the Fournier logo on one side and 48 on the other. Available in blister packs of 30 tablets.

## INFORMATION FOR THE CONSUMER

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

LIPIDIL EZ reduces levels of low density cholesterol (LDL-C or bad cholesterol), and other lipids called triglycerides (fatty substances found in the blood), while increasing levels of high density cholesterol (HDL-C or good cholesterol) in the blood.

LIPIDIL EZ is used, in conjunction with the appropriate diet, in the treatment of adult patients with :

- a. type 2 diabetes (non-insulin dependent), with dyslipoproteinemia (abnormal lipid levels in the blood, including high cholesterol), with or without elevated triglycerides, Fredrickson classification types IIa and IIb);
- b. high serum triglyceride levels (Fredrickson classification types IV and V), who are at high risk for complications.

LIPIDIL EZ may be taken with another medicine known as ezetimibe, in addition to diet and other lifestyle changes. Ezetimibe adds to the cholesterol-lowering effect of LIPIDIL EZ. Ezetimibe works by decreasing the absorption of cholesterol in the small intestine. LIPIDIL EZ lowers cholesterol in a different way; it works in the liver.

LIPIDIL EZ 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 lifestyle measures.

Take exactly as instructed by your doctor. Do not change the dose without your doctor's advice. Consult your doctor before stopping treatment.

### ***DO NOT USE LIPIDIL EZ IF:***

- you suffer from liver or kidney disease;
- you already have gallbladder problems;
- you are allergic to fenofibrate or similar drug or if you are allergic to any of the ingredients in LIPIDIL EZ tablets (***see What Does LIPIDIL EZ Contain?***)
- you are allergic to peanuts or arachis oil or soya lecithin or related products due to risk of allergic reaction.
- you are pregnant or breastfeeding; in the event of pregnancy during treatment, your doctor should be informed and LIPIDIL EZ should be discontinued;
- you have a photoallergy (skin sensitivity to sunlight or UV light) when taking a fibrate (a class of drugs used for lowering cholesterol, which includes LIPIDIL EZ and gemfibrozol) or an anti-inflammatory drug called ketoprofen.

***BEFORE STARTING TREATMENT WITH THIS MEDICINE***, your doctor must know:

- if you have had an allergic reaction to (or poorly tolerated) LIPIDIL EZ, **any of its ingredients** (see ***What Does LIPIDIL EZ Contain?***), or any other lipid treatment;
- if you suffer from liver or kidney problems;
- if you have a gallbladder 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 any other medicine, prescription or non-prescription. Of particular concern are:
  - Statins (a class of drugs, which includes atorvastatin, pravastatin, simvastatin, etc., used to lower cholesterol)
  - Oral anticoagulants (blood thinning agents, such as warfarin)
  - Cyclosporine (a drug which may be taken following an organ transplant)
  - Cholestyramine or similar drug (another type of cholesterol lowering agent)
  - Estrogens (hormones which may be found in oral contraceptives or hormone replacement therapy)
  - Rosiglitazone (a drug used to treat type 2 diabetes)

### ***PROPER USE OF THE MEDICINE***

- LIPIDIL EZ (NanoCrystal<sup>®</sup> formulation) may be taken once daily, anytime, with or without food.
- The usual recommended dose of LIPIDIL EZ in adults is one 145 mg tablet.
- In elderly patients and those with mild to moderate kidney disease, the doctor may initiate treatment with one 48 mg tablet daily, taken anytime, with or without food. The doctor may later decide to increase this dose.
- Never change the dose unless directed by your doctor.
- LIPIDIL EZ is not recommended for use in children.
- The safety of using LIPIDIL EZ in combination with a statin has not been extensively studied in patients. Therefore, the combined use of fenofibrate with a statin should be avoided unless recommended by your doctor.
- Another type of cholesterol lowering agent called ezetimibe can also be taken with LIPIDIL EZ.
- Tell your doctor about any health problem that occurs while you are taking LIPIDIL EZ. If you need other medical treatment while taking LIPIDIL EZ, let your doctor know that you are taking LIPIDIL EZ.

### ***SIDE EFFECTS***

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

Tell your doctor if you feel in any way unwell while taking LIPIDIL EZ.

Some common side effects may include abdominal pain, constipation, diarrhea, nausea, headache, dizziness, skin reactions and fatigue. This is not a complete list of side effects. If you experience any unexpected symptoms while taking LIPIDIL EZ, contact your doctor or pharmacist.

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

Your doctor will ask you to have regular medical check-ups and appropriate laboratory tests. It is important to respect the dates proposed for these tests: we strongly recommend that you keep these appointments faithfully so that any abnormalities that may occur can be identified promptly.

### ***WHAT DOES LIPIDIL EZ CONTAIN?***

LIPIDIL EZ contains, in addition to fenofibrate, the following nonmedicinal ingredients: crospovidone, docusate sodium, hypromellose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose, sodium lauryl sulfate, sucrose.

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**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.**

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Last revised: July 15, 2011

## 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.

### 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 (LIPIDIL Micro), at a daily dose of 200 mg.

Specific clinical studies were performed with fenofibrate, micronized formulation (LIPIDIL Micro).

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 micronized 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 ( $\pm$  S.D.) averaged per patient and per segment at baseline and at the end of study (ITT population)**

	<b>Fenofibrate</b>	<b>Placebo</b>	<b>p-value*</b>
<b>Per patient analysis</b>	<b>N=207</b>	<b>N=211</b>	
<b>- Mean segment diameter (mm)</b>			
Baseline	2.70 (0.45)	2.67 (0.45)	0.494
Final	2.62 (0.49)	2.56 (0.50)	0.173
<b>- Minimum segment diameter (mm)</b>			
Baseline	2.14 (0.44)	2.10 (0.44)	0.457
Final	2.05 (0.46)	1.98 (0.48)	0.028
<b>- Percent diameter stenosis (%)</b>			
Baseline	21.8 (7.8)	21.8 (7.4)	0.958
Final	24.1 (9.8)	25.7 (10.8)	0.02

	<b>Fenofibrate</b>	<b>Placebo</b>	<b>p-value*</b>
<b>Per segment analysis</b>	<b>N=1884</b>	<b>N=1993</b>	
<b>- Mean diameter (mm)</b>			
Baseline	2.76 (0.84)	2.72 (0.83)	0.145
Final	2.68 (0.87)	2.62 (0.87)	0.037
<b>- Minimum diameter (mm)</b>			
Baseline	2.20 (0.82)	2.16 (0.81)	0.077
Final	2.11 (0.84)	2.03 (0.83)	0.541
<b>% stenosis</b>			
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*
<b>-Total cholesterol (mmol/L)</b>			
Baseline	5.56 (0.80)	5.58 (0.72)	0.751
Final	4.93 (0.83)	5.42 (0.79)	< 0.001
<b>- Total triglycerides (mmol/L)</b>			
Baseline	2.56 (1.23)	2.52 (1.22)	0.706
Final	1.65 (0.90)	2.16 (1.20)	< 0.001
<b>- HDL-C (mmol/L)</b>			
Baseline	1.00 (0.19)	1.04 (0.21)	0.045
End of study	1.06 (0.26)	1.06 (0.24)	0.045
<b>- Calc. LDL-C (mmol/L)</b>			
Baseline	3.36 (0.71)	3.39 (0.72)	0.532
Final	3.12 (0.69)	3.38 (0.73)	0.042
<b>TC / HDL-C</b>			
Baseline	5.63 (1.08)	5.51 (1.10)	0.115
Final	4.87 (1.27)	5.35 (1.25)	< 0.001
<b>Apo AI (g/L)</b>			
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)

#### Co-administration with ezetimibe:

In a multicenter double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. Patients with an LDL-C  $\geq 3.4$  mmol/L [130 mg/dL] and  $\leq 5.7$  mmol/L [220 mg/dL] (for non-diabetics) or  $\geq 2.6$  mmol/L [100 mg/dL] and  $\leq 4.7$  mmol/L [180 mg/dL] (for diabetics), and with TG  $\geq 2.3$  mmol/L [200 mg/dL] and  $\leq 5.7$  mmol/L [500 mg/dL] were randomized to receive placebo, ezetimibe alone, 160 mg fenofibrate alone, or ezetimibe and 160 mg fenofibrate. In general, the groups were balanced with regard to body weight, sex, age, race and baseline lipids; at entry into the study the mean LDL-C was 4.2 mmol/L [161 mg/dL] while the mean age was 54 years and 56% were male.

Ezetimibe co-administration with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate or ezetimibe administration alone. The percent decrease in TG and percent increase in HDL-C for ezetimibe co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see table below).

**Response to ezetimibe and fenofibrate initiated concurrently in patients with mixed hyperlipidemia (Mean<sup>a</sup> % change from untreated baseline<sup>b</sup> at 12 weeks)**

<b>Treatment (Daily Dose)</b>	<b>N</b>	<b>Total-C</b>	<b>LDL-C</b>	<b>Apo B</b>	<b>TG<sup>a</sup></b>	<b>HDL-C</b>	<b>Non-HDL-C</b>
Placebo	63	0	0	-1	-9	3	0
Ezetimibe	185	-12	-13	-11	-11	4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	19	-16
Ezetimibe + Fenofibrate 160 mg	183	-22	-20	-26	-44	19	-30

<sup>a</sup>For triglycerides, median % change from baseline

<sup>b</sup>Baseline- on no lipid-lowering drug

Improvements in lipid endpoints after 1 year of treatment were consistent with the 12-week data displayed above.

### Clinical Pharmacology

#### **Uricosuric action**

Fenofibrate decreased the plasma uric acid levels in normal as well as hyperuricemic subjects. In a study involving 10 healthy 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 testes.

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 testes 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 clofibrinic 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 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 clofibrinic acid and gemfibrozil as well as fenofibric acid. However, clofibrinic 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 clofibrac acids to proteins was readily observed, no binding to DNA was demonstrated after oral administration of C<sup>14</sup>-labeled fenofibric or clofibrac 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 clofibrac acid and gemfibrozil on DNA synthesis in mouse testicular tissue, as measured by the incorporation of <sup>3</sup>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, clofibrac acid and fenofibric acid showed a negative response. None caused nuclear labeling 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. 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.
2. 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.
3. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 1987; 83 (suppl 5B.): 26- 36.
4. Blane GF. Reviews of European clinical experience with fenofibrate. *Cardiology* 1989; 76 (suppl. 1): 1-13.
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. Boissonnat P et al. The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. *Transplantation* 1994; 58(2): 245 – 247.
7. Bridgman JF, Rosen SM, Thorp JM. Complications during clofibrate treatment of nephrotic-syndrome hyperlipoproteinaemia. *The Lancet* September 1972: 506 – 509.
8. Brunova E, Valek J, Vondra K, Slabochova Z, Grafnetter D, Bruna J. Treatment of Hyperlipoproteinemia with Procetofen. *Curr Ther Res* 1982; 31: 37-44.
9. Chanu B, Bakir R, Goy-Loefer 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.
10. Chicaud P, Demange J, Debry G. Long-term (18 months) effects of fenofibrate in young hypercholesterolemic subjects. *Presse Med.*, 1984,13: 417-419.
11. Desager JP, Harvengt C. Clinical pharmacokinetic study of procetofen, a new hypolipidemic drug, in volunteers. *Int J Clin Pharmacol Res* 1978; 16: 570-574.
12. Desager JP, Hulhoven R, Harvengt C. Uricosuric effect of fenofibrate in healthy volunteers. *J Clin Pharmacol* 1980; 20: 560-564.
13. 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.

14. 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.
15. EZETROL Product Monograph, Merck Frosst/ Schering Pharmaceuticals, Kirkland, QC, December 2006.
16. 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.
17. Farnier M, Freeman M, Macdonell G, Perevozskaya I, Davies M, Mitchel Y, Gumbiner B. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J* 2005;26:897-905.
18. 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.
19. 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.
20. 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: 151-163.
21. Guichard JP, Blouquin P, Qing Y. A new formulation of fenofibrate: suprabioavailable tablets. *Curr Med Res Opin*. 2000;16(2): 134-138.
22. Guichard, JP, Strollin-Benedetti M, Houin G, Albarede JL. Pharmacokinetics of Lipanthyl in the elderly. *Drugs Affecting Lipid Metabolism* 1987; 328-33
23. Gurrieri J, Le Lous M, Renson FJ, Tourne C, Voegelin H, Majoie B, Wulfert E. Experimental study of a new potent hypolipidemic drug, isopropyl-[4'-] p-chlorobenzoyl-2-phenoxy-2-methyl]-propionate (LF178) *Arzneimittelforschung* 1976; 26: 889-894.
24. Harvengt C, Heller F, Desager JP. Hypolipidemic and Hypouricemic Action of Fenofibrate in Various Types of Hyperlipoproteinemias. *Artery* 1980; 7: 73-82.
25. Hawkins, D. Drug interactions with lipid-lowering agents, *Cardiology (Special Edition)*, 2002, 8: 51-54.
26. Hunninghake DB. Treatment of hypertriglyceridemia with fenofibrate. *Practical Cardiology* 1989; 15: 38-39.
27. Jacobson TA, Zimmerman FH. Fibrates in combination with statins in the management of dyslipidemia. *The Journal of Clinical Hypertension*. January 2006;8(1): 35 – 41.

28. 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.
29. 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.
30. 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.
31. Langer T, Levy R. Acute muscular syndrome associated with administration of clofibrate. *NEJM* October 1968; 279(16): 856-858.
32. Lethonen A and Viikari J. Fenofibrate and Cholestyramine in type II hyperlipoproteinemia. *Artery* 1982; 10: 353-367.
33. Martin PD, Dane AL, Schneck DW, Warwick MJ. An open-label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. *Clin Ther.* 2003; 25:459-71
34. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia*, 2003, 46(3): 347-351.
35. Pan WJ, Gustavson LE, Achari R, Rieser MJ, Ye X, Gutterman C, Wallin BA. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol.* 2000; 40:316-23.
36. Podda M, Zuin M. Effects of fenofibrate on biliary lipids and bile acid pool size in patients type IV hyperlipoproteinemia. *Atherosclerosis* 1985; 55: 135-142.
37. Rouffy J, Sauvanet JP, Chanu B, Bakir R, Goy-Loeper J, Saya C, Pinaroli F. Evaluation à long terme de l'activité hypolipémiante 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: 3747-3751.
38. 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.
39. Seidehamel RJ. Fenofibrate in type IV and type V hyperlipoproteinemia. *Cardiology* 1989; 76 (suppl. 1): 23-32.

40. 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. ([www.nhlbi.nih.gov/guidelines/cholesterol/index.htm](http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm))