

PRODUCT MONOGRAPH

PrFenomax™
(Fenofibrate Capsules)

100 mg and 160 mg capsules

Professed Standard

Lipid Metabolism Regulator

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Imported and Distributed by:
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Fenomax™
(Fenofibrate Capsules)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules, 100 mg and 160 mg	Lauroyl macrogol glyceride, polyethylene glycol, hydroxypropylcellulose, and sodium starch glycolate. The capsule shells contain titanium dioxide and gelatin.

INDICATIONS AND CLINICAL USE

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

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

Fenomax™ is not indicated for treatment of Type I hyperlipoproteinemia.

Geriatrics (> 65 years of age):

Fenomax™ is also indicated in geriatric patients. Very minor changes in pharmacokinetic parameters were observed in elderly subjects.

Pediatrics (< 18 years of age):

Safety and effectiveness have not been established in this population. See WARNINGS.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction (creatinine clearance < 20ml/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 in pregnant or lactating patients.
5. Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.

WARNINGS AND PRECAUTIONS

General

Initial therapy: Before instituting fenofibrate therapy, attempts should be made to control serum lipids with appropriate diet, exercise and weight loss in obese patients. Other medical problems, such as diabetes mellitus and hypothyroidism, should also be controlled. In patients at high risk, consideration should be given to the control of other risk factors such as smoking, excessive alcohol intake, hormonal contraceptive use and inadequately controlled hypertension.

Long-term therapy: Because long-term administration of fenofibrate is recommended, the potential risks and benefits should be carefully weighed. Adequate pretreatment laboratory studies should be performed to ensure that patients have elevated serum cholesterol and/or triglycerides or low HDL-cholesterol levels. Periodic determination of serum lipids, fasting glucose, creatinine and ALT (SGPT) should be considered during fenofibrate treatment, particularly during the first months of therapy.

Carcinogenesis and Mutagenesis

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.

Cardiovascular

Not applicable.

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Not applicable.

Endocrine and Metabolism

Not applicable.

Gastrointestinal

Not applicable.

Genitourinary

Not applicable.

Hematologic

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.

Hepatic/Biliary/Pancreatic

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. If cholelithiasis is suspected, gallbladder studies are indicated. Fenomax™ therapy should be discontinued if gallstones are found.

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.

Immune

Not applicable.

Neurologic

Not applicable.

Ophthalmologic

Not applicable.

Peri-Operative Considerations

Not applicable.

Psychiatric

Not applicable.

Renal

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

Respiratory

Not applicable.

Sensitivity/Resistance

Not applicable.

Sexual Function/Reproduction

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.

Skeletal Muscle

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

Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels (10 times the upper limit of normal) occur or myopathy is diagnosed.

Skin

Not applicable.

Special Populations

Pregnant Women: Strict birth control procedures must be exercised by women of childbearing potential. If pregnancy occurs despite birth control procedures, Fenomax™ should be discontinued. Women who are planning pregnancy should discontinue Fenomax™ several months prior to conception.

Nursing Women: in the absence of information concerning the presence of fenofibrate in human breast milk, Fenomax™ should not be used by nursing mothers.

Pediatrics (< 18 years of age): 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).

Geriatrics (> 65 years of age): No specific warnings or precautions.

Monitoring and Laboratory Tests

Abnormal liver function tests have been observed occasionally during fenofibrate administration, including elevations of transaminases, and decreases or, rarely, increases in alkaline phosphatase. However, these abnormalities disappear when therapy with fenofibrate is discontinued. Therefore, periodic liver function tests (AST [SGOT], ALT [SGPT] and GGT [if originally elevated]) in

addition to other baseline tests are recommended after 3 to 6 months and at least yearly thereafter. Fenomax™ should be terminated if abnormalities persist.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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).

Clinical Trial Adverse Drug Reactions

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	3 (0.8%)
ALT increased (> 3 x ULN)	4 (1.1%)
AST increased (> 3 x ULN)	1 (0.3%)
Creatine kinase increased (> 5 x ULN)	
Nervous system	
Dizziness	2 (0.5%)
Libido decreased	2 (0.5%)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

No information available.

Abnormal Hematologic and Clinical Chemistry Findings

In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of AST [SGOT] and ALT [SGPT] 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 ULN) due to fenofibrate therapy appears to be dose related; 0.6% (80 mg tablet), 1.9% (160 mg tablet) and 4.0% (240 mg tablet). Values usually return to normal without interruption of treatment. (see **WARNINGS AND 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 CPK elevations and changes in haematologic parameters which generally subside when the drug is discontinued (see **WARNINGS AND PRECAUTIONS**). In the clinical studies conducted in Canada and Germany, the reported frequency of CPK elevations above 5 times the upper limit of normal was approximately 0.3% of the patients treated with fenofibrate, microcoated formulation.

Post-Market Adverse Drug Reactions

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).

DRUG INTERACTIONS

Overview

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome P450 (CYP) isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Drug-Drug Interactions

Table 2- Established or Potential Drug-Drug Interactions

Fenofibrate	Ref	Effect	Clinical comment
Oral anticoagulants	C	↑ INR	Caution should be exercised when oral anticoagulants are given in conjunction with Fenomax™. 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	C	Myositis, Rhabdomyolysis	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	C	Fibrate absorption impaired	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	T	Possible ↑ lipid levels	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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

None known.

Drug-Herb Interactions

None known.

Drug-Laboratory Interactions

None known.

Drug-Lifestyle Interactions

None known.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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 Fenomax™, and should continue on this diet during treatment with Fenomax™. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Fenomax™, 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, Fenomax™ should be discontinued.

Recommended Dose and Dosage Adjustment

The recommended dose for Fenomax™ in adults is 160 mg daily. The maximum recommended total daily dose of Fenomax™ is 200 mg.

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

Missed Dose

If a patient misses a dose of Fenomax™, they should take it as soon as they remember. However, if it is almost time for the next dose, they should skip the dose and take only the next regularly scheduled dose. The patient should not take a double dose of Fenomax™.

Administration

Take with the main meal.

Reconstitution: Not applicable

OVERDOSAGE

While there have been no reported cases 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 γ), 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.

Pharmacodynamics

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.

Pharmacokinetics

Absorption: 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.

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

Metabolism: Fenofibrate is metabolized by hydrolysis to its active form, fenofibric acid.

Excretion: In man, fenofibric acid is eliminated conjugated with glucuronic acid. The elimination half-life of fenofibric acid is about 20-24 hours. This value is not modified after multiple dosing. In man it is mainly excreted through the kidney.

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.

Special Populations and Conditions

Pediatrics: No information to report.

Geriatrics: Very minor changes of pharmacokinetic parameters were observed in elderly subjects.

Gender: No sex related differences in pharmacokinetics and metabolism were observed.

Race: No information to report.

Hepatic Insufficiency: No information to report.

Renal Insufficiency: In patients with severe renal failure, significant accumulation was observed with a large increase of the half-life.

Genetic Polymorphism: No information to report.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fenomax™ 100 mg Capsules: each white opaque hard gelatin capsule (size #2) is imprinted in light blue with the Oryx Pharmaceuticals logo and “100”, and contains 100 mg fenofibrate. Fenomax™ 100 mg is available in bottles of 7 (professional sample), 30 and 90 capsules.

Fenomax™ 160 mg Capsules: each white opaque hard gelatin capsule (size #0) is imprinted in dark blue with the Oryx Pharmaceuticals logo and “160”, and contains 160 mg fenofibrate. Fenomax™ 160 mg is available in bottles of 7 (professional sample), 30 and 90 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

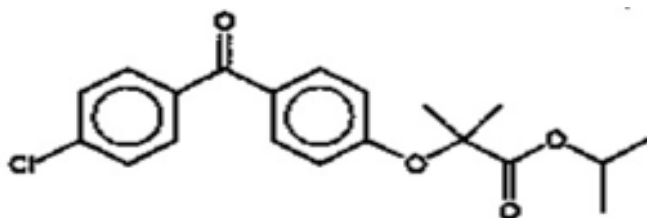
Proper name: Fenofibrate

Chemical name: Isopropyl 2-[4-(4-Chlorobenzoyl) phenoxy]-2-methylpropanoate

Molecular formula: C₂₀H₂₁O₄Cl

Molecular weight: 360.8

Structural formula:



Description: Fenofibrate is a white to off white crystalline powder.

Melting point: Between 79 to 82°C

Solubilities: Fenofibrate is very soluble in dichloromethane, soluble in ethanol, and insoluble in water.

CLINICAL TRIALS

Bioequivalence to Lipidil Supra® (fenofibrate microcoated) Tablets

In a bioequivalence study comparing Fenomax™ 160 mg Capsules and Lipidil Supra® 160 mg, dosed with a high fat breakfast, Fenomax™ was found to be bioequivalent for both peak concentration (C_{max}) and the total amount absorbed into the systemic circulation (AUC) (see Table 1) . The study was a blinded, randomized two period study and included 25 male volunteers, with a 1 week washout between dose periods. Blood sampling times were pre-dose (0), 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24, 48 and 72 hours. The plasma was analyzed for fenofibric acid by LC-MS/MS with a limit of quantitation of 0.0500 µg/mL.

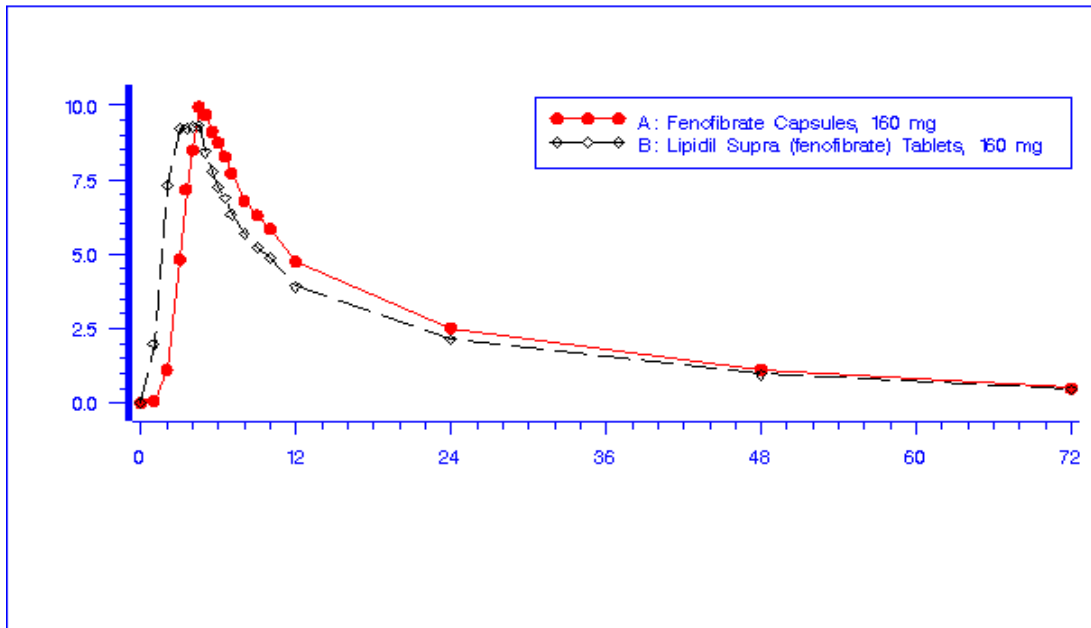
**Table 1: Summary Comparative Bioavailability Data
Single Dose, Fed Bioequivalence Study of Fenomax™ and Lipidil Supra® (n = 25)
(1 x 160 mg)
From measured data
Analyte: Fenofibric Acid**

Parameter	Fenomax™	Lipidil Supra® (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval
	Geometric Mean Arithmetic Mean (CV%)			
AUC ₀₋₇₂ (µg. h/mL)	167.86 175.04 (28)	155.00 163.21 (32)	108.30	104.10 - 112.67
AUC _{0-inf} (µg. h/mL)	180.19 190.19 (32)	166.24 177.18 (36)	108.39	104.60 - 112.32
C _{max} (µg/mL)	10.5 10.8 (21)	10.4 10.5 (20)	101.45	94.30 - 109.14
T _{max} ^a (h)	4.5 (3.5-10)	3.0 (2.0-6.5)		-
T _½ ^b (h)	18.29 (26)	18.89 (24)		-

^a For T_{max}, median (range) is expressed.

^b Expressed as arithmetic mean (CV%) only.

Figure 1: Mean Plasma Fenofibric Acid Concentration ($\mu\text{g/mL}$) vs Time (h) Curves (N=25)



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 ≥ 4 , and either low-density lipoprotein cholesterol (LDL-C) from 3.5 to 4.5 mmol/l with triglycerides (TG) ≤ 5.2 mmol/l, or TG from 1.7 to 5.2 mmol/l with LDL-C ≤ 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 Table 3). The change in mean segment diameter was minimal in both groups over the treatment period, with no statistical difference between groups.

Table 3: 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)

	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
	Fenofibrate	Placebo	p-value*
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 Table 4 for both the fenofibrate- and placebo-treated groups.

Table 4: DAIS study: Mean major lipid values (\pm S.D.) at baseline and at the end of the study (ITT population)

	Fenofibrate	Placebo	p-value*
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
Final	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. Table 5 summarizes the incidence of adverse events, by body system, observed in the fenofibrate and placebo treatment groups.

Table 5: 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%)

DETAILED 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 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 to increase 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.

MICROBIOLOGY

Not applicable.

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 [SGOT] levels were raised in treated rats but ALT[SGPT] levels remained within the normal range for rats on normal diet and were only slightly elevated in rats on the high cholesterol diet. Dose-related hepatomegaly and proliferation of peroxisomes occurred, at doses above 30 mg/kg/day. In a second but similar study of drug 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 [SGOT] and ALT[SGPT] values were increased at 500 and 1000 mg/kg. Hepatomegaly was a consistent finding at all dose-levels reaching a maximum of 78 % increase in weight compared to controls but appeared to regress rapidly. There were no other significant findings in the histological examination.

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

Fenofibrate (0, 12, 50 or 500 mg/kg) or clofibrate (200 mg/kg/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 feeding 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 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 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 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 clofibric acids to proteins was readily observed, no binding to DNA was demonstrated after oral administration of C¹⁴-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 ³H-thymidine. Any response is representative of changes in DNA synthesis in any testicular cells such as germ, Sertoli, Leydig or interstitial cells undergoing scheduled or unscheduled synthesis.

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

The increase in DNA synthesis as observed in mouse testicular tissue with fenofibric acid and gemfibrozil is difficult to evaluate in the absence of a positive control or historical data for this recently developed test, nevertheless such an effect might be anticipated of such agents which are known to cause peroxisome proliferation and which produce increased cell turnover. The occurrence of increased cell turnover would be in keeping with a non-genotoxic but promoting mode of such compounds in mice.

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

Cell growth or malignant transformation *in vitro*: fenofibric acid was without effect on growth or malignant transformation of cultured mammalian cell lines.

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PART III: CONSUMER INFORMATION

Fenomax™
Fenofibrate Capsules

This leaflet is part III of a three-part "Product Monograph" published when Fenomax™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fenomax™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Fenomax™ reduces blood cholesterol, in particular cholesterol associated with low and very low density lipoproteins ("bad" cholesterol). Fenomax™ also reduces high triglyceride levels associated with hypercholesterolemia (too much cholesterol in the blood) and increases the high density lipoprotein (HDL) cholesterol fraction ("good" cholesterol). Because of its effect on these measures, Fenomax™ is also 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 Fenomax™ treatment.

What it does:

See above.

When it should not be used:

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

Fenomax™ is not recommended during pregnancy. In the event of pregnancy during treatment, Fenomax™ should be discontinued and the physician should be informed.

It is not recommended to take Fenomax™ while breast-feeding.

What the medicinal ingredient is:

Fenofibrate

What the important nonmedicinal ingredients are:

Hydroxypropylcellulose, lauroyl macrogol glyceride, polyethylene glycol, sodium starch glycolate. The capsule shells contain titanium dioxide and gelatin.

What dosage forms it comes in:

100 mg and 160 mg capsules

WARNINGS AND PRECAUTIONS

BEFORE you use Fenomax™ talk to your doctor or pharmacist if:

- you have had an allergic reaction to (or poorly tolerated) Fenomax™, any of its ingredients, or any other lipid treatment;
- you suffer from liver or kidney problems;
- you have a gall bladder or gallstone problem;
- you are pregnant, or intend to become pregnant, or are breast-feeding, or intend to breast feed;
- you are taking other medicines, in particular an oral anticoagulant such as warfarin.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Fenomax™ include: oral anticoagulants, statins, cyclosporine, resins and estrogens.

PROPER USE OF THIS MEDICATION

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.

This medicine should only be used to supplement an appropriate diet recommended by your doctor 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. Follow the prescription exactly. 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.

- Fenomax™ should be taken with a main meal, 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. We strongly recommend that you keep these appointments.
- Inform your doctor of any health problem that occurs while you are taking Fenomax™ as well as any prescription or non-prescription medicine. If you need other medical treatment let the doctor know that you are taking Fenomax™.
- Tell your doctor if you feel in any way unwell while taking Fenomax™ (see **SIDE EFFECTS**).
- Contact your doctor promptly if you suffer any unexplained muscle pain, tenderness or weakness.
- The effects of Fenomax™ in preventing heart attacks, atherosclerosis or heart disease are not yet known.

Usual dose:

One capsule per day, taken with your main meal of the day.

Overdose:

If overdose is suspected, contact your local poison control center or emergency room immediately.

Missed Dose:

If you miss a dose of Fenomax™, take it as soon as you remember. However, if it is almost time for the next dose, you should skip the dose and take only the next regularly scheduled dose. You should not take a double dose of Fenomax™ to catch-up.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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.

This is not a complete list of side effects. For any unexpected effects while taking Fenomax™, contact your doctor or pharmacist.

HOW TO STORE IT

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax: 866-678-6789

By email: cadtmp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness
Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.oryxpharma.com>

or by contacting Oryx Pharmaceuticals Inc., at:
1-866-260-6291

This leaflet was prepared by Cipher Pharmaceuticals Ltd.

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