Product Monograph

Including Patient Medication Information

Pr LIPIDIL EZ ®

fenofibrate film-coated tablets (NanoCrystal® Formulation)

For Oral use

48 mg and 145 mg of fenofibrate

Manufacturer's Standard

Lipid Metabolism Regulator

BGP Pharma ULC

85 Advance Road

Etobicoke, Ontario

M8Z 2S6

Date of Authorization:

2025-12-05

Control Number: 298755

Recent Major Label Changes

None at time of the most recent authorization	

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

LIPIDIL EZ (fenofibrate) 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:

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

1.1. Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LIPIDIL EZ in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2. Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with significant differences in safety or efficacy.

2. Contraindications

LIPIDIL EZ is contraindicated for:

- Patients who are hypersensitive to fenofibrate or to any ingredients in the formulation of components of the container including peanut or arachis oil or soya lecithin or related products. For complete listing, see the 6 Dosage Forms, Strengths, Composition, and Packaging.
- Patients with hepatic insufficiency (including primary biliary cirrhosis and unexplained persistent liver function abnormality).
- Patients with pre-existing gallbladder disease (see 7 Hepatic/Biliary/Pancreatic).
- Patients with severe renal dysfunction (creatinine clearance < 30ml/min).
- Patients with chronic or acute pancreatitis.

- Pregnant and breast-feeding women.
- Patients with known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- Co-administration with HMG-CoA reductase inhibitors (statins) in patients with pre-disposing factors for myopathy.

4. Dosage and Administration

4.1. 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 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.

4.2. Recommended Dose and Dosage Adjustment

- The usual recommended dose for LIPIDIL EZ in adults, is one 145 mg tablet daily, taken any time with or without food. Tablets should be swallowed whole with a glass of water. 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.
- LIPIDIL EZ can be taken in combination with ezetimibe 10 mg once daily orally with or without food, preferably at the same time each day.
- Initial Therapy: Before instituting fenofibrate therapy, laboratory tests should be conducted to ensure that lipid levels are consistently abnormal. Attempts should be made to control serum lipids with appropriate diet, exercise and weight loss in obese patients. Secondary causes of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment and excessive alcohol intake should be adequately treated before fenofibrate therapy is initiated. In patients at high risk, consideration should be given to the control of other risk factors such as smoking, use of preparations containing estrogen and inadequately controlled hypertension.
- Long-term therapy: Because long-term administration of fenofibrate is recommended, the potential risks and benefits should be carefully weighed. Adequate pretreatment laboratory studies should be performed to ensure that patients have elevated serum cholesterol and/or triglycerides or low HDL-cholesterol levels.
- Response to therapy should be monitored by determination of serum lipid values (e.g. total

cholesterol, LDL-C, triglycerides). If a significant serum lipid response is not obtained in three months, LIPIDIL EZ should be discontinued.

- LIPIDIL EZ is not recommended for use in patients with hepatic impairment due to the lack of data.
- LIPIDIL EZ should not be used in patients with severe renal dysfunction including patients on dialysis.

4.4. Administration

Tablets can be taken any time with or without food and should be swallowed whole (not crushed or chewed) with a glass of water.

4.5. Missed Dose

If a dose is missed, the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

5. Overdose

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Film-coated tablet 48 mg	colloidal silicon dioxide, crospovidone, docusate sodium, D&C Yellow #10 Aluminum Lake, FD&C yellow #6/sunset yellow FCF Aluminum Lake, FD&C Blue #2/Indigo carmine FCF Aluminum Lake, hypromellose, lactose monohydrate, soybean lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium lauryl sulfate, sucrose, talc, titanium dioxide, xanthan gum.
	Film-coated tablet 145 mg	colloidal silicon dioxide, crospovidone, docusate sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium lauryl sulfate, soybean lecithin, sucrose, talc, titanium dioxide,

		xanthan gum.

Availability

LIPIDIL EZ (fenofibrate) film-coated tablets are formulated for oral administration containing fenofibrate and are available in two strengths: 48 mg and 145 mg.

Composition

LIPIDIL EZ 48 mg tablets are supplied as yellow, oval, film-coated tablets (NanoCrystal® formulation) and are embossed with "FI" on one side. The tablets are available in blister packs of 30 tablets.

LIPIDIL EZ 145 mg tablets are supplied as white, oval, film-coated tablets (NanoCrystal® formulation) and are embossed with the Fournier logo on one side and 145 on the other. The tablets are available in blister packs of 30 tablets.

7. Warnings and Precautions

General

Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)

The concomitant administration of LIPIDIL EZ (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 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, severe myositis, 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.

Concomitant administration with ezetimibe: When LIPIDIL EZ (fenofibrate) is to be administered with ezetimibe, the ezetimibe Product Monograph should be consulted. 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 9.4 Drug-Drug Interactions, and Product Monograph for ezetimibe).

Carcinogenesis and Genotoxicity

In long-term animal toxicity and carcinogenicity studies, fenofibrate has been shown to be tumorigenic for the 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 liver in male rats at 12 times the human dose. At this dose level in male rats there was also an increase peroxisome proliferation has been observed following fenofibrate administration to

rats (see 16 Non-Clinical Toxicology, Carcinogenicity). Such changes have not been found in the human liver after up to 3.5 years of fenofibrate administration.

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

Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis.

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 8 Adverse Reactions).

Pancreatitis: In common with some other fibrates, pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct. In patients with severe hypertriglyceridemia, cases of acute pancreatitis have been reported.

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.

Monitoring and Laboratory Tests

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 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 8 Adverse Reactions).

Musculoskeletal

The use of fibrates alone, including LIPIDIL EZ, may occasionally be associated with myositis, myopathy

or rhabdomyolysis, usually in patients with impaired renal function and in cases of hypoalbuminemia. Patients receiving LIPIDIL EZ should be advised to promptly report diffuse myalgias/muscle pain, muscle cramps, tenderness, or weakness, particularly if accompanied by malaise or fever. They should have prompt medical evaluation for myopathy, including serum creatine phosphokinase level determination. If markedly elevated CK levels (5 times the upper limit of normal), myopathy and or myositis is suspected or diagnosed, LIPIDIL EZ therapy should be stopped.

Patients with pre-disposing factors for myopathy may be at an increased risk of developing rhabdomyolysis (see 7 General, Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)). For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease (see 7 General, Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)). Consequently, the co-administration of fenofibrate with a HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidemia and high cardiovascular risk without any history of muscular disease or other pre-disposing factors for myopathy (see 7 General, Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)) and with a close monitoring of potential muscle toxicity.

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.

Renal

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 7 Skeletal Muscle, 4 Dosage and Administration, and 10 Clinical Pharmacology).

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.

Reproductive Health

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 (see 16 Non-Clinical Toxicology).

7.1. Special Populations

7.1.1. 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^2 surface area). There are no adequate

and well-controlled studies in pregnant women. Fenofibrate should not be used during pregnancy (see 16 Non-Clinical Toxicology).

7.1.2. Breastfeeding

It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore LIPIDIL EZ should not be used during breast-feeding (see 16 Non-Clinical Toxicology).

7.1.3. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada to establish the safety and efficacy of fenofibrate in children and adolescents younger than 18 years. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (>65 years of age): 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 4 Dosage and Administration).

8. Adverse Reactions

8.1. Adverse Reaction Overview

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).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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.

Adverse events, regardless of their causality, reported in more than 1% of patients are shown in Table 2.

Table 2 – Number (%) of Patients Reporting Adverse Events

	Fenofibrate n = 477	Placebo n = 386
Body as a whole	68 (14.3%)	51 (13.2%)
Abdominal pain	12 (2.5%)	8 (2.1%)
Asthenia	14 (2.9%)	7 (1.8%)
Headache	15 (3.1%)	11 (2.8%)
Cardiovascular system	15 (3.1%)	13 (3.4%)
Digestive system	63 (13.2%)	47 (12.2%)
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%)
Endocrine system	1 (0.2%)	1 (0.3%)
Haemic & lymphatic system	3 (0.6%)	1 (0.3%)
Metabolic & nutritional disorders	18 (3.8%)	14 (3.6%)
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%)
Musculo-skeletal system	31 (6.5%)	21 (5.4%)
Arthralgia	11 (2.3%)	11 (2.8%)
Myalgia	3 (0.6%)	4 (1.0%)
Nervous system	31 (6.5%)	11 (2.8%)
Dizziness	5 (1.0%)	4 (1.0%)
Respiratory system	34 (7.1%)	25 (6.5%)
Rhinitis	10 (2.1%)	4 (1.0%)
Skin and appendages	24 (5.0%)	12 (3.1%)

	Fenofibrate n = 477	Placebo n = 386
Rash	11 (2.3%)	3 (0.8%)
Pruritus	10 (2.1%)	3 (0.8%)
Special senses	14 (2.9%)	10 (2.6%)
Urogenital system	14 (2.9%)	9 (2.3%)

Safety was monitored for 3 years during the placebo-controlled DAIS study (see 14 Clinical Trials) 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 3 below summarizes the incidence of adverse events, by body system, observed in both treatment groups.

Table 3 – DAIS study: Incidence of adverse events (AEs) by system, experienced by type 2 diabetic patients during treatment with fenofibrate or placebo (ITT population)

Body System	Fenofibrate n = 207		Placebo n = 211	
Total # pts. with at least 1 AE	AEs	Patients	Aes	Patients
	Total AEs: 1710	201 (97.1%)	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 4 are the adverse events possibly or probably related to fenofibrate, microcoated formulation and reported by more than 0.5% of the patients.

Table 4 – Number (%) of Patients Reporting Adverse Events Possibly or Probably Related to Fenofibrate

Canadian and German multicenter studies (12-week treatment)	
Adverse Events	**Microcoated Fenofibrate n = 375**
Digestive system	
Gastrointestinal disorder	4 (1.1%)
Nausea	3 (0.8%)
Flatulence	2 (0.5%)
Diarrhea	2 (0.5%)
Liver function tests abnormal	2 (0.5%)
Dyspepsia	2 (0.5%)
Gastritis	2 (0.5%)
Constipation	2 (0.5%)
Body as a whole	
Abdominal pain	4 (1.1%)
Headache	2 (0.5%)
Asthenia	2 (0.5%)
Lab test abnormal	2 (0.5%)
Metabolic and Nutritional Disorders	
ALT increased (> 3 x UNL)	3 (0.8%)
AST increased (> 3 x UNL)	4 (1.1%)
Creatine kinase increased (> 5 x UNL)	2 (0.5%)
Nervous system	
Dizziness	2 (0.5%)
Libido decreased	2 (0.5%)

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

Other adverse events include commonly reported cases of vomiting and increase in levels of blood homocysteine*. Uncommonly reported cases of pancreatitis and venous thromboembolism (pulmonary embolism and deep vein thrombosis). Rarely reported cases of alopecia, sexual asthenia, rhabdomyolysis, myositis and muscular cramps. Episodes of hepatitis have been reported. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued (see 7 Monitoring and Laboratory Tests).

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.

* The average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.

Combination with ezetimibe:

When LIPIDIL EZ (fenofibrate) 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 9.4 Drug-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.

8.3. Less Common Clinical Trial Adverse Reactions

See Table 4.

8.5. Post-Market Adverse Reactions

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

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease.

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

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

Nervous system disorders: Fatigue

9. Drug Interactions

9.2. Drug Interactions Overview

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.

9.3. Drug-Behaviour Interactions

The interaction of LIPIDIL EZ with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

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 7 General, Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)).

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 – Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Atorvastatin	CT	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 no change in the atorvastatin mean Cmax value (range: from a 60% decrease to a 136% increase). No significant pharmacokinetic interaction was observed in the mean fenofibric acid	Although atorvastatin co-administration had no effect on the pharmacokinetics of fenofibrate and fenofibrate co-administration had only little effect on the pharmacokinetics of atorvastatin, combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.

		AUC (2.3% decrease, range: from a 39% decrease to a 40 % increase) or in the mean Cmax (3.8% decrease, range: from a 29% decrease to a 42% increase) when fenofibrate was co-administered with multiple doses of atorvastatin.	
Bile Acid Sequestrants	CT, C	The absorption of fibrates is impaired by cholestyramine.	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.
Estrogens	P	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.
Ezetimibe	CT	In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. The safety and effectiveness of fenofibrate co-administered with ezetimibe have been evaluated in a clinical study (see 7 General, Fenofibrate and HMG-CoA Reductase Inhibitors (Statins), Hepatic/Biliary/Pancreatic, Monitoring and Laboratory Tests, and Musculoskeletal, 8 Adverse Reactions, and 14 Clinical Trials). Co-administration of ezetimibe with other fibrates has not	If ezetimibe and fenofibrate are co-administered, monitor patients for signs and symptoms of cholelithiasis, particularly during initiation of therapy and during upward dose titration. If cholelithiasis is suspected, initiate gallbladder studies and consider alternative lipid-lowering therapy.

		been studied (see ezetimibe Product Monograph).	
Oral Anticoagulants	C	Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding.	Caution should be exercised when oral anticoagulants are given in conjunction with LIPIDIL EZ. 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.
Pravastatin	CT	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 Cmax and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with pravastatin also increased the mean Cmax and AUC of the major metabolite, 3-alpha-hydroxy-iso-pravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24%	Fenofibrate co-administration had modest effect on the pharmacokinetics of pravastatin and combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.

		decrease to a 261% increase), respectively.	
Rosiglitazone	C	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.	It is recommended to monitor HDL-cholesterol if rosiglitazone is added to the other and stopping of either therapy if HDL-cholesterol is too low.
Rosuvastatin	CT	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.	Although co-administration of rosuvastatin and fenofibrate did not lead to a significant change in plasma concentrations of either drug, combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.
Simvastatin	CT	The mean AUC of simvastatin acid, decreased by 42% (range: from a 77% decrease to a 50% increase). No change in the mean simvastatin acid Cmax (range: from a 67% decrease to a 92% increase). The mean fenofibric acid Cmin plasma levels increased by 14% (range: from a 7% decrease to a 48% increase).	Although co-administration of fenofibrate and simvastatin had only little effect on the pharmacokinetics of either drug, combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.
Cyclosporine	C	Severe myositis and rhabdomyolysis have occurred when	Therefore, the benefits and risks of using fenofibrate concomitantly with these

		cyclosporine was administered in combination therapy with a fibrate. Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporine.	drugs should be carefully considered. 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.

Legend: C = Case Study; CT = Clinical Trial; P = Potential

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

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

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

10.2. Pharmacodynamics

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated by the activation of a specific nuclear receptor called peroxisome proliferator activated receptor alpha (PPARα), which produces:

- a reduction in apo C-III, and therefore a reduction in the level of dense atherogenic LDL particles;
- a stimulation of mitochondrial beta-oxidation, and therefore a reduction in triglyceride secretion;

- a rise in lipoprotein lipase production, and therefore an acceleration of triglyceride rich lipoprotein breakdown;
- a rise in apo A-I and apo A-II production.

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 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.

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.

10.3. Pharmacokinetics

Absorption

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.

Distribution

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

Metabolism

After oral administration, fenofibrate is rapidly hydrolysed to fenofibric acid, the active metabolite.

Elimination

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 to 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.

Special populations and conditions

- **Pediatrics:** Safety and effectiveness have not been established in pediatric patients.

- **Sex:** No gender-related differences in pharmacokinetics and metabolism have been observed.
- **Hepatic Insufficiency:** No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.
- **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 30 to 60 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 to 48 mg in patients who have moderate renal impairment.

  If no low dose is available, then fenofibrate is not recommended.

  In patients with severe renal impairment (creatinine clearance < 30ml/min), fenofibrate is contraindicated.

11. Storage, Stability, and Disposal

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

Part 2: Scientific Information

13. Pharmaceutical Information

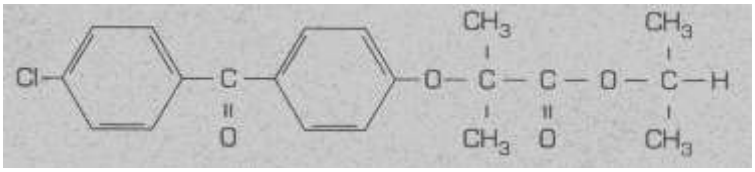
Drug Substance

Non-proprietary name of the drug substance(s): fenofibrate

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

Molecular formula and molecular mass: $C_{20}H_{21}O_4Cl$ 360.83

Structural formula:



Physicochemical properties: 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.

14. Clinical Trials

14.1. Clinical Trials by Indication

Study design and study population

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 ≥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.

Study results

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 6). The change in mean segment diameter was minimal in both groups over the treatment period, with no statistical difference between groups.

Table 6 – DAIS study: Mean coronary angiogram values (± S.D.) averaged per patient and per segment at baseline and at the end of study (ITT population)

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

	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 the following Table 7 for both the fenofibrate- and placebo-treated groups.

Table 7 – DAIS study: Mean major lipid values (±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
End of study	1.06 (0.26)	1.06 (0.24)	0.045
- **Calc. LDL-C (mmol/L)**			

Baseline	3.36 (0.71)	3.39 (0.72)	0.532
Final	3.12 (0.69)	3.38 (0.73)	0.042
TC / HDL-C			
Baseline	5.63 (1.08)	5.51 (1.10)	0.115
Final	4.87 (1.27)	5.35 (1.25)	< 0.001
Apo AI (g/L)			
Baseline	1.24 (0.18)	1.26 (0.277)	0.277
Final	1.33 (0.22)	1.29 (0.20)	0.02

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

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 ≥ 3.4mmol/L [130 mg/dL] and ≤ 5.7 mmol/L [220 mg/dL] (for non-diabetics) or ≥ 2.6 mmol/L [100 mg/dL] and ≤ 4.7 mmol/L [180 mg/dL] (for diabetics), and with TG ≥ 2.3 mmol/L [200 mg/dL] and≤ 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 8 below).

Table 8 – Response to ezetimibe and fenofibrate initiated concurrently in patients with mixed hyperlipidemia (Mean[a] % change from untreated baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
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

[a]For triglycerides, median % change from baseline
[b]Baseline- on no lipid-lowering drug

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

14.2. Comparative Bioavailability Studies

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 9 – 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_T (µg.h/mL)	148.47 153.5 (27%)	170.49 174.2 (25%)	87.1%	85.2-89.0%
AUC_I (µg.h/mL)	151.69 157.4 (28%)	176.03 180.4 (27%)	86.2%	84.3-88.1%
C_{MAX} (µg/mL)	8.646 8.80 (19%)	8.582 8.87 (26%)	100.8%	96.8-104.9%
T_{MAX}* (h)	3.5 (35%)	4.4 (38%)		
$T_{½}$* (h)	20.7 (24%)	22.0 (34%)		

* Expressed as the arithmetic mean (CV %) only.

Table 10 – 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_T	148.29	170.49	87.0%	85.1-88.9%

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**
(µg.h/mL)	153.3 (27%)	174.2 (25%)		
AUC_I (µg.h/mL)	151.34 157.0 (29%)	176.03 180.4 (27%)	86.0%	84.3-88.1%
C_{MAX} (µg/mL)	8.399 8.54 (19%)	8.582 8.87 (26%)	97.9%	94.0-101.9%
T_{MAX}* (h)	3.6 (35%)	4.4 (38%)		
$T_{½}$* (h)	20.1 (23%)	22.0 (34%)		

* Expressed as the 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 11 – Summary Table of the Comparative Bioavailability Data:

A Single Dose Study (LIPIDIL EZ 145 mg tablet vs. LIPIDIL Supra 160 mg tablet)

Analyte: Fenofibric Acid From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test: LIPIDIL EZ 145 mg tablet**	**Reference: LIPIDIL Supra 160 mg tablet**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (µg.h/mL)	103.52 107.99 (29%)	103.93 108.96 (29%)	99.6%	96.2-103.1%
AUC_I (µg.h/mL)	105.00 109.53 (29%)	105.80 110.86 (29%)	99.2%	96.0-102.6%
C_{MAX} (µg/mL)	8.02 8.14 (17%)	6.73 6.91 (23%)	119.2%	111.5-127.4%
T_{MAX}*	2.88 (42%)	3.72 (31%)		

Analyte: Fenofibric Acid From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test: LIPIDIL EZ 145 mg tablet**	**Reference: LIPIDIL Supra 160 mg tablet**	**% Ratio of geometric means**	**90% Confidence Interval**
(h)				
$T_{½}$* (h)	17.15 (20%)	18.74 (20%)		

* Expressed as the 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 12 – Summary Table of the Comparative Bioavailability Data:

A Single Dose Study (LIPIDIL EZ 145 mg tablets (High Fat Fed vs. Fasted Conditions)

Analyte: Fenofibric Acid From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test: 145 mg high fat fed**	**Reference: 145 mg fasted**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (µg.h/mL)	123.0 127.9 (27.7%)	116.5 121.6 (28.1%)	105.4%	102.0-109.0%
AUC_I (µg.h/mL)	124.8 129.9 (28.0%)	118.5 123.8 (28.8%)	105.2%	101.8-108.8%
C_{MAX} (µg/mL)	7.82 7.96 (18.5)	7.77 7.94 (20.1%)	100.7%	96.3-105.4%
T_{MAX}* (h)	4.27 (45.5%)	2.33 (31.4%)		
$T_{½}$* (h)	17.8 (23.3%)	18.9 (24.9%)		

* Expressed as the arithmetic mean (CV %) only.

Table 13 – Summary Table of the Comparative Bioavailability Data:

A Single Dose Study (LIPIDIL EZ 145 mg tablets (Low Fat Fed vs. Fasted Conditions)

Analyte: Fenofibric Acid From measured and log transformed data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test: 145 mg low fat fed**	**Reference: 145 mg fasted**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (µg.h/mL)	118.1 123.2 (28.4%)	116.5 121.6 (28.1%)	101.3%	98.1-104.7%
AUC_I (µg.h/mL)	119.8 125.1 (28.7%)	118.5 123.8 (28.8%)	101.2%	97.8-104.6%
C_{MAX} (µg/mL)	7.84 7.96 (17.9%)	7.77 7.94 (20.1%)	100.9%	96.4-105.5%
T_{MAX}* (h)	3.56 (33.1%)	2.33 (31.4%)		
$T_{½}$* (h)	18.7 (19.5%)	18.9 (24.9%)		

* Expressed as the 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.

16. Non-Clinical Toxicology

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

General toxicology

Acute toxicity

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

Chronic toxicity studies

Rats with normal or high cholesterol diet were treated for 7 days by gavage with fenofibrate at 0, 3, 10, 30, 100 and 300 mg/kg/day or clofibrate at 20, 60, 200 and 600 mg/kg/day. 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.

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I -slow oxidative- myofibres) and cardiac degeneration, anemia and decreased body weight were seen at exposure levels ≥50- fold the human exposure for the skeletal toxicity and >15 fold for the cardiomyotoxicity. Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated during 3 months at exposures approximately 7-fold the clinical AUC.

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.

Genotoxicity

Gene mutations: *In vitro* tests for mutagenicity with either fenofibrate or fenofibric acid in the presence or absence of activating rat or human microsomal enzyme preparations, have all given negative results. Thus, fenofibric acid was without effect on gene mutation frequency in bacteria (Ames), yeast and mouse lymphoma cells in culture.

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

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

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

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

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

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

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

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

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

In a rat primary hepatocyte unscheduled DNA synthesis (UDS) assay *in vitro*, gemfibrozil, clofibric acid and fenofibric acid showed a negative response. None caused nuclear 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.

Carcinogenicity

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.

Reproductive and developmental toxicology

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]LIPIDIL EZ®

fenofibrate film-coated tablets (NanoCrystal® formulation)

This Patient Medication Information is written for the person who will be taking **LIPIDIL EZ**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **LIPIDIL EZ**, talk to a healthcare professional.

What LIPIDIL EZ is used for:

LIPIDIL EZ is used in combination with lifestyle changes (low-fat diet, weight loss, and exercise) and other medications to lower the levels of cholesterol and triglycerides (types of fats) in the blood. It is used to treat high blood fat levels in adults:

- with uncontrolled type 2 diabetes.
- who are at high risk of developing other complications due to high fats in the blood.

LIPIDIL EZ can also be used in combination with ezetimibe to lower cholesterol levels in adults with high levels of cholesterol and other fats in the blood.

How LIPIDIL EZ works:

LIPIDIL EZ belongs to a class of medicines known as "lipid metabolism regulators". It works by speeding the natural processes that remove cholesterol and other fats from the body. Along with changes to your diet and exercise, LIPIDIL EZ can help your body:

- decrease LDL (bad) cholesterol and triglyceride levels.
- increase HDL (good) cholesterol levels.

The ingredients in LIPIDIL EZ are:

Medicinal ingredient: fenofibrate

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, docusate sodium, D&C Yellow #10 Aluminum Lake (48 mg tablet only), FD&C yellow #6/sunset yellow FCF Aluminum Lake (48 mg tablet only), FD&C Blue #2/Indigo carmine FCF Aluminum Lake (48 mg tablet only), hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium lauryl sulfate, soybean lecithin, sucrose, talc, titanium dioxide, and xanthan gum.

LIPIDIL EZ comes in the following dosage form:

Film-coated tablets: 48 mg and 145 mg of fenofibrate.

Do not use LIPIDIL EZ if:

- you are allergic to:
  - fenofibrate or to any other ingredients in LIPIDIL EZ.
  - peanuts, peanut oil, soya lecithin or related products.

- you have severe liver problems, including cirrhosis of the liver and persistent abnormal liver test results.
- you have gallbladder disease.
- you have severe kidney problems, including if you are undergoing dialysis.
- you have pancreatitis (inflammation of the pancreas).
- you are pregnant, think you might be pregnant or planning to get pregnant. Tell your healthcare professional **right away** if you discover that you are pregnant.
- you are breast-feeding or planning to breast-feed. It is not known if LIPIDIL EZ can pass into breast milk and harm a breast-fed baby.
- you ever had an allergic reaction to sunlight or UV light while taking fibrate medicines or ketoprofen (used to treat pain and inflammation).
- you are taking statins (another type of medicine used to lower cholesterol) and have muscle problems or are at risk of developing muscle problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIPIDIL EZ. Talk about any health conditions or problems you may have, including if you:

- are taking statins, used to treat high blood cholesterol (e.g., atorvastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, lovastatin).
- have type 2 diabetes that cannot be controlled by insulin or other medicines.
- have high blood pressure that cannot be controlled by medicine.
- have abnormal levels of proteins in your urine and/or blood. This can be caused by certain conditions (e.g., nephrotic syndrome, kidney failure).
- have gallstones.
- have obstructive liver disease (a condition where the flow of bile from the liver to the gallbladder and small intestine is blocked).
- are a smoker.
- are taking medicines containing estrogen (e.g., birth control pills or hormone replacement therapy).
- are intolerant to lactose or sucrose as LIPIDIL EZ contains both.
- have risk factors for muscle problems. This includes if you:
    - have, have had or have a family history of muscle disorders.
    - had any past problems with muscles (pain, tenderness) after using statins.
    - currently take other fibrates (such as gemfibrozil and bezafibrate), niacin (nicotinic acid) or ezetimibe.
    - have thyroid problems.
    - regularly drink **three or more** alcoholic drinks daily.
    - do excessive physical exercise.
    - are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
    - are over 70 years of age.
    - have liver or kidney problems.
    - have diabetes accompanied with excess fat build-up in your liver.
    - had surgery or other tissue injury.
    - have a condition that causes weakness or frailty.
    - have a serious infection.

- have any conditions or take any medicines that may increase the level of LIPIDIL EZ in the blood. Talk to your healthcare professional if you are unsure.

Other warnings you should know about:

Muscle disorders: LIPIDIL EZ may cause serious muscle disorders, especially when taken together with a statin (another medicine used to treat high blood cholesterol). These problems may be accompanied with kidney problems and can lead to death. Tell your healthcare professional **right away** if you have any severe muscle pain, tenderness, soreness or weakness while taking LIPIDIL EZ.

Gallbladder problems: LIPIDIL EZ may cause gallbladder problems such as gallstones. Tell your healthcare professional **right away** if you experience:

- sudden and rapid intense pain in the right upper side or center of your abdomen;
- back pain between your shoulder blades or in your right shoulder.

The pain may last a few minutes to several hours and may be accompanied by nausea or vomiting.

Check-ups and testing: Your healthcare professional may do blood tests before you start LIPIDIL EZ and regularly during your treatment. These tests will check:

- the amount of cholesterol and other fats in your blood.
- the health of your liver and kidneys.
- the amount of red blood cells, white blood cells and platelets in your blood.

Depending on your test results, your healthcare professional may adjust your dose, temporarily stop, or discontinue your treatment with LIPIDIL EZ.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LIPIDIL EZ:

- Medicines used to lower blood cholesterol levels. This includes other fibrates (e.g., gemfibrozil, bezafibrate), statins (e.g., atorvastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, lovastatin), bile acid sequestrants (e.g., cholestyramine, colestipol, colesevelam) and ezetimibe.
- Medicines containing estrogen (e.g., birth control pills or hormone replacement therapy).
- Medicines used to prevent blood clots (also known as “blood thinners”).
- Rosiglitazone, used to treat type 2 diabetes.
- Cyclosporine, used to suppress the immune system.

How to take LIPIDIL EZ:

- Take LIPIDIL EZ exactly as your healthcare professional has told you.
- LIPIDIL EZ is taken once a day at anytime, with or without food.
- Swallow the tablet whole with a glass of water.
- Do NOT crush or chew the tablet.
- Carefully follow any measures that your healthcare professional has recommended for diet, exercise or weight control.
- Your healthcare professional may also prescribe other medications to be taken in combination with LIPIDIL EZ. Take them exactly as directed by your healthcare professional.

Usual dose:

The usual adult dose is one 145 mg tablet daily. The maximum dose is 145 mg per day.

If you are elderly or have kidney problems the recommended starting dose is 48 mg per day.

Overdose:

If you think you, or a person you are caring for, have taken too much LIPIDIL EZ, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take a dose, skip the missed dose and take the next dose as scheduled. Do not take a double dose to make up for a missed dose.

Possible side effects from using LIPIDIL EZ:

These are not all the possible side effects you may have when taking LIPIDIL EZ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with LIPIDIL EZ may include:

- Abdominal pain, upset stomach, constipation, diarrhea, feeling gassy, nausea or vomiting
- Headache
- Dizziness
- Lack of energy
- Stuffy or runny nose
- Trouble sleeping
- Low sex drive
- Skin rashes, redness and itching of the skin, hives, sensitivity of the skin to sunlight or UV light
- Hair loss
- Weight loss
- Joint pain

LIPIDIL EZ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Allergic reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
throwing up, hives or rash, swelling of the face, lips, tongue or throat			
Pulmonary embolism (blood clot in the lung): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath			✓
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): swelling, pain, arm or leg may be warm to the touch and may appear red		✓	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen		✓	
Rare			
Muscle disorders such as: • **Myalgia / myopathy / myositis** (muscle pain or weakness): aching muscle, tenderness or weakness that you cannot explain • **Rhabdomyolysis** (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine		✓	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness, unexplained loss of appetite		✓	
Gallstones (hardened lumps of cholesterol blocking the bile duct): sudden and rapid intense pain in the upper abdomen, pain in right shoulder, results in nausea, and		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
vomiting, fever or chills, yellowing of the skin and eyes (jaundice)			
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough		✓	
Serious skin reactions: redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 15°C to 30°C. Protect from light and moisture.
- Keep out of reach and sight of children.

If you want more information about LIPIDIL EZ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.viatris.ca); or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC, Etobicoke, Ontario M8Z 2S6.

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