

## PRODUCT MONOGRAPH

### **Pr SANDOZ FENOFIBRATE E**

Fenofibrate tablets

48 mg and 145 mg

Manufacturer's standard

Lipid Metabolism Regulator

Sandoz Canada Inc.  
145 Jules-Léger  
Boucherville, QC, Canada  
J4B 7K8

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## PRODUCT MONOGRAPH

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## PART 1: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of administration | Dosage Form/Strength     | All Nonmedicinal Ingredients   |
|-------------------------|--------------------------|--|
| Oral                    | Tablets 48 mg and 145 mg | <p>croscarmellose sodium, hypromellose, lactose anhydrous, magnesium stearate, simethicone emulsion and sodium lauryl sulphate.</p> <p>Ingredients of the simethicone emulsion: benzoic acid, glycerides, methyl cellulose, polyethylene glycol sorbitan tristearate, polyethylene glycol stearate, simethicone, sorbic acid, sulfuric acid and xanthan gum.</p> |

### INDICATIONS AND CLINICAL USE

Sandoz Fenofibrate E (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:

1. Treatment of patients, including patients with type 2 diabetes (non-insulin dependent), with dyslipoproteinemia (hypercholesterolemia, Fredrickson classification Types IIa and IIb mixed hyperlipidemia), to regulate lipid levels by reducing serum triglycerides and LDL cholesterol levels and increasing HDL cholesterol.
2. Treatment of adult patients with very high serum triglyceride levels, Fredrickson classification Type IV and Type V hyperlipidemia, who are at a high risk of sequelae and complications (i.e., pancreatitis) from their hyperlipidemia.

Sandoz Fenofibrate E, 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.

Sandoz Fenofibrate E alone may not be adequate therapy in some patients with familial

combined hyperlipidemia with Type IIb and Type IV hyperlipoproteinemia.

Sandoz Fenofibrate E is not indicated for the treatment of Type I hyperlipoproteinemia.

**Pediatrics (<18 years of age):**

Sandoz Fenofibrate E is not recommended for pediatric subjects under 18 years. See WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics.

**CONTRAINDICATIONS**

- Patients who are hypersensitive to fenofibrate or to any ingredients in the formulation of components of the container. For complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Hepatic insufficiency (including primary biliary cirrhosis and unexplained persistent liver function abnormality).
- Pre-existing gallbladder disease (see WARNINGS AND PRECAUTIONS).
- Severe renal dysfunction (creatinine clearance < 30ml/min).
- Chronic or acute pancreatitis.
- Hypersensitivity to fenofibrate, any component of this medication or other drugs of the fibrate class.
- The drug should not be used during pregnancy and breast-feeding.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- When Sandoz Fenofibrate E is to be administered with ezetimibe, the contraindications to ezetimibe should be reviewed before starting concomitant therapy.
- Should not be co-administered with HMG-CoA reductase inhibitors (statins) in patients with pre-disposing factors for myopathy.
- Under 18 years of age.

**WARNINGS AND PRECAUTIONS**

**General**

When Sandoz Fenofibrate E is to be administered with ezetimibe, the ezetimibe Product Monograph should be consulted.

**Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)**

**The concomitant administration of fenofibrate and statins should be avoided unless the benefit for further alteration in lipid levels is likely to outweigh the increased risk of this combination.**

**The concomitant administration of fenofibrate (equivalent to 145 mg Fenofibrate Nano) with Pravastatin (40 mg) once daily for 10 days, in healthy adults, increased the mean C<sub>max</sub> and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase)**

and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with Pravastatin also increased the mean  $C_{max}$  and AUC of the major metabolites, 3-alpha-hydroxy-isopravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively.

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

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

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

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

### **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, fenofibrate should be discontinued.

## **Carcinogenesis and Mutagenesis**

### **Carcinogenicity**

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. Such changes have not been found in the human liver after up to 3.5 years of fenofibrate administration.

## **Hematologic**

### **Haematologic changes**

Mild hemoglobin, haematocrit and white blood cell decreases have been observed occasionally in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

## **Hepatic/Biliary/Pancreatic**

### **Hepatobiliary disease**

Fenofibrate is not recommended for use in patients with hepatic impairment due to the lack of data.

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

### **Concomitant administration with ezetimibe:**

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of ezetimibe and fibrates other than fenofibrate is not recommended (see WARNINGS AND PRECAUTIONS – Drug Interactions, and Product Monograph for ezetimibe).

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (See 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. Sandoz Fenofibrate E therapy should be discontinued if gallstones are found.

### **Liver Function**

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

### **Concomitant administration with ezetimibe:**

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

## **Renal**

### **Renal Function**

Fenofibrate should not be used in patients with severe renal dysfunction including patients on dialysis. In patients with hypoalbuminemia, e.g., nephrotic syndrome, and in patients with renal insufficiency, the dosage of fenofibrate must be reduced and renal function should be monitored regularly (see WARNINGS AND PRECAUTIONS, Skeletal muscle, DOSAGE AND ADMINISTRATION and ACTION AND 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.

## **Sexual Function/Reproduction**

### **Reproductive studies**

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

## **Special Populations**

### **Pregnant Women**

Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and in rabbits when given in doses 9 times the MRHD (on the basis of mg/m<sup>2</sup> surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should not be used during pregnancy.

### **Nursing Women**

It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore fenofibrate should not be used during breast-feeding.

### **Pediatrics (< 18 years of age)**

The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data are available. Therefore the use of fenofibrate is not recommended in pediatric subjects under 18 years.

### **Geriatrics**

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

## **Other**

### **Skeletal Muscle**

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

Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CK levels (5 times the upper limit of normal) occur or myopathy is diagnosed.

Patients with pre-disposing factors for myopathy may be at an increased risk of developing rhabdomyolysis (see WARNINGS AND PRECAUTIONS). 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



WARNINGS AND PRECAUTIONS). Consequently, the co-administration of fenofibrate with a HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease or other pre-disposing factors for myopathy (see WARNINGS AND PRECAUTIONS) and with a close monitoring of potential muscle toxicity.

Concomitant administration with ezetimibe:

Post marketing reports of adverse events have included rare cases of myopathy/rhabdomyolysis occurring in patients taking ezetimibe. Myopathy/ rhabdomyolysis should be considered in patients presenting with muscle pain during treatment with ezetimibe and fenofibrate, and consideration given to discontinuation of the drugs. Most cases of myopathy/rhabdomyolysis resolved when drugs were discontinued.

**ADVERSE REACTIONS**

**Adverse Drug 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).

**Clinical Trials Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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 1.

**TABLE 1: Number (%) of Patients Reporting Adverse Events**

|                        | <b>Fenofibrate<br/>N= 477</b> | <b>Placebo<br/>N= 386</b> |
|------------------------|-------------------------------|---------------------------|
| <b>Body as a whole</b> | 68 (14.3%)                    | 51 (13.2%)                |
| Abdominal pain         | 12 (2.5%)                     | 8 (2.1%)                  |

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

Safety was monitored for 3 years during the placebo-controlled DAIS study (see CLINICAL 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 2 below summarizes the incidence of adverse events, by body system, observed in both treatment groups.

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

| <b>Body System</b>              | <b>Fenofibrate<br/>(N=207)</b> |                 | <b>Placebo<br/>(N=211)</b> |                 |
|---------------------------------|--------------------------------|-----------------|----------------------------|-----------------|
|                                 | <b>AEs</b>                     | <b>Patients</b> | <b>AEs</b>                 | <b>Patients</b> |
| Total # pts. with at least 1 AE | Total AEs:<br>1710             | 201 (97.1%)     | Total AEs:<br>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/<br>nutritional       | 50 (2.9%)                      | 32 (15.5%)      | 70 (4.9%)                  | 41 (19.4%)      |

| Body System                     | Fenofibrate<br>(N=207) |             | Placebo<br>(N=211) |             |
|---------------------------------|------------------------|-------------|--------------------|-------------|
|                                 | AEs                    | Patients    | AEs                | Patients    |
| Total # pts. with at least 1 AE | Total AEs:<br>1710     | 201 (97.1%) | Total AEs:<br>1759 | 202 (95.7%) |
| 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 3 are the adverse events possibly or probably related to fenofibrate, microcoated formulation and reported by more than 0.5% of the patients.

**TABLE 3: Number (%) of Patients Reporting Adverse Events Possibly or Probably Related to Fenofibrate**

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

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

Other adverse events include commonly reported cases of vomiting 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 WARNINGS AND PRECAUTIONS).

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  $\mu\text{mol/L}$ , 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 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 WARNINGS AND PRECAUTIONS – Drug Interactions). There were no CPK elevations  $> 10X$  ULN in either treatment group in this study. No cases of myopathy, rhabdomyolysis, or pancreatitis were reported in this 12 weeks study.

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

See Table 3.

#### **Post-Market Adverse Drug Reaction:**

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

## **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.

## Drug-Drug Interactions

| <b>Table 4</b>   |            |   |   |
|--|------------|---|---|
| <b>Established or Potential Drug-Drug Interactions with Sandoz Fenofibrate E</b> |            |   |   |
| <b>Concomitant Medication</b>  | <b>Ref</b> | <b>Effect</b>   | <b>Clinical Comments</b>  |
| <u>Atorvastatin</u>  | CT         | Concomitant administration of fenofibrate (equivalent to 145 mg fenofibrate) with atorvastatin (20 mg) once daily for 10 days resulted in a 14% decrease in the mean atorvastatin AUC value (range: from a 67% decrease to a 44% increase) in 22 healthy males. There was a 0% change in the atorvastatin mean C <sub>max</sub> value (range: from a 60% decrease to a 136% increase). No significant pharmacokinetic interaction was observed in the mean fenofibric acid AUC (2.3% decrease, range: from a 39% decrease to a 40 % increase) or in the mean C <sub>max</sub> (3.8% decrease, range: from a 29% decrease to a 42% increase) when fenofibrate was co-administered with multiple doses of atorvastatin. |   |
| <u>Bile Acid Sequestrants</u>  | 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. |
| <u>Estrogens</u>   | 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.                                 |
| <u>Ezetimibe</u>   | CT         | In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.<br><br>The safety and effectiveness of fenofibrate co-administered with ezetimibe have been evaluated in a clinical study (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and CLINICAL TRIALS). Co-administration of ezetimibe with other fibrates has not been studied (see ezetimibe Product Monograph).  | Co-administration of ezetimibe with fibrates other than fenofibrate is not recommended until use in patients is studied.  |

**Table 4**  
**Established or Potential Drug-Drug Interactions with Sandoz Fenofibrate E**

| <b>Concomitant Medication</b> | <b>Ref</b> | <b>Effect</b>   | <b>Clinical Comments</b>  |
|-------------------------------|------------|---|---|
| <u>Oral Anticoagulants</u>    | C          |   | Caution should be exercised when oral anticoagulants are given in conjunction with fenofibrate. The dosage of oral anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Careful monitoring of prothrombin time is therefore recommended until it has been definitely determined that the prothrombin level has been stabilized. |
| <u>Pravastatin</u>            | CT         | Concomitant administration in 23 healthy adults of fenofibrate (equivalent to 145 mg fenofibrate) with pravastatin, 40 mg once daily for 10 days, has been shown to increase the mean C <sub>max</sub> and AUC values for pravastatin by 36% (range: from a 69% decrease to a 321% increase) and 28% (range: from a 54% decrease to a 128% increase), respectively. Co-administration of fenofibrate with pravastatin also increased the mean C <sub>max</sub> and AUC of the major metabolite, 3-alpha-hydroxy-iso-pravastatin by 55% (range: from a 32% decrease to a 314% increase) and 39% (range: from a 24% decrease to a 261% increase), respectively. |   |
| <u>Rosiglitazone</u>          | 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.   |   |
| <u>Rosuvastatin</u>           | 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.  |   |
| <u>Simvastatin</u>            | CT         | In a 10-day trial, fenofibrate (equivalent to 145 mg fenofibrate) was taken once daily. On day 10, simvastatin 40 mg was added to the fenofibrate regimen. The mean AUC of simvastatin acid, the main active metabolite, decreased by 42% (range: from a 77% decrease to a 50% increase) in the presence of   |   |

| <b>Table 4</b>   |            |  |   |
|--|------------|--|---|
| <b>Established or Potential Drug-Drug Interactions with Sandoz Fenofibrate E</b> |            |  |   |
| <b>Concomitant Medication</b>  | <b>Ref</b> | <b>Effect</b>  | <b>Clinical Comments</b>  |
|  |            | fenofibrate. Fenofibrate had no impact (0%) on the mean simvastatin acid C <sub>max</sub> (range: from a 67% decrease to a 92% increase). The mean fenofibric acid C <sub>min</sub> plasma levels increased by 14% (range: from a 7% decrease to a 48% increase) following the co-administration of simvastatin, indicating that fenofibric acid concentrations are not significantly affected by the addition of a 40 mg dose of simvastatin. |   |
| <u>Statin</u>  | P          | No drug-drug interaction studies with fenofibrate and statins have been conducted in patients.<br><br>Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying disease and use of concomitant medications (see WARNINGS AND PRECAUTIONS).   |   |
| <u>Statins and Cyclosporine</u>  | C          | Severe myositis and rhabdomyolysis have occurred when a statin or cyclosporine was administered in combination therapy with a fibrate.<br><br>Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporine. o change in didanosine pharmacokinetics in HIV-infected patients (n=12).   | Therefore, the benefits and risks of using fenofibrate concomitantly with these drugs should be carefully considered.<br><br>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                             |            |  |   |

### **Drug-Laboratory Interactions:**

In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of AST and ALT elevations was variable; in the clinical studies conducted in Canada and Germany elevations above three times the upper limit of normal were observed in 2.0% of the patients (7/375) treated with fenofibrate, microcoated formulation. In two dose-ranging studies, the incidence of increases in transaminases (>3 x ULN) due to fenofibrate therapy appears to be dose related; 0.6% (1/157) (80 mg tablet), 1.9% (3/158) (160 mg tablet) and 4.0% (6/149) (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 heptoglobin concentration has been observed in some patients with Type IV hyperlipidemia during long-term use of fenofibrate. However, this decrease in heptoglobin was not associated with any other sign of blood dyscrasia and/or haemolysis.

The mean plasma levels of urea and creatinine showed increases, particularly during long-term fenofibrate treatment, most of them remaining within the limits of normal values.

Fenofibrate also has the potential to provoke CK elevations and changes in haematologic parameters, which generally subside when the drug is discontinued (see WARNINGS AND PRECAUTIONS). In the clinical studies conducted in Canada and Germany, the reported frequency of CK elevations above five times the upper limit of normal was approximately 0.3% (2/375) of the patients treated with fenofibrate, microcoated formulation (Fenofibrate Supra).

## **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 Sandoz Fenofibrate E (fenofibrate), and should continue on this diet during treatment with Sandoz Fenofibrate E. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Sandoz Fenofibrate E, 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, Sandoz Fenofibrate E should be discontinued.

### **Recommended Dose and Dosage Adjustment**

The usual recommended dose for Sandoz Fenofibrate E 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 fenofibrate is 145 mg.

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

### Concomitant administration with ezetimibe:

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

**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.

**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.

**OVERDOSAGE**

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

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

**ACTION AND CLINICAL PHARMACOLOGY**

**Mechanism of Action**

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.

**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 (PPAR $\alpha$ ), which produces:

- a reduction in apo C-III, and therefore a reduction in the level of dense atherogenic LDL

- particles;
- a stimulation of mitochondrial beta-oxidation, and therefore a reduction in triglyceride secretion;
- a rise in lipoprotein lipase production, and therefore an acceleration of triglyceride rich lipoprotein breakdown;
- a rise in apo A-I and apo A-II production.

**Absorption:**

Absorption of a micronized fenofibrate formulation (Fenofibrate 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 (Fenofibrate 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 (Fenofibrate Nano 145 mg tablets), and 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.

**Excretion:**

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.

**Gender:**

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 fenofibrate 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 < 30 ml/min), fenofibrate is contraindicated.

#### **Other:**

##### 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.**

#### **STORAGE AND STABILITY**

Store between 15°C and 30°C.

#### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Sandoz Fenofibrate E 145 mg and 48 mg tablets contain, in addition to fenofibrate, the following nonmedicinal ingredients: croscarmellose sodium, hypromellose, lactose anhydrous, magnesium stearate, simethicone emulsion and sodium lauryl sulphate.

Ingredients of the simethicone emulsion: benzoic acid, glycerides, methyl cellulose, polyethylene glycol sorbitan tristearate, polyethylene glycol stearate, simethicone, sorbic acid, sulfuric acid and xanthan gum.

Sandoz Fenofibrate E 145 mg tablets: each white to off-white biconvex, oblong tablet contains 145 mg of fenofibrate and is embossed with the “F” on one side and “145” on the other. Available in blister packs of 30 tablets and bottles of 100 tablets.

Sandoz Fenofibrate E 48 mg tablets: each white to off-white biconvex, oblong tablet contains 48 mg of fenofibrate, and is embossed with “F” on one side and “48” on the other. Available in blister packs of 30 tablets and bottles of 30 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

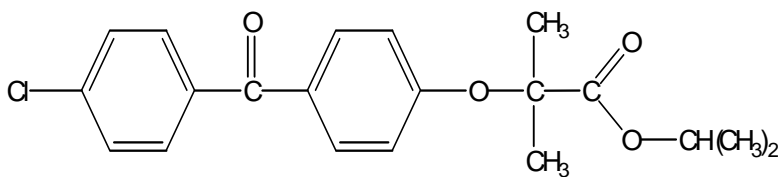
Proper name: fenofibrate

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

Molecular formula:  $C_{20}H_{21}ClO_4$

Molecular mass: 360.8 g/mol

Structural formula:



Physicochemical properties:

Description: Fenofibrate is a white or almost white crystalline powder.

Melting point: 79 to 82°C.

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

## CLINICAL TRIALS

### Comparative Bioavailability

A randomised, two-way crossover, single-dose comparative bioavailability study of Sandoz Fenofibrate E 145 mg tablets (fenofibrate) versus Lipidil EZ<sup>®</sup> 145 mg tablets (fenofibrate) of Fournier Canada, Inc. in 19 healthy, adult subjects (12 male and 7 female) under fasting conditions following administration of a 145 mg dose. Bioavailability data were measured and the results are summarized in the following table.

**Summary Table of the Comparative Bioavailability Data**

| Fenofibric Acid<br>(1 x 145 mg)<br>Geometric Mean<br>Arithmetic Mean (CV %) |                                |                                |                            |                         |
|---|--------------------------------|--------------------------------|----------------------------|-------------------------|
| Parameter   | Test*                          | Reference†                     | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>0-t</sub><br>(ng·h/mL)   | 168995.23<br>178122.83 (35.95) | 164578.30<br>173803.01 (37.34) | 102.68%                    | 97.18% to 108.50%       |
| AUC <sub>∞</sub><br>(ng·h/mL)   | 175955.72<br>186453.06 (37.16) | 169373.90<br>179553.14 (37.74) | 103.89%                    | 99.09 to 108.9%         |
| C <sub>max</sub><br>(ng/mL)   | 10292.22<br>10615.38 (26.15)   | 10706.28<br>10920.57 (21.27)   | 96.13%                     | 89.25% to 103.54%       |
| T <sub>max</sub> <sup>§</sup><br>(h)  | 2.16 (1.00 – 3.53)             | 2.26 (1.00 – 5.00)             |                            |                         |
| T <sub>½ el</sub> <sup>#</sup><br>(h)                                       | 19.09 (26.08)                  | 18.18 (23.64)                  |                            |                         |

\*Sandoz Fenofibrate E (fenofibrate) 145 mg tablet, (manufactured for Sandoz Canada Inc.)

†LIPIDIL EZ<sup>™</sup> (fenofibrate) 145 mg tablet, (manufactured by Fournier Canada, Inc. and purchased in Canada).

§ Expressed as the median (range) only

# Expressed as the arithmetic mean (CV%) only

A randomised, two-way crossover, single-dose comparative bioavailability study of Sandoz Fenofibrate E 145 mg tablets (fenofibrate) versus Lipidil EZ<sup>®</sup> 145 mg tablets (fenofibrate) of Fournier Canada, Inc. in 19 healthy, adult subjects (2 male and 17 female) under fed conditions following administration of a 145 mg dose. Bioavailability data were measured and the results are summarized in the following table.

**Summary Table of the Comparative Bioavailability Data**

| Fenofibric Acid<br>(1 x 145 mg)<br>Geometric Mean<br>Arithmetic Mean (CV %) |                                |                                |                            |                         |
|---|--------------------------------|--------------------------------|----------------------------|-------------------------|
| Parameter   | Test*                          | Reference†                     | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>0-t</sub><br>(ng·h/mL)   | 125241.23<br>129784.16 (27.73) | 125427.48<br>129601.23 (26.76) | 99.85%                     | 95.89% to 103.98%       |

| Fenofibric Acid<br>(1 x 145 mg)<br>Geometric Mean<br>Arithmetic Mean (CV %) |                                |                                |                            |                         |
|---|--------------------------------|--------------------------------|----------------------------|-------------------------|
| Parameter   | Test*                          | Reference†                     | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>∞</sub><br>(ng·h/mL)   | 127487.42<br>132014.14 (27.51) | 127577.33<br>131844.95 (26.92) | 99.93%                     | 96.04% to 103.97%       |
| C <sub>max</sub><br>(ng/mL)   | 10342.61<br>10445.81 (16.62)   | 10461.44<br>10614.26 (17.64)   | 98.86%                     | 94.72% to 103.19%       |
| T <sub>max</sub> <sup>#</sup><br>(h)  | 2.82 (47.80)                   | 2.84 (48.38)                   |                            |                         |
| T <sub>½ el</sub> <sup>#</sup><br>(h)                                       | 14.33 (24.13)                  | 14.16 (24.31)                  |                            |                         |

\*Sandoz Fenofibrate E (fenofibrate) 145 mg tablet, (manufactured for Sandoz Canada Inc.)

†LIPIDIL EZ™ (fenofibrate) 145 mg tablet, (manufactured by Fournier Canada, Inc. and purchased in Canada).

# Expressed as the arithmetic mean (CV%) only

## Study demographic and trial design

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

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

The first clinical trial followed a double-blind, parallel group versus placebo design. One hundred and eighty-nine patients (Type IIa; 120 and Type IIb; 69) were randomized in three groups: placebo, 200 mg micronized fenofibrate and 3 x 100 mg non-micronized fenofibrate. The ages of the patients ranged from 18 to 75 years. The intent-to-treat analysis indicated an efficacy level after 3 months (as assessed by the number of patients who experienced a cholesterol reduction > 15%) which was significantly greater in the micronized fenofibrate group (71.9%) than in the placebo group (14.8%). Micronized fenofibrate treatment was significantly more active than placebo in reducing total cholesterol (-18%), LDL-cholesterol (-22%), triglycerides (-19%) and apolipoprotein B (-24%).

The second clinical trial evaluated the effectiveness of micronized fenofibrate on lipid parameters. Of 131 eligible patients, 94 (31 Type IIa, 23 Type IIb and 40 Type IV) were evaluated for efficacy. Of those with Type IIa and Type IIb, 45.1% and 69.6%, respectively, were classified as good responders for total cholesterol. Of patients with Type IIb and IV, 71.4% and 77.7%, respectively, were considered good responders for triglycerides. After 3 months of treatment, the mean value of total cholesterol was lowered in patients with Type IIa from



311.4 mg/dl to 258.3 mg/dl with a mean decrease of 17 %. In patients with Type IIb, the mean value of total cholesterol was lowered from 328.0 mg/dl to 266.5 mg/dl, with a mean decrease of 18.6 %. The mean value of triglycerides was lowered in patients with Type IIb from 254.8 mg/dl to 165.7 mg/dl with a mean decrease of 34.4 %. In patients with Type IV, the mean value of triglycerides was lowered from 383.8 mg/dl to 231.1 mg/dl with a mean decrease of 37.9 %.

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

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

**TABLE 5: DAIS study: Mean coronary angiogram values ( $\pm$  S.D.) averaged per patient and per segment at baseline and at the end of study (ITT population)**

|  | <b>Fenofibrate</b> | <b>Placebo</b> | <b>p-value*</b> |
|--|--------------------|----------------|-----------------|
| <b>Per patient analysis</b>            | <b>N=207</b>       | <b>N=211</b>   |                 |
| <b>- Mean segment diameter (mm)</b>    |                    |                |                 |
| Baseline                               | 2.70 (0.45)        | 2.67 (0.45)    | 0.494           |
| Final                                  | 2.62 (0.49)        | 2.56 (0.50)    | 0.173           |
| <b>- Minimum segment diameter (mm)</b> |                    |                |                 |
| Baseline                               | 2.14 (0.44)        | 2.10 (0.44)    | 0.457           |
| Final                                  | 2.05 (0.46)        | 1.98 (0.48)    | 0.028           |
| <b>- Percent diameter stenosis (%)</b> |                    |                |                 |
| Baseline                               | 21.8 (7.8)         | 21.8 (7.4)     | 0.958           |
| Final                                  | 24.1 (9.8)         | 25.7 (10.8)    | 0.02            |
|  | <b>Fenofibrate</b> | <b>Placebo</b> | <b>p-value*</b> |
| <b>Per segment analysis</b>            | <b>N=1884</b>      | <b>N=1993</b>  |                 |
| <b>- Mean diameter (mm)</b>            |                    |                |                 |
| Baseline                               | 2.76 (0.84)        | 2.72 (0.83)    | 0.145           |
| Final                                  | 2.68 (0.87)        | 2.62 (0.87)    | 0.037           |

|                                | Fenofibrate | Placebo     | p-value* |
|--------------------------------|-------------|-------------|----------|
| <b>- Minimum diameter (mm)</b> |             |             |          |
| Baseline                       | 2.20 (0.82) | 2.16 (0.81) | 0.077    |
| Final                          | 2.11 (0.84) | 2.03 (0.83) | 0.541    |
| <b>- (%) stenosis</b>          |             |             |          |
| Baseline                       | 21.0 (13.1) | 21.4 (12.8) | 0.309    |
| Final                          | 23.0 (15.9) | 24.9 (17.2) | 0.059    |

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

The changes in lipid levels were also monitored in the type 2 diabetic patients included in the DAIS study. The major lipid values at baseline and at the end of the study are shown in the following Table 6 for both the fenofibrate- and placebo-treated groups.

**TABLE 6: DAIS study: Mean major lipid values (±S.D.) at baseline and at the end of the study (ITT population)**

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

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

#### Co-administration with ezetimibe:

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

54 years and 56% were male.

Ezetimibe co-administration with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate or ezetimibe administration alone. The percent decrease in TG and percent increase in HDL-C for ezetimibe co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 7 below).

**TABLE 7: Response to ezetimibe and fenofibrate initiated concurrently in patients with mixed hyperlipidemia (Mean<sup>a</sup> % change from untreated baseline<sup>b</sup> at 12 weeks)**

| Treatment (Daily Dose)         | N   | Total-C | LDL-C | Apo B | TG <sup>a</sup> | 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       |

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

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

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

### 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 Fenofibrate Nano or three 48 mg Fenofibrate Nano tablets were compared to one 200 mg micronized capsule (Fenofibrate 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 8: Summary Table of the Comparative Bioavailability Data: A Single Dose Study Fenofibrate Nano 145 mg tablet vs. Fenofibrate Micro 200 mg capsule)**

| Analyte: Fenofibric Acid   |                                      |  |                               |                               |
|--|--------------------------------------|--|-------------------------------|-------------------------------|
| From measured and log transformed data Geometric Mean Arithmetic Mean (CV %) |                                      |  |                               |                               |
| Parameter  | Test :<br>Fenofibrate Nano<br>145 mg | Reference :<br>Fenofibrate Micro<br>200 mg | % Ratio of<br>Geometric Means | 90%<br>Confidence<br>Interval |
| AUC <sub>T</sub><br>(mcg.h/mL)   | 148.47<br>153.5 (27%)                | 170.49<br>174.2 (25%)                      | 87.1%                         | 85.2-89.0%                    |
| AUC <sub>I</sub><br>(mcg.h/mL)   | 151.69<br>157.4 (28%)                | 176.03<br>180.4 (27%)                      | 86.2%                         | 84.3-88.1%                    |
| C <sub>MAX</sub><br>(mcg/mL)   | 8.646<br>8.80 (19%)                  | 8.582<br>8.87 (26%)                        | 100.8%                        | 96.8-104.9%                   |
| T <sub>MAX</sub> *<br>(h)  | 3.5 (35%)                            | 4.4 (38%)                                  |                               |                               |
| T <sub>1/2</sub> *<br>(h)  | 20.7 (24%)                           | 22.0 (34%)                                 |                               |                               |

\*expressed as arithmetic mean (CV%) only

**TABLE 9: Summary Table of the Comparative Bioavailability Data: A Single Dose Study (Fenofibrate Nano 3 x 48 mg tablet vs. Fenofibrate Micro 200 mg capsule)**

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

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

These data demonstrate that comparable bioavailability was achieved between Fenofibrate Nano, 145 mg or 3x48 mg tablets, and Fenofibrate 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 Fenofibrate Nano tablet was compared to one 160 mg Fenofibrate 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 10: Summary Table of the Comparative Bioavailability Data: A Single Dose Study (Fenofibrate Nano 145 mg tablet vs. Fenofibrate Supra 160 mg tablet)**

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

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

These data demonstrate that comparable bioavailability was achieved between, 145 mg Fenofibrate Nano tablets and Fenofibrate 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 Fenofibrate Nano 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 11: Summary Table of the Comparative Bioavailability Data:  
A Single Dose Study (Fenofibrate Nano 145 mg tablets (High Fat Fed vs. Fasted Conditions))**

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

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

**1.TABLE 12: Summary Table of the Comparative Bioavailability Data:  
A Single Dose Study (Fenofibrate Nano 145 mg tablets (Low Fat Fed vs. Fasted Conditions))**

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

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

These data demonstrate that Fenofibrate Nano 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.

## **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 healthy male volunteers, single doses of 300 mg of fenofibrate, non-micronized formulation, were compared to benzbromarone. A uricosuric action was observed with both drugs. During a 14-day study in hyperlipidemic patients, a 28 % decrease in plasma uric acid concentration was observed less than four days after the onset of treatment with 300 mg/day of fenofibrate, non-micronized formulation. This effect remained constant until the end of the study. An additional study conducted in healthy volunteers confirmed the rapid onset of the fenofibrate-induced hypouricemic effect and demonstrated the increased capability of the kidneys under these conditions to eliminate uric acid without damage to the proximal tubules.

#### **Effect on lithogenic index**

By virtue of structural similarity to other fibrates, fenofibrate might be suspected of increasing the risk of gallstones as a result of increased cholesterol excretion via the bile.

The biliary lithogenic index in fenofibrate-treated patients was evaluated. In most studies, the lithogenic index was shown to be increased but the effect of fenofibrate was not marked and the degree of significance varied from one study to another. The relative proportions of bile lipids were also affected by fenofibrate treatment.

It is not known how fenofibrate treatment modifies the lipid composition of the bile.

#### **Human liver biopsies**

Two specific studies have been conducted in hyperlipidemic patients to evaluate the potential hepatocellular toxicity of fenofibrate. Examination of biopsies from liver samples of 38 patients including 28 receiving fenofibrate, non-micronized formulation, over a mean period of

approximately 2 years did not show any difference between treated and untreated patients. Peroxisomes were relatively rare, and macroscopic light and electron-microscopic observations revealed no sign of treatment-associated cellular abnormality. A similar study, taking biopsies from 10 patients who had, on average, received fenofibrate, non-micronized formulation, for 9 months, and comparing these with tissue from 13 hyperlipidemic patients who had only received dietary treatment did not show any morphological difference between the two groups or any significant difference in the number or in the size of peroxisomes.

## **TOXICOLOGY**

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

### **Acute toxicity**

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

### **Chronic toxicity studies**

Rats with normal or high cholesterol diet were treated for 7 days by gavage with fenofibrate at 0, 3, 10, 30, 100 and 300 mg/kg/day or clofibrate at 20, 60, 200 and 600 mg/kg/day. AST levels were raised in treated rats but ALT levels remained within the normal range for rats on normal diet and were only slightly elevated in rats on the high cholesterol diet. Dose-related hepatomegaly and proliferation of peroxisomes occurred, at doses above 30 mg/kg/day. In a second but similar study of drug metabolising enzymes, rats were treated daily by gavage for 7 days with fenofibrate at 0 or 100 mg/kg or clofibrate 200 mg/kg. The absence of significant change in the parameters measured suggests that the mechanisms resulting in hepatomegaly caused by both fibrates had little effect on cell organelles involved in drug metabolism and protein synthesis. In a third study in rats, oral doses of fenofibrate (0 to 1000 mg/kg) were given for 3 months. Depression of blood lipids was seen at all dose levels. AST and ALT values were increased at 500 and 1000 mg/kg. Hepatomegaly was a consistent finding at all dose-levels reaching a maximum of 78 % increase in weight compared to controls but appeared to regress rapidly. There were no other significant findings in the histological examination.

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  $\geq 50$ -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.

### **Carcinogenicity studies**

Five rodent studies have shown that target organs for tumorigenic effects of fenofibrate are liver, pancreas and testes.

Mice showed increased liver weight with intrahepatic cholestasis and some degenerative changes but not liver tumors with 50 mg/kg/day for 22 months.

Dose-related increases in liver and kidney weight were seen in mice treated with 10 to 200 mg/kg/day of fenofibrate for 80 weeks.

When given at a dose of 200 mg/kg/day, both fenofibrate and clofibrate produced gross hepatomegaly associated with cholestasis and occasional cholangitis and periportal fibrosis. Neoplastic lesions were confined to the liver with significant increases in hepatocellular carcinoma at the high dose of fenofibrate in both sexes. Hepatocellular adenomas were also increased in males. In clofibrate-treated mice there was an excess of hepatic adenomas in females but not in males.

Both fenofibrate and clofibrate were found to be associated with an increased incidence of hepatocellular hypertrophy, lobular dysplasia and Kupffer cell pigmentation in another long-term toxicity study (93 weeks) on mice. In both sexes the incidence of total hepatic neoplasms and carcinomas was significantly increased by the high dose of fenofibrate (200 mg/kg). At the intermediate dose (60 mg/kg) the combined tumor incidence was almost significant in males but not in females, while incidence of carcinomas was not significantly increased in males and absent in females. Also, clofibrate (400 mg/kg) significantly increased the total tumor incidence but not carcinomas in males; females were unaffected.

Rats, which received fenofibrate (0, 10, 45 or 200 mg/kg/day) or clofibrate (200 mg/kg/day) mixed with their diet for a 2-year period showed no significant differences in mortality over the study period. Significant increases in incidences of hepatocellular carcinoma were found in the high dose fenofibrate group of animals of both sexes, in mid-dose fenofibrate males, and in clofibrate treated males. Mid-dose fenofibrate males and clofibrate-treated males and females also showed significantly increased incidence of hepatocellular adenomas. Well-differentiated pancreatic acinar cell carcinomas and adenomas were increased in a dose-related manner in the fenofibrate treated males, and higher incidences were also evident in the clofibrate males.

The chronic toxicity and carcinogenicity of fenofibrate was further studied in rats (0, 10 and 60 mg/kg/day) in order to compare treatment-related responses with those produced by clofibrate



(400 mg/kg/day) and gemfibrozil (250 mg/kg/day) during 117 weeks of treatments. The absolute and relative weights of the liver were increased in all treatment groups except with 10 mg/kg fenofibrate. Although comparatively low, an incidence of hepatocellular carcinoma was observed in gemfibrozil-treated rats, and neoplastic nodules were also found in the livers of 50 % of the males, which survived up to the termination of the study. Fewer neoplastic nodules were seen in the clofibrate-treated rats but these animals had a high incidence of hepatocellular carcinoma at termination. A significantly increased incidence of pancreatic acinar cell adenoma was seen in the 60 mg/kg fenofibrate males, while this increase in females was not significant. A significant increase in acinar adenoma and a slight increase in acinar carcinoma occurred with clofibrate (400 mg/kg) and some adenomas were seen in gemfibrozil-treated rats. There was some excess of benign interstitial cell tumors of the testes in all treatment groups except the group that received 10 mg/kg of fenofibrate.

### **Reproduction and teratology studies**

There was no evidence of any increase in malformation frequency in mice, rabbits and rats after administration of fenofibrate compared to that seen in controls. Examination of offspring from fenofibrate-treated dams and those having received clofibrate did not disclose any significant abnormalities when compared to offspring from the controls.

With the highest dose levels at which the mothers were adversely affected, there was evidence of embryotoxicity in rats and rabbits.

### **Genetic toxicity studies**

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

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

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

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

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

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

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

In a second *in vivo* test the effects of fenofibric acid were compared with those of clofibrac acid and gemfibrozil on DNA synthesis in mouse testicular tissue, as measured by the incorporation of 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, clofibrac acid and fenofibric acid showed a negative response. None caused nuclear labeling significantly different from the control and no dose-related trends were evident.

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

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## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PATIENT MEDICATION INFORMATION

#### Pr SANDOZ FENOFIBRATE E

##### Fenofibrate tablets

Read this carefully before you start taking Sandoz Fenofibrate E and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sandoz Fenofibrate E.

#### **What is Sandoz Fenofibrate E used for?**

Sandoz Fenofibrate E is used in adults, including adults with type 2 diabetes, to lower cholesterol and blood fat levels.

Sandoz Fenofibrate E is used together with ezetimibe to lower cholesterol in adults with a specific type of high cholesterol called “mixed hyperlipidemia”.

Sandoz Fenofibrate E is to be used together with dietary and lifestyle changes.

#### **How does Sandoz Fenofibrate E work?**

Sandoz Fenofibrate E lowers cholesterol by reducing the amount of bad cholesterol (LDL) and fatty substances in the blood (triglycerides). It also increases the amount of good cholesterol (HDL) in the blood.

#### **What are the ingredients in Sandoz Fenofibrate E?**

Medicinal ingredient: fenofibrate

Non-medicinal ingredients: croscarmellose sodium, hypromellose, lactose anhydrous, magnesium stearate, simethicone emulsion and sodium lauryl sulphate.

Ingredients of the simethicone emulsion: benzoic acid, glycerides, methyl cellulose, polyethylene glycol sorbitan tristearate, polyethylene glycol stearate, simethicone, sorbic acid, sulfuric acid and xanthan gum.

#### **Sandoz Fenofibrate E comes in the following dosage forms:**

Tablets: 48 mg and 145 mg.

#### **Do not use Sandoz Fenofibrate E if you:**

- have serious liver or kidney problems;
- have gallbladder problems;
- have pancreatitis (an inflamed pancreas which causes abdominal pain);
- are allergic (hypersensitive) to fenofibrate or similar drugs or if you are allergic to any of the ingredients in Sandoz Fenofibrate E tablets;

- are allergic (hypersensitive) to lactose or related products due to risk of allergic reaction;
- are pregnant, think you may be pregnant or are planning to get pregnant. If you get pregnant while taking Sandoz Fenofibrate E, contact your healthcare professional immediately;
- are breast-feeding or planning to breast-feed;
- have a photoallergy (skin sensitivity to sunlight or UV light) when taking a fibrate (a class of drugs used for lowering cholesterol, which includes Sandoz Fenofibrate E and gemfibrozil) or an anti-inflammatory drug called ketoprofen;
- are taking statins (another type of drug used to lower cholesterol) and have muscle problems or have potential risks of developing muscle problems;
- are under 18 years of age.

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

- have liver or kidney problems;
- have pancreas problems;
- have gallstones;
- have thyroid problems;
- Sandoz Fenofibrate E contains lactose. Talk to your healthcare professional before taking Sandoz Fenofibrate E if you have been told that you cannot tolerate or digest some sugars.

**Other warnings you should know about:**

You should have regular check-ups with your healthcare professional while taking Sandoz Fenofibrate E. Your healthcare professional will also do regular blood work to make sure you are responding well to Sandoz Fenofibrate E and that you are not experiencing side effects. These side effects can include serious muscle problems, which can cause kidney damage or even death. The risk of muscle problems is higher in some patients. Tell your healthcare professional if you:

- are over 70 years old;
- have kidney or liver problems;
- have thyroid problems;
- or a close family member has muscle problems which run in the family;
- drink large amounts of alcohol;
- have a serious infection or have recently had surgery or suffered a trauma;
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
- are taking drugs called statins to lower cholesterol such as simvastatin, atorvastatin, pravastatin, rosuvastatin or fluvastatin;
- have ever had muscle problems during treatment with fibrates such as fenofibrate, bezafibrate or gemfibrozil.

While taking Sandoz fenofibrate E if you experience muscle pain, tenderness or weakness, especially with a fever, contact your healthcare professional immediately.



**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 Sandoz Fenofibrate E:**

- Statins (other drugs used to lower cholesterol) such as atorvastatin, pravastatin, simvastatin, etc. Taking a statin at the same time as Sandoz Fenofibrate E may increase the risk of serious muscle problems.
- Blood thinners, such as warfarin;
- Cyclosporine (a drug which may be taken following an organ transplant);
- Cholestyramine or similar drugs (used to lower cholesterol);
- Estrogens (hormones which may be found in birth control pills or hormone replacement therapy);
- Some drugs used to treat diabetes, such as rosiglitazone or pioglitazone.

**How to take Sandoz Fenofibrate E:**

- Sandoz fenofibrate E can be taken with or without food.
- Swallow the tablet whole with a glass of water.
- Do not crush or chew the tablet.

**Usual adult dose:**

- The recommended dose of Sandoz Fenofibrate E is one 145 mg tablet daily.
- If you are elderly or have kidney problems the recommended dose is one 48 mg tablet daily.

**Overdose:**

If you think you have taken too much Sandoz Fenofibrate E, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed dose:**

If you forget a dose, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**What are possible side effects from using Sandoz Fenofibrate E?**

These are not all the possible side effects you may feel when taking Sandoz Fenofibrate E. If you experience any side effects not listed here contact your health care professional.

Side effects may include:

- Stomach pain, constipation, diarrhea, gas
- Nausea, vomiting
- Headache
- Dizziness
- Fatigue
- Trouble sleeping

- Low sex drive
- Skin rashes, redness and itching, sensitivity of the skin to light
- Hair loss
- Weight loss
- Joint pain

Sandoz Fenofibrate E 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   |                                      |              |   |
|--|--------------------------------------|--------------|---|
| Symptom / effect   | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|  | Only if severe                       | In all cases |   |
| <b>UNCOMMON</b>  |                                      |              |   |
| <b>Allergic reaction:</b> swelling of the face, lips, tongue or throat, which may cause difficulty in breathing                        |                                      |              | √   |
| <b>Blood clot in the lung:</b> sudden chest pain and trouble breathing   |                                      |              | √   |
| <b>Blood clot in the leg:</b> pain, redness or swelling in the legs  |                                      |              | √   |
| <b>Inflammation of the pancreas:</b> stomach pain that lasts and gets worse when you lie down, nausea, vomiting                        |                                      |              | √   |
| <b>RARE</b>  |                                      |              |   |
| <b>Serious muscle problems:</b> muscle pain or cramps, or muscle weakness, especially together with fever and generally feeling unwell |                                      |              | √   |
| <b>Liver problems:</b> yellowing of the skin and whites of the eyes, dark urine  |                                      |              | √   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

**Storage:**

Store between 15°C and 30°C.

Keep out of reach and sight of children.

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.

**If you want more information about Sandoz Fenofibrate E:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website [www.sandoz.ca](http://www.sandoz.ca) or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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