PRODUCT MONOGRAPH

[Pr] FENOFIBRATE-S

Fenofibrate
Micronized Formulation
Film-Coated Tablets

100mg and 160mg

Lipid Metabolism Regulator

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet / 100mg, 160mg	lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

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

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

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

FENOFIBRATE-S (fenofibrate, micronized formulation) is not indicated for the treatment of Type I hyperlipoproteinemia.

Geriatrics:
No data is available.

Pediatrics:
Limited experience is available in children and adolescents (See **WARNINGS AND PRECAUTIONS**)

CONTRAINDICATIONS

- Hepatic insufficiency (including primary biliary cirrhosis and unexplained persistent liver function abnormality).
- Pre-existing gallbladder disease (**see WARNINGS AND PRECAUTIONS**).
- Severe renal dysfunction.
- Chronic or acute pancreatitis.
- Hypersensitivity to fenofibrate, any component of this medication or other drugs of the fibrate class.
- Should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions.
- The drug should not be used during pregnancy and breast-feeding.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- 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
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 lipids values (e.g. total cholesterol, LDL-C, triglycerides). If a significant serum lipidil response is not obtained in 3 months, FENOFIBRATE-S should be discontinued.

Fenofibrate and HMG-CoA Reductase Inhibitors (Statins)

The concomitant administration of FENOFIBRATE-S (fenofibrate, microcoated formulation) 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, microcoated formulation with Pravastatin (40 mg) once daily for 10 days, in healthy adults, increased the mean C_{max} 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-alphahydroxy-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 FENOFIBRATE-S, may occasionally be associated with myositis, myopathy or rhabdomyolysis. Patients receiving FENOFIBRATE-S 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, FENOFIBRATE-S therapy should be stopped.

Carcinogenesis and Mutagenesis

In long-term animal toxicity and carcinogenicity studies fenofibrate has been shown to be tumorigenic for the liver in male rats at 12 times the human dose. At this dose level in male rats there was also an increase in benign Leydig cell tumors. Pancreatic acinar cell tumors were increased in male rats at 9 and 40 times the human dose. However, mice and female rats were unaffected at similar doses. Florid hepato-cellular peroxisome proliferation has been observed following fenofibrate administration to rats. Such changes have not been found in the human liver after up to 3.5 years of fenofibrate administration.

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

Hepatic/Biliary/Pancreatic

Hepatic Biliary Disease:

FENOFIBRATE-S 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.

Cholelithiasis:
Fenofibrate may increase cholesterol excretion into the bile, and may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. FENOFIBRATE-S (fenofibrate, micronized formulation) therapy should be discontinued if gallstones are found.

Hepatic:
Abnormal liver function tests have been observed occasionally 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-S (fenofibrate, micronized formulation) should be terminated if abnormalities persist and/ or AST and ALT levels increase to more than 3 times the upper limit of normal.**

Pancreatic:
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.

Renal
FENOFIBRATE-S 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 fibrates must be reduced and renal function should be monitored regularly (see **WARNINGS AND PRECAUTIONS, Skeletal Muscle and DOSAGE AND ADMINISTRATION**).

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

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 hypoalbuminaemia. 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.

Reproduction

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

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^2 surface

area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should not be used during pregnancy. (See **CONTRAINDICATIONS**).

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-S should not be used during breast-feeding.

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

The safety and efficacy of fenofibrate in children have not yet been established. Only limited paediatric data are available. Therefore the use of FENOFIBRATE-S is not recommended in paediatric subjects under 18 years.

Geriatric:

Fenofibrate is excreted by the kidney. Therefore, the risk of adverse reactions to FENOFIBRATE-S 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**).

Monitoring and Laboratory Tests
In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of AST and ALT elevations was variable; in the clinical studies conducted in Canada and Germany elevations above three times the upper limit of normal were observed in 2.0% of the patients (7/375) treated with fenofibrate, microcoated formulation. In two dose-ranging studies, the incidence of increases in transaminases (>3 x UNL) 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 WARNING AND PRECAUTIONS). Reductions in alkaline phosphatase levels have also been observed.

Mild decreases in hemoglobin, haematocrit, and white blood cell counts have been observed occasionally in patients following initiation of fenofibrate therapy but these observations were without clinical significance. However, these levels stabilize during long-term administration. In addition, a decrease in haptoglobin concentration has been observed in some patients with Type IV hyperlipidemia during long-term use of fenofibrate. However, this decrease in haptoglobin was not associated with any other sign of blood dyscrasia and/or haemolysis.

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

Fenofibrate also has the potential to provoke 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial 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.

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

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

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

Safety was monitored for 3 years during the placebo-controlled DAIS study (See **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)

Body System	**Fenofibrate (N=207)**		**Placebo (N=211)**	
Total # pts. with at least 1 AE	AEs	Patients	AEs	Patients
	Total AEs: 1710	201 (97.1%)	Total AEs: 1759	202 (95.7%)
Body as a whole	371 (21.7%)	136 (65.7%)	362 (20.6%)	146 (69.2%)
Cardiovascular	183 (10.7%)	84 (40.6%)	220 (12.5%)	96 (45.5%)
Digestive	196 (11.5%)	86 (41.6%)	194 (11.0%)	87 (41.2%)
Endocrine	11 (0.6%)	10 (4.8%)	19 (1.1%)	11 (5.2%)
Haemie/lymphatic	31(1.8%)	19 (9.2%)	23 (1.3%)	15 (7.1%)
Metabolic/ nutritional	50 (2.9%)	32 (15.5%)	70 (4.9%)	41 (19.4%)
Musculo-skeletal	155 (9.1%)	84 (40.6%)	180 (10.2%)	84 (39.8%)
CNS	103 (6.0%)	59 (28.5%)	98 (5.6%)	58 (27.5%)
Respiratory	301 (17.6%)	108 (52.2%)	279 (15.9%)	105 (49.8%)
Skin/appendage	107 (6.3%)	58 (28.0%)	107 (6.1%)	48 (22.8%)
Special senses	73 (4.3%)	44 (21.3%)	90 (5.1%)	50 (23.7%)
Urogenital	118 (6.9%)	55 (26.6%)	103 (5.9%)	46 (21.8%)
Other	11 (0.6%)	9 (4.4%)	14 (0.8%)	11 (5.2%)

In two open, non- controlled clinical studies conducted in Canada and Germany, a total of 375 patients on fenofibrate, microcoated formulation, were evaluated for adverse events. Listed in Table 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 (12-week treatment)	
Adverse Events	**microcoated fenofibrate (n = 375) (%)**
Digestive system	
Gastrointestinal disorder	4 (1.1%)
Nausea	3 (0.8%)
Flatulence	2 (0.5%)
Diarrhea	2 (0.5%)
Liver function tests abnormal	2 (0.5%)
Dyspepsia	2 (0.5%)
Gastritis	2 (0.5%)
Constipation	2 (0.5%)
Body as a whole	
Abdominal pain	4 (1.1%)
Headache	2 (0.5%)
Asthenia	2 (0.5%)
Lab test abnormal	2 (0.5%)
Metabolic and Nutritional Disorders	
ALT increased (> 3 x UNL)	3 (0.8%)
AST increased (>3 x UNL)	4 (1.1%)
Creatine kinase increased (>5 x UNL)	1 (0.3%)
Nervous System	
Dizziness	2 (0.5%)
Libido decreased	2 (0.5%)

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

Other adverse events include commonly reported cases of vomiting. Uncommonly reported cases of pancreatitis and venous thromboembolism (pulmonary embolism and deep vein thrombosis). Rarely reported cases of alopecia, sexual asthenia, myositis and muscular cramps. Very rarely reported cases of rhabdomyolysis and interstitial pneumopathies. Episodes of hepatitis have been reported. When symptoms 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.

Post-Market Adverse Drug Reactions

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

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)

Abnormal Hematologic and Clinical Chemistry Findings

In most trials, sporadic and transient increases in aminotransferase levels have been associated with the use of fenofibrate. The reported frequency of AST 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 UNL) 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 haptoglobin concentration has been observed in some patients with Type IV hyperlipidemia during long-term use of fenofibrate. However, this decrease in haptoglobin was not associated with any other sign of blood dyscrasia and/or haemolysis.

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

Fenofibrate also has the potential to provoke CK elevations and changes in haematologic parameters, which generally subside when the drug is discontinued (see **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.

DRUG INTERACTIONS

Drug-Drug Interactions

General

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

Statins

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

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

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

Atorvastatin
Concomitant administration of 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 Cmax 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 Cmax (3.8% decrease, range: from a 29% decrease to a 42% increase) when fenofibrate was co-administered with multiple doses of atorvastatin.

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

mg dose of simvastatin.

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

Ezetimibe
The safety and effectiveness of ezetimibe and fibrate combination therapy have not been established, therefore co-administration is not recommended until use in patients has been studied.

Oral anticoagulants

Caution should be exercised when oral anticoagulants are given in conjunction with FENOFIBRATE-S. The dosage of oral anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Careful monitoring of prothrombin time is therefore recommended until it has been definitely determined that the prothrombin level has been stabilized.

Statins and cyclosporine:

Severe myositis and rhabdomyolysis have occurred when a statin or cyclosporine was administered in combination therapy with a fibrate. Therefore, the benefits and risks of using fenofibrate, micronized formulation, concomitantly with these drugs should be carefully considered.

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

Bile Acid Sequestrants

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

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

Rosiglitazone

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

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

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

Prior to initiating therapy with Fenofibrate-S (fenofibrate, micronized formulation), 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, FENOFIBRATE-S (fenofibrate, micronized formulation) should be discontinued.

Recommended Dose and Dosage Adjustment
The usual recommended dose for FENOFIBRATE-S (fenofibrate, micronized formulation) in adults is one 160 mg tablet daily taken with the main meal. Tablets should be swallowed whole with a glass of water.

The maximum recommended total daily dose of FENOFIBRATE-S (fenofibrate, micronized formulation) is 200 mg (2 tablets of 100 mg)..

In patients with renal insufficiency (creatinine clearance between 20 and 100 ml/min), FENOFIBRATE-S (fenofibrate, micronized formulation) treatment should be initiated at the dose of 100 mg/day and increased only after evaluation of the tolerance and effects on the lipid

parameters. FENOFIBRATE-S (fenofibrate, micronized formulation) should not be used when the creatinine clearance is lower than 20 ml/min.

Missed Dose
If a dose of FENOFIBRATE-S (fenofibrate, micronized formulation) is missed, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
FENOFIBRATE-S (fenofibrate, micronized formulation) 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.

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

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

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

Pharmacokinetics

Absorption

Fenofibrate's absorption is low and variable when the product is administered under fasting conditions. Fenofibrate's absorption is increased when the compound is given with food.

Metabolism and Excretion

After oral administration, fenofibrate is rapidly hydrolysed to fenofibric acid, the active metabolite. In man it is mainly excreted through the kidney. Half-life is about 20 hours.

Distribution

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

Renal Insufficiency

In patients with severe renal failure, significant accumulation was observed with a large increase in half-life. Therefore, the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance.

Special Populations and Conditions

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

The safety and efficacy of fenofibrate in children have not yet been established. Only limited paediatric data are available. Therefore the use of FENOFIBRATE-S is not recommended in paediatric subjects under 18 years.

Geriatric:

Fenofibrate is excreted by the kidney. Therefore, the risk of adverse reactions to FENOFIBRATE-S 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).**

Very minor changes of pharmacokinetic of fenofibric acid parameters were observed in elderly subjects.

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

Race: Pharmacokinetics of fenofibrate based on race has not been studied.

Hepatic Insufficiency: Pharmacokinetics of fenofibrate in individuals with hepatic insufficiency has not been studied.

Renal Insufficiency: in patients with severe renal failure, significant accumulation was observed with a large increase of the half-life. Therefore, the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance.

Genetic Polymorphism: Pharmacokinetics of fenofibrate based on genetic polymorphism has not been studied.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

FENOFIBRATE-S 100mg: White to off white, oval shaped film coated tablet, debossed with "FM" on one side and "100" on the other. FENOFIBRATE-S 100mg is available in blister packs of 30 tablets and bottles of 100 and 500.

FENOFIBRATE-S 160mg: White to off white, oval shaped film coated tablet, debossed with "93" on one side and "7331" on the other. FENOFIBRATE-S 160mg is available in blister packs of 30 tablets and bottles of 100 and 500.

FENOFIBRATE contains, in addition to fenofibrate, the following excipients: colloidal anhydrous silica, croscarmellose sodium, crospovidone, lactose monohydrate, lecithin (soya), microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulphate, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide and xanthum gum.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Fenofibrate

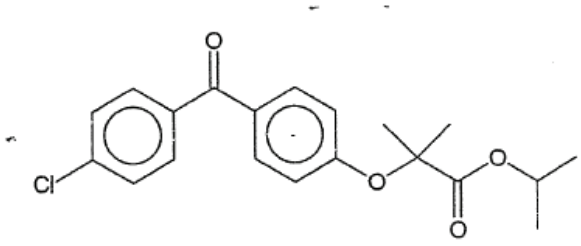
Chemical name: 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate

Or

Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

Molecular formula and molecular mass: $C_{20}H_{21}ClO_4$ 360.8

Structural formula:



Physicochemical properties:
Description: Fenofibrate is a white to off-white crystalline powder.
Solubilities: Fenofibrate is practically insoluble in water; very soluble in dichloromethane, and chloroform; freely soluble in acetone and ether; soluble in alcohol and sparingly soluble in methanol
pH: Fenofibrate is insoluble in water, therefore pH cannot be measured.
Melting Point: 79-82°C

CLINICAL TRIALS

Comparative Bioavailability Study

The comparative bioavailability study consisted of a 2-way, blinded, single-dose, randomized, crossover, bioequivalence design with a 14 day washout period. Twenty one healthy, non-smoking, male subjects, 18 to 55 years of age (inclusive), under **fed** condition completed both arms of the study. The 2-way study involved FENOFIBRATE TABLETS 160 mg (Sanis Health Inc., Canada) and LIPIDIL® SUPRA Tablets 160 mg (Laboratories Fournier S.A., Canada).

Fenofibric Acid (1 x 160 mg) From measured data **Least-Square Mean** **Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Least-Square Means**	**90% Confidence Interval**
AUC_{0-T} (ng.h/mL)	135715 140625 (27%)	139861 145394 (28%)	97%	94% to 100%
AUC_{0-inf} (ng.h/mL)	142158 148450 (30%)	146926 54402 (33%)	97%	94% to 100%
C_{MAX} (ng/mL)	9135 9311 (19%)	9489 9714 (22%)	96%	89% to 104%
T_{MAX}§ (h)	4 (55%)	4 (41%)		
$T_{1/2\ el}$§ (h)	16 (24%)	16 (34%)		

* Fenofibrate Tablets, (Sanis Health Inc., Canada)

† Lipidil® Supra Tablets (manufactured by Laboratories Fournier SA. France, distributed by Fournier Pharma Inc., Canada) were purchased in Canada.

§ Expressed as the arithmetic mean (CV%).

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.

Pharmacokinetics

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

In man, the elimination half-life of fenofibric acid is about 20-24 hours. This value is not modified after multiple dosing. Very minor changes of pharmacokinetic parameters were observed in elderly subjects, but in patients with severe renal failure, significant accumulation was observed with a large increase of the half-life.

No sex related differences in pharmacokinetics and metabolism were observed.

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

Clinical Studies

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

The activity of fenofibrate has been evaluated in more than 150 clinical trials performed in the U.S., Canada and Europe. The majority of these were conducted with fenofibrate, micronized formulation, at a daily dose of 200 mg.

Specific clinical studies were performed with fenofibrate, micronized formulation

The first clinical trial followed a double-blind, parallel group versus placebo design. One hundred and eighty-nine patients (Type IIa; 120 and Type IIb; 69) were randomized in three

groups: placebo, 200 mg micronized fenofibrate and 3 x 100 mg non micronized fenofibrate. The ages of the patients ranged from 18 to 75 years. The intent-to-treat analysis indicated an efficacy level after 3 months (as assessed by the number of patients who experienced a cholesterol reduction >15%) which was significantly greater in the micronized fenofibrate group (71.9%) than in the placebo group (14.8%). Micronized fenofibrate treatment was significantly more active than placebo in reducing total cholesterol (-18%), LDL-cholesterol (-22%), triglycerides (-1 9%) and apolipoprotein B (-24%).

The second clinical trial evaluated the effectiveness of micronized fenofibrate on lipid parameters. Of 131 eligible patients, 94 (31 Type IIa, 23 Type IIb and 40 Type IV) were evaluated for efficacy. Of those with Type IIa and Type IIb, 45.1% and 69.6%, respectively, were classified as good responders for total cholesterol. Of patients with Type IIb and IV, 71.4% and 77.7%, respectively, were considered good responders for triglycerides After 3 months of treatment, the mean value of total cholesterol was lowered in patients with Type IIa from 311.4 mg/dl to 258.3 mg/dl with a mean decrease of 17 % In patients with Type IIb, the mean value of total cholesterol was lowered from 328.0 mg/dl to 266.5 mg/dl, with a mean decrease of 18.6 %. The mean value of triglycerides was lowered in patients with Type IIb from 254.8 mg/dl to 165 7 mg/dl with a mean decrease of 34.4 %. In patients with Type IV, the mean value of triglycerides was lowered from 383.8 mg/dl to 231.1 mg/dl with a mean decrease of 37.9%.

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

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

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

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

	Fenofibrate	Placebo	p-value*
Per patient analysis	**N = 207**	**N = 211**	
-Mean segment diameter (mm)	2.70(0.45)		
Baseline		2.67 (0.45)	0.494
Final	2.62 (0.49)	2.56 (0.50)	0.173
-Minimum diameter (mm)			
Baseline	2.14 (0.44)	2.10 (0.44)	0.457
Final	2.05 (0.46)	1.98 (0.48)	0.028
- Percent diameter stenosis (%)			
Baseline	21.8 (7.8)	21.8 (7.4)	0.958
Final	24.1 (9.8)	25.7 (10.8)	0.02
Per segment analysis	N = 1884	N = 1993	
- Mean diameter (mm)			
Baseline	2.76 (0.84)	2.72 (0.83)	0.145
Final	2.68 (0.87)	2.62 (0.87)	0.037
- Minimum diameter (mm)			
Baseline	2.20 (0.82)	2.16 (0.81)	0.077
Final	2.11 (0.84)	2.03 (0.83)	0.541
% stenosis			
Baseline	21.0 (13.1)	21.4 (12.8)	0.309
Final	23.0 (15.9)	24.9 (17.2)	0.059
*p-values for Student's t test and for covariance analysis to compare treatment groups, respectively, at baseline and at the end of the study (last available value on treatment). Statistical significance was established at 0.025			

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

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

	Fenofibrate	Placebo	p-values*
-Total cholesterol (mmol/L)			
Baseline	5.56 (0.80)	5.58 (0.720)	0.751
Final	4.93 (0.83)	5.42 (0.79)	<0.001
- Total triglycerides (mmol/L)			
Baseline	2.56 (1.23)	2.52 (1.22)	0.706
Final	1.65 (0.90)	2.16 (1.20)	<0.001
- HDL-C (mmol/L)			
Baseline	1.00 (0.19)	1.04 (0.21)	0.045
End of study	1.06 (0.26)	1.06 (0.24)	0.045
-Calc. LDL-C (mmol/L)			
Baseline	3.36 (0.71)	3.39 (0.72)	0.532
Final	3.12 (0.69)	3.38 (0.73)	0.042
TC / HDL-C			
Baseline	5.63 (1.08)	5.51 (1.10)	0.115
Final	4.87 (1.27)	5.35 (1.25)	<0.001
Apo AI (g/L)			
Baseline	1.24 (0.18)	1.26 (0.277)	0.277
Final	1.33 (0.22)	1.29 (0.20)	0.02
*p-values for Student's t test and for covariance analysis to compare treatment groups at baseline and at the end of the study (last available value on treatment)			

Safety was closely monitored in the DAIS study for both adverse events and laboratory anomalies. Fenofibrate was used safely in type 2 diabetic patients, as the overall incidence and severity of adverse events were comparable for the two treatment groups. The table below summarizes the incidence of adverse events, by body system, observed in the fenofibrate and placebo treatment groups.

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

Body System	**Fenobibrate (N = 207)**		**Placebo (N = 211)**	
	AEs	**Patients**	**AEs**	**Patients**
Total # pts. with at least 1 AE	**Total AEs: 1710**	**201 (97.1%)**	**Total AEs: 1759**	**202 (95.7%)**
Body as a whole	371 (21.7%)	136 (65.7%)	362 (20.6%)	146 (69.2%)
Cardiovascular	183 (10.7%)	84 (40.6%)	220 (12.5%)	96 (45.5%)
Digestive	196 (11.5%)	86 (41.6%)	194 (11.0%)	87 (41.2%)
Endocrine	11 (0.6%)	10 (4.8%)	19 (1.1%)	11 (5.2%)
Hemic/lymphatic	31 (1.8%)	19 (9.2%)	23 (1.3%)	15 (7.1%)
Metabolic/nutritional	50 (2.9%)	32 (15.5%)	70 (4.9%)	41 (19.4%)
Musculo-skeletal	155 (9.1%)	84 (40.6%)	180 (10.2%)	84 (39.8%)
CNS	103 (6.0%)	59 (28.5%)	98 (5.6%)	58 (27.5%)
Respiratory	301 (17.6%)	108 (52.2%)	279 (15.9%)	105 (49.8%)
Skin/appendage	107 (6.3%)	58 (28.0%)	107 (6.1%)	48 (22.8%)

Body System	Fenobibrate (N = 207)		Placebo (N = 211)	
	AEs	Patients	AEs	Patients
Total # pts. with at least 1 AE	**Total AEs: 1710**	**201 (97.1%)**	**Total AEs: 1759**	**202 (95.7%)**
Special senses	73 (4.3%)	44 (21.3%)	90 (5.1%)	50 (23.7%)
Urogenital	118 (6.9%)	55 (26.6%)	103 (5.9%)	46 (21.8%)
Other	11 (0.6%)	9 (4.4%)	14 (0.8%)	11 (5.2%)

Clinical Pharmacology

Uricosuric action
Fenofibrate decreased the plasma uric acid levels in normal as well as hyperuricemic subjects. In a study involving 10 normal male volunteers, single doses of 300 mg of fenofibrate, non-micronized formulation, were compared to benzbromarone. A uricosuric action was observed with both drugs. During a 14 day study in hyperlipidemic patients, a 28% decrease in plasma uric acid concentration was observed less than four days after the onset of treatment with 300 mg/day of fenofibrate, non-micronized formulation. This effect remained constant until the end of the study. An additional study conducted in healthy volunteers confirmed the rapid onset of the fenofibrate-induced hypouricemic effect and demonstrated the increased capability of the kidneys under these conditions to eliminate uric acid without damage to the proximal tubules.

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

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

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

Human liver biopsies
Two specific studies have been conducted in hyperlipidemic patients to evaluate the potential hepatocellular toxicity of fenofibrate. Examination of biopsies from liver samples of 38 patients including 28 receiving fenofibrate, non-micronized formulation, over a mean period of approximately 2 years did not show any difference between treated and untreated patients. Peroxisomes were relatively rare, and macroscopic light and electron-microscopic observations revealed no sign of treatment-associated cellular abnormality. A similar study, taking biopsies from 10 patients who had, on average, received fenofibrate, non-micronized formulation, for 9 months, and comparing these with tissue from 13 hyperlipidemic patients who had only received dietary treatment did not show any morphological difference between the two groups or any significant difference in the number or in the size of peroxisomes.

TOXICOLOGY

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

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

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

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

Fenofibrate (0, 12, 50 or 500 mg/kg/day) or clofibrate (200 mg/kg/day) was administered in the food of Rhesus monkeys for 12 months. No fenofibrate-related effect with regard to toxicity was noted in any of the test groups during the study. No evidence of compound-related histomorphologic alterations was present in the animals sacrificed. The Rhesus monkey resembles man where biopsy studies show no signs of peroxisome proliferation during up to 2 years of fenofibrate treatment.

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

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

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

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

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

Rats, which received fenofibrate (0, 10, 45 or 200 mg/kg/day) or clofibrate (200 mg/kg/day) mixed with their diet for a 2-year period showed no significant differences in mortality over the study period. Significant increases in incidences of hepatocellular carcinoma were found in the high dose fenafibrate 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 gemfibrazil (250 mg/kg/day) during 117 weeks of treatments The absolute and relative weights of the liver were increased in all treatment groups except with 10 mg/kg fenofibrate. Although comparatively low, an incidence of hepatocellular carcinoma was observed in gemfibrozil-treated rats, and neoplastic nodules were also found in the livers of 50% of the males, which survived up to the termination of the study. Fewer neoplastic nodules were seen in the clofibrate-treated rats but these animals had a high incidence of hepatocellular carcinoma at termination. A significantly increased incidence of pancreatic acinar cell adenoma was seen in the 60 mg/kg fenofibrate males, while this increase in females was not significant. A significant increase in acinar adenoma and a slight increase in acinar carcinoma occurred with clofibrate (400 mg/kg) and some adenomas were seen in gemfibrozil-treated rats. There was some excess of benign interstitial cell tumors of the testis in all treatment groups except the group that received 10 mg/kg of fenofibrate.

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

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

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

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

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

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

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

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

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

In a second in vivo test the effects of fenofibric acid were compared with those of clofibric acid and gemfibrozil on DNA synthesis in mouse testicular tissue, as measured by the incorporation

of ^{3}H-thymidine. Any response is representative of changes in DNA synthesis in any testicular cells such as germ, Sertoli, Leydig or interstitial cells undergoing scheduled or unscheduled synthesis.

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

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

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

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

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PART III: CONSUMER INFORMATION

FENOFIBRATE-S

(fenofibrate, micronized, film-coated tablets)

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

ABOUT THIS MEDICATION

What the medication is used for:
FENOFIBRATE-S is used for the treatment of dyslipoproteinemia (abnormal lipoproteins in the blood) in adult patients, including patients with type 2 diabetes.

This medicine should only be used to supplement an appropriate diet recommended and followed up by your doctor for the long-term treatment of raised lipid levels; prescription of this medicine in no way replaces dietary treatment. In addition, depending on the situation, your doctor may recommend further physical exercise, weight loss or other measures. Take exactly as instructed by your doctor. Do not change the dose without your doctor's advice. Consult your doctor before stopping treatment since to do so may result in an increase in your blood lipid levels.

What it does:
FENOFIBRATE-S reduces blood cholesterol, in particular cholesterol associated with low and very low density lipoproteins (bad cholesterol). FENOFIBRATE-S reduces high triglyceride levels associated with hypercholesterolemia (excess of cholesterol in the blood) and increases the high density lipoprotein (HDL) cholesterol fraction (good cholesterol).
Blood uric acid levels are also reduced by FENOFIBRATE-S treatment.

When it should not be used:

- If you have liver or kidney problems;
- If you have a gallbladder problems;
- If you have pancreatitis (an inflamed pancreas which causes abdominal pain);
- If you are allergic to fenofibrate or similar drug or if you are allergic to any of the ingredients in FENOFIBRATE-S tablets (**see** What the non medicinal ingredient are).
- If you are allergic (hypersensitive) to peanuts or arachis oil or soya lecithin or related products due to risk of allergic reaction;
- If you are pregnant, think you may be pregnant or are planning to have a baby; in the event of pregnancy during treatment, your doctor should be informed and FENOFIBRATE-S should be discontinued;
- If you are breast-feeding or planning to breast-feed your baby.
  If you have a photoallergy (skin sensitivity to sunlight or UV light) when taking a fibrate (a class of drugs used for lowering cholesterol, which includes FENOFIBRATE-S and gemfibrozol) or an anti-inflammatory drug called ketoprofen.
- If you are taking statins and have muscle problems or have potential risks of developing muscle problems.
- If you are under 18 years of age.

What the medicinal ingredient is:
Fenofibrate, micronized.

What the nonmedicinal ingredients are:
colloidal anhydrous silica, croscarmellose sodium, crospovidone, lactose monohydrate, lecithin (soya), microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulphate, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide and xanthum gum.

What dosage forms it comes in:
Film coated tablets, 100 mg and 160 mg

WARNINGS AND PRECAUTIONS

BEFORE you use FENOFIBRATE-S talk to your doctor or pharmacist if:

- You have had an allergic reaction to (or poorly tolerated) FENOFIBRATE-S **any of its ingredients** (**see** What the non medicinal ingredient are) or any other lipid treatment
- You suffer from liver or kidney problems;
- You have an inflamed liver (hepatitis) - signs include yellowing of the skin and the whitesof the eyes (jaundice) and an increase in liver enzymes (shown in blood tests);

- You have pancreas problems;
- You have a gall bladder or gallstone problem;
- You have an under-active thyroid gland (hypo-thyroidism);
- You are pregnant, or intend to become pregnant, or are breast-feeding, or intend to breastfeed;
- You are taking other medicines, prescription or non-prescription. Of particular concern are:
  - Statins (a class of drugs, which includes atorvastatin, pravastatin, simvastatin, etc., used to lower cholesterol). Taking a statin at the same time as FENOFIBRATE-S may increase the risk of muscle problems
  - Ezetimibe (another type of cholesterol lowering agent)
  - Oral anticoagulants (blood thinning agents, such as warfarin)
  - Cyclosporine (a drug which may be taken following an organ transplant)
  - Cholestyramine or similar drug (another type of cholesterol lowering agent)
  - Estrogens (hormones which may be found in oral contraceptives or hormone replacement therapy)
- a particular class of medicines to treat diabetes (such as rosiglitazone or pioglitazone)

Your doctor will ask you to have regular medical check-ups and laboratory tests. It is important to respect the dates proposed for these tests: we strongly recommend that you keep these appointments faithfully so that any abnormalities that may occur can be identified promptly. These problems can include muscle inflammation and breakdown, which can cause kidney damage or even death. The risk of muscle breakdown is higher in some patients. Tell your doctor if:

- you are over 70 years old;
- you have kidney problems;
- you have thyroid problems;
- you or a close family member has muscle problem which runs in the family;
- you drink large amounts of alcohol;
- you are taking medicines called statins to lower cholesterol such as simvastatin, atorvastatin,
  pravastatin, rosuvastatin or fluvastatin;
- you have ever had muscle problems during treatment with fibrates such as
- , bezafibrate or gemfibrozil.

- FENOFIBRATE-S is not recommended during pregnancy. In the event of pregnancy during treatment, FENOFIBRATE-S should be discontinued and your doctor should be informed;
- It is not recommended to take FENOFIBRATE-S while breast-feeding;
- Safety of use in children and young adolescents has not been established with FENOFIBRATE-S.

INTERACTIONS WITH THIS MEDICATION

BEFORE you use FENOFIBRATE-S, talk to your doctor or pharmacist if you are taking other medicines, in particular an oral anticoagulant such as warfarin.

PROPER USE OF THIS MEDICATION

Usual dose:

- FENOFIBRATE-S should be taken with meals, as directed by your doctor. Swallow the tablet with a glass of water. Do not crush or chew the tablet.
- It is particularly important to follow this advice because fenofibrate is less well absorbed and hence less effective when not taken with food.
- The recommended dose of FENOFIBRATE-S is one 160 mg tablet daily.
- Never change the dose unless directed by your doctor.
- FENOFIBRATE-S is not recommended for use in children.

The safety of using FENOFIBRATE-S in combination with a statin has not been extensively studied in patients. Therefore, the combined use of fenofibrate with a statin should be avoided unless recommended by your doctor.

Tell your doctor about any health problem that occurs while you are taking FENOFIBRATE-S. If you need other medical treatment while taking FENOFIBRATE-S, let your doctor know that you are taking FENOFIBRATE-S.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Tell your doctor if you feel in any way unwell while taking FENOFIBRATE-S.

Some common side effects may include abdominal pain, constipation, diarrhea, flatulence, nausea, vomiting, headache, dizziness, skin reactions, fatigue and raised levels of liver enzymes in the blood. This is not a complete list of side effects. If you experience any unexpected symptoms while taking FENOFIBRATE-S, contact your doctor or pharmacist.

Stop taking FENOFIBRATE-S and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

- allergic reaction - the signs may include swelling of the face, lips, tongue or throat, which may cause difficulty in breathing
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis)
- chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis)
- yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis).

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

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

HOW TO STORE IT

FENOFIBRATE-S is only available on prescription. Store at 15-30°C. Protect from light and moisture.

ep away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 070 IE
    Ottawa, ON KIA OK9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting,
Sanis Health Inc. at:

Phone: 1-866-236-4076

or quality@sanis.com

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