AUSTRALIAN PRODUCT INFORMATION

FENOFIBRATE VIATRIS

fenofibrate tablet

1 NAME OF THE MEDICINE

Fenofibrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 48 mg or 145 mg of fenofibrate as the active ingredient.

Excipients with known effect: Soya bean products, sulfites and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

48 mg tablets: Yellow, oval, film-coated tablets engraved with "FI" on one side.

145 mg tablets: White, oval, film-coated tablets engraved "145" on one side and "Fournier logo" on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FENOFIBRATE VIATRIS is indicated as an adjunct to diet in the treatment of:

- hypercholesterolaemia;
- types II, III, IV and V dyslipidaemia;
- dyslipidaemia associated with type 2 diabetes.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults (Dyslipidaemia)

FENOFIBRATE VIATRIS is presented as a 145 mg tablet and a 48 mg tablet. The usual dose of fenofibrate is 1 x 145 mg tablet. Although 3 x 48 mg tablets are equivalent to 1 x 145 mg tablet, the 48 mg tablets are only recommended when a decreased dosage is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Renal Impairment).

Patients should never be administered any combination of the 48 mg tablet and the 145 mg tablet of fenofibrate. There is no indication for use of fenofibrate dosages above 145 mg per day. FENOFIBRATE VIATRIS 145 mg and 48 mg tablets should be swallowed whole with a glass of water. FENOFIBRATE VIATRIS 145 mg and 48 mg may be given at any time of the day, with or without food, but it is recommended that they be taken at the same time each day. Dietary measures instituted before therapy should be continued.

Elderly

In elderly patients without renal impairment, the normal adult dose is recommended.

Renal Impairment

FENOFIBRATE VIATRIS Dosage reduction is required in patients with renal impairment.

In moderate renal dysfunction (eGFR between 30 and 60ml/min/1.73m^2 or creatinine clearance between 30 and 60mL/min) start with one FENOFIBRATE VIATRIS 48mg tablet once daily. The dose may be increased

to two FENOFIBRATE VIATRIS 48mg tablets daily only after evaluation of the effects on renal function and lipid levels at the lower dose.

In patients with severe renal dysfunction (eGFR < 30mL/min/1.73m^2 or creatinine clearance < 30mL/min), fenofibrate is contraindicated.

Hepatic Disease

Patients with hepatic disease have not been studied.

4.3 CONTRAINDICATIONS

FENOFIBRATE VIATRIS is contraindicated in:

- children;
- patients with liver dysfunction, including primary biliary cirrhosis and unexplained persistent liver function abnormality;
- patients with severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2);
- patients with existing gallbladder disease;
- co-administration with another fibrate;
- patients hypersensitive to fenofibrate, or any excipients, and in cases of known photoallergy or phototoxic reactions during treatment with fibrates or ketoprofen;
- chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia.
- patients allergic to peanuts or arachis oil or soya lecithin or related products due to risk of hypersensitivity reactions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Initial therapy

Laboratory analysis should be performed to ascertain that the lipid levels are consistently abnormal before instituting FENOFIBRATE VIATRIS therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy

Periodic determinations of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of FENOFIBRATE VIATRIS. If an adequate response has not been achieved after three months of treatment with the maximum recommended dose of one 145 mg tablet per day, complementary or different therapeutic measures should be considered.

Mortality and Coronary Heart Disease Morbidity

The effects of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality have not been established (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials). Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus overall.

Use in Renal Impairment

FENOFIBRATE VIATRIS is contraindicated in patients with severe renal dysfunction (eGFR <30 mL/min/1.73m^2) (see Section 4.3 CONTRAINDICATIONS). In renal dysfunction (eGFR <60 mL/min/1.73m^2 or CrCl <60 mL/min) the dose of fenofibrate may need to be reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). This should also be considered in elderly patients with impaired renal function.

Serum Creatinine

Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. In the FIELD study, plasma creatinine remained on average 10-12 micromol/L higher on fenofibrate than in the placebo group from 4 months after randomisation until the end of the study. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and thereafter periodically. Monitoring of creatinine should also be considered for patients taking fenofibrate at risk for renal insufficiency such as the elderly and patients with diabetes. Treatment should be interrupted in case of an increase in creatinine levels > 50% of upper limit of normal).

Use in Hepatic Impairment

Increased liver function test abnormalities have been observed during fenofibrate therapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Clinically significant liver injury has been reported rarely. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis. The incidence of liver function test abnormalities or hepatic injury when fenofibrate is administered in combination with other potentially hepatotoxic agents has not been studied.

Transaminases

Fenofibrate at doses equivalent to 145 mg per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appears to be dose related. Baseline and ongoing monitoring (every 3 months during the first 12 months of treatment and thereafter periodically) of liver function should be performed for the duration of fenofibrate therapy. Therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. Also, if symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Cholelithiasis

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. FENOFIBRATE VIATRIS therapy should be discontinued if gallstones are found.

Myopathy

There have been reports of elevations (sometimes marked) of creatine phosphokinase (CPK), myositis and myopathy associated with fibrates as well as other systemically absorbed lipid modifying drugs. Rhabdomyolysis has also been reported rarely. Patients receiving fenofibrate and complaining of muscle pain, tenderness or weakness should have prompt medical evaluation for myositis, including serum creatinine level determination. If myositis is suspected or if CPK rises to ≥ 5 times the upper limit of normal, fenofibrate therapy should be withdrawn. Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, hypoalbuminaemia, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up. The risk of serious muscle toxicity is increased if fenofibrate is used concomitantly

with HMG-CoA reductase inhibitors or other fibrates (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. 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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Estrogens

For hyperlipidaemic patients taking estrogens or contraceptives containing estrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral estrogen).

Patients with rare hereditary problems of fructose and galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

FENOFIBRATE VIATRIS should not be taken in patients allergic to lecithin or related products due to the risk of hypersensitivity reactions.

Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1.4%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1.1%) in the fenofibrate group ($p = 0.022$).

Haematologic Changes

Mild to moderate haemoglobin, haematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilise during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrate. Periodic monitoring of red and white blood cell counts are recommended during the first 12 months of treatment.

Hypersensitivity Reactions

Acute hypersensitivity reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis requiring patient hospitalisation and treatment with steroids have been reported in individuals treated with fenofibrates. Urticaria was seen in 1.3 vs. 0%, and rash in 1.5 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Paradoxical Decreases in HDL-Cholesterol (HDL-C) Levels

There have been post marketing and clinical trial reports of severe decreases in HDL-C levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Oral Anti-coagulants

Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

HMG-CoA Reductase Inhibitors

There have been reports of severe myositis and myoglobinuria (rhabdomyolysis) when fenofibrate and HMG-CoA reductase inhibitors were used concurrently. The risk of serious muscle toxicity is increased if fenofibrate is used concomitantly with HMG-CoA reductase inhibitors. This reaction may occur at any point throughout therapy. Such combination therapy should be used with caution in patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and patients monitored closely for chronic signs of muscle toxicity although toxicity may occur even in the presence of such monitoring. However, data from fenofibrate- HMG-CoA Reductase Inhibitors interaction studies have shown that, contrary to gemfibrozil, the co-administration of fenofibrate with pravastatin, atorvastatin and simvastatin is associated with moderate pharmacokinetic interactions.

Pravastatin

Concomitant administration of fenofibrate (dose equivalent to FENOFIBRATE VIATRIS 145 mg tablet once daily over 10 days) and pravastatin (40 mg once daily for 15 days) resulted in an increase of the mean AUC and C_{max} for pravastatin by 27 and 36%, respectively and its metabolite 3-hydroxy-iso-pravastatin (which activity represents only 2.5 to 10% of the activity of pravastatin) by 39 and 55%, respectively. The clinical significance of this finding has not been studied. A previous single dose study showed that pravastatin had no effect on the pharmacokinetics of fenofibric acid.

Atorvastatin

Concomitant administration over 10 days of fenofibrate (dose equivalent to FENOFIBRATE VIATRIS 145 mg tablet once daily) and atorvastatin (20 mg once daily) resulted in a slight decrease in the mean atorvastatin AUC (14%). Atorvastatin C_{max} was not affected by fenofibrate. The pharmacokinetics of fenofibric acid was not significantly modified by atorvastatin (-3% and 4% for AUC and C_{max}, respectively).

Simvastatin

Concomitant administration of fenofibrate (160 mg tablet once daily for 10 days) and simvastatin (single dose of 40 mg taken simultaneously with the last dose of fenofibrate) resulted in no significant change in simvastatin AUC (-8%), but in significant decrease in simvastatin acid AUC (-42%) the main active metabolite. However, recently published data, while showing similar PK results, provide data on HMG-CoA reductase inhibition, and show that despite the significant reduction in exposure to simvastatin acid, the pharmacological activity of simvastatin measured by active HMG-CoA reductase inhibitors, is not significantly impacted by concomitant treatment with fenofibrate. No significant effect was observed on C_{max}. The pharmacokinetics of fenofibric acid was not significantly modified by simvastatin (+14% for C_{min}).
Patients receiving fenofibrate and complaining of muscle pain, tenderness or weakness should have prompt medical evaluation for myositis, including serum creatinine level determination. If myositis is suspected or diagnosed, fenofibrate therapy should be withdrawn.

Fibrates

The risk of serious toxicity is increased if fibrates are used concomitantly. Such combination therapy is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Ciclosporin

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

Glitazones

Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if one of these components is added to the other and stopping of either therapy if HDL-cholesterol is too low.

Other concomitant therapy

The potential for fenofibrate/fenofibric acid to affect the metabolism of other drugs has not been fully investigated in vitro or in vivo. Interactions cannot be predicted, and therefore, caution is therefore recommended if fenofibrate is combined with other drugs. In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2 dependent metabolism, weakly inhibits CYP2C19 and CYP2A6 dependent metabolism, and exhibits a mild-to-moderate inhibition of CYP2C9 dependent metabolism at therapeutic concentrations. In vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites.
Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Fertility was not affected in rats at oral doses up to 300 mg/kg/day. Based on AUC after single PO dose in rats, the exposure at 300 mg/kg/day is approximately 16x the clinical exposure at steady state.

Use in Pregnancy

Category B3

There are no adequate and well-controlled studies in pregnant women. Embryofetal toxicity was observed in animals (see below). It is recommended that fenofibrate should not be administered to pregnant women.

In rats, fenofibrate treatment during organogenesis (gestation days 6-15) caused an increase in fetal abnormalities (domed head, rounded body, hunched shoulders, supernumerary ribs and misshapen vertebrae) at 300 mg/kg/day and stunting at 150 and 300 mg/kg/day (approximately 10x and 16x the clinical exposure based on AUC, respectively). When administered to rats during gestation and lactation, fenofibrate prolonged gestation, increased stillbirths and reduced birth weight, pup weight gain and survival at 300 mg/kg/day PO, and decreased birth weight, pup survival and pup weight gain at 75 mg/kg/day PO (approximately 6x the clinical exposure based on AUC). The above findings were associated with maternal toxicity (decreased body weight gain). In rabbits, fenofibrate caused abortion at 150 and 300 mg/kg/day and increased fetal deaths at 300mg/kg/day, associated with maternal body weight loss at 300 mg/kg/day (not at 150 mg/kg/day). The oral doses of 150 and 300 mg/kg/day in rabbits were 12.5x and 25x the MRCD, based on BSA.

Use in Lactation

It is not known whether fenofibrate is excreted into human milk. Fenofibrate should not be administrated to breastfeeding women.

As described above in the 'Use in Pregnancy' section, fenofibrate treatment during gestation and lactation in rats at oral doses of 75 and 300 mg/kg/day decreased pup survival and pup weight gain.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The frequencies of adverse events are ranked according to the following: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports; and during post marketing experience[†].

Gastrointestinal disorders

Common

digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity

Uncommon

pancreatitis*

Post-marketing[†]

pancreatitis

Hepato-biliary disorders

Common

moderately elevated levels of serum transaminases

Uncommon

development of gallstones

Rare

episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable

Post-marketing[†]

jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic), hepatitis, cirrhosis

Skin and subcutaneous tissue disorders

Uncommon

rashes, pruritus, urticaria or photosensitivity reactions

Rare

alopecia

Very rare

cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sunlamp) in individual cases (even after many months of uncomplicated use)

Post-marketing†

severe cutaneous reactions (e.g. erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis)

Musculoskeletal, connective tissue and bone disorders

Uncommon

diffuse myalgia, myositis, muscular cramps and weakness

Very rare

rhabdomyolysis

Post-marketing†

muscle spasm, myalgia, rhabdomyolysis, arthralgia, asthenia

Cardiovascular system

Uncommon:

Thromboembolism (pulmonary embolism, deep vein thrombosis).

Blood and lymphatic system disorders

Rare

decrease in haemoglobin and leukocytes

Post-marketing†

anaemia, decreases in haemoglobin, decreases in haematocrit, white blood cell decreases

Immune system disorders

Rare

Hypersensitivity

Nervous system disorders

Uncommon

headache

Post-marketing†

fatigue

Reproductive system and breast disorders

Uncommon

Sexual dysfunction

Rare

sexual asthenia

Respiratory, thoracic and mediastinal disorders

Very rare

interstitial pneumopathies

Post-marketing†

interstitial lung disease

Renal disorders

Post-marketing†

acute renal failure

Investigations

Common

Increases in serum homocysteine level**

Uncommon

Increases in serum creatinine and urea.

Post-marketing†

severely depressed HDL-cholesterol levels

Notes:

†Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*In the FIELD-study, a randomised placebo-controlled trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031).

**In the FIELD study, the average increase in serum homocysteine level in patients treated with fenofibrate was 6.5µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level.

Adverse events reported by 1% or more of patients with dyslipidaemia or type 2 diabetes treated with fenofibrate during double blind, placebo-controlled trials, regardless of causality, at the time of registration are listed in Table 1.

Table 1: Adverse events reported by 1% or more of patients with dyslipidaemia or type 2 diabetes treated with fenofibrate during double blind, placebo-controlled trials, regardless of causality.

Adverse events	**Dyslipidaemia**		**Type 2 diabetes**	
	fenofibrate N= 473 (%)	**Placebo N= 397 (%)**	**fenofibrate N=207 (%)**	**Placebo N=211 (%)**
Body as a whole	20.3	20.1	65.7	69.2
Abdominal pain	5.1	4.5	15.9	11.9
Back pain	3.8	2.8	15.0	19
Asthenia	2.5	2.8	6.8	5.7

Headache	3.6	3.3	5.8	6.2
Accidental injury	1.5	2.0	18.4	18.5
Flu syndrome	1.7	2.0	17.9	18.0
Chest pain	1.9	1.3	10.1	8.5
Malaise	1.5	0.2	2.4	0.5
Cardiovascular system	4.9	4.0	40.6	45.5
Digestive system	21.8	17.6	41.6	41.2
Diarrhoea	2.9	4.8	7.3	5.7
Nausea	2.3	2.3	0.5	1.9
Constipation	2.3	1.5	5.3	3.8
Dyspepsia	2.7	2.5	3.9	5.7
Endocrine system	0.4	0	4.8	5.2
Haemic & lymphatic system	2.1	1.0	9.2	7.1
Metabolic & nutritional disorders	7.6	5.5	15.5	19.4
CPK increase	2.7	1.2	1.9	2.8
ALAT increase	3.4	1.5	3.9	1.4
ASAT increase	4.0	0.5	1.0	1.9
Musculoskeletal system	4.9	5.3	40.6	39.8
Arthralgia	1.9	1.8	25.1	22.1
Myalgia	0.8	1.0	3.4	3.8
Nervous system	4.4	6.0	28.5	27.5
Dizziness	1.5	1.0	7.3	5.7
Insomnia	1.05	0.5	1.9	2.4
Respiratory system	12.9	12.1	52.2	49.8
Respiratory dis.	6.3	5.5	6.8	4.3
Sinusitis	1.9	2.5	7.7	7.6
Pharyngitis	2.9	2.5	7.8	7.6
Rhinitis	2.7	1.8	23.2	21.2
Bronchitis	1.3	1.3	16.4	14.7
Skin and appendages	7.0	2.5	28.0	22.8
Rash	1.5	0.75	7.3	4.3
Pruritus	2.1	0.5	3.4	2.8
Urticaria	1.3	0	0	0
Special senses	3.2	2.8	21.3	23.7
Conjunctivitis	1.05	1.0	1.9	4.3
Urogenital system	4.4	5.0	26.6	21.8

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment for overdose with FENOFIBRATE VIATRIS. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. Because fenofibrate is highly bound to plasma proteins, haemodialysis should not be considered. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The majority of clinical trials have been conducted with a micronised fenofibrate 200 mg capsule formulation. The micronised fenofibrate 200 mg capsule, 3 tablets of 48 mg and the 145 mg tablet have been demonstrated to be bioequivalent in a bioequivalence study carried out under fed conditions.

Mechanism of Action

The lipid-lowering properties of fenofibrate seen in clinical practice have been explained in vivo in transgenic mice and in human hepatocyte cultures by the activation of Peroxisome Proliferator Activated Receptor type α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apoprotein C-III. Activation of PPARα also induces an increase in the synthesis of Apoproteins A-I, A-II and of HDL-cholesterol.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in the very low- and low-density (VLDL and LDL) fractions containing apoprotein B and to an increase in the high-density lipoprotein (HDL) fraction containing apoprotein AI and AII.

In addition, through modulation of the synthesis and the catabolism of VLDL fractions fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk of coronary heart disease. Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy. The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Clinical Trials

Dyslipidaemia

During clinical trials with fenofibrate total cholesterol was reduced by 20 to 25%, triglycerides by 40-50% and HDL-cholesterol was increased by 10 to 30%. In hypercholesterolaemic patients, where LDL-cholesterol levels were reduced by 20 to 30%, the overall effect on cholesterol resulted in a decrease in the ratios of total cholesterol to HDL-cholesterol, LDL-cholesterol to HDL-cholesterol, and Apo B to Apo AI, all of which are markers of atherogenic risk. Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The long-term effects of fenofibrate were assessed in an open-label, prospective six month trial that examined the efficacy of fenofibrate 145 mg/day equivalent (see Section 5 PHARMACOLOGICAL PROPERTIES) in 1334 patients with type IIa, IIb or IV dyslipidaemia. The results of the trial are summarized in Table 2.

Table 2: Change in lipid parameters compared to baseline after 6 months

Parameter (mmol/L):	Baseline	Month 6	Absolute change
Type IIa patients:			
LDL-C	5.55	3.98	-1.57
Total Cholesterol	7.68	6.05	-1.63
HDL-C	1.47	1.57	0.10
Triglycerides	1.46	1.10	-0.36
Type IIb patients:			
LDL-C	5.25	4.15	-1.10
Total Cholesterol	7.91	6.39	-1.52
HDL-C	1.15	1.32	0.17
Triglycerides	3.77	2.11	-1.66
Type IV patients:			
LDL-C	3.24	3.12	-0.12
Total Cholesterol	7.65	6.13	-1.52
HDL-C	0.95	1.13	0.18
Triglycerides	3.72	2.60	-1.12

DAIS Study

The Diabetes Atherosclerosis Intervention Study (DAIS) was a double-blind, randomised, placebo-controlled study in 418 patients with type 2 diabetes and hyperlipoproteinaemia. Patients were randomised to fenofibrate 145 mg/day equivalent (see Section 5 PHARMACOLOGICAL PROPERTIES) or placebo for at least 3 years. Patients had stable glycaemic control, (mean HbA1c 7.5%), mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion.

The primary efficacy criterion was the mean segment diameter averaged per patient across all pairs of analysable coronary segments, a criterion believed to reflect diffuse coronary artery disease. Among the secondary criteria were other angiographic parameters (mean diameter averaged per segment and minimum segment diameter averaged per patient and per segment).

Results (see Table 3) showed that fenofibrate significantly reduces the angiographic progression of focal coronary atherosclerosis characterized by minimum segment diameter and percent diameter stenosis in patients with type 2 diabetes and hyperlipoproteinaemia (mean total cholesterol 5.57 mmol/L, triglycerides 2.54 mmol/L, LDL-cholesterol 3.37 mmol/L and HDL-cholesterol 1.03 mmol/L).

The reduction in the progression of angiographic coronary disease was associated with a reduction in lipid parameters (total cholesterol, LDL-cholesterol, triglycerides, TC/HDL-C), and an increase in HDL-cholesterol and therefore results apply to patients who respond to treatment. This trial did not assess whether the observed change in angiographic endpoints, particularly in asymptomatic patients, had any effect on cardiovascular events or mortality.

Table 3: Coronary angiogram values (mean ± SD) averaged per patient at baseline and at the end of study (ITT population)

	Fenofibrate (n=207)	**Placebo (n=211)**	**p-values***
Mean segment diameter (mm)			
Baseline	2.70 ± 0.45	2.67 ± 0.45	0.494
End of study	2.62 ± 0.49	2.56 ± 0.50	0.173
Minimum segment diameter (mm)			
Baseline	2.14 ± 0.44	2.10 ± 0.44	0.457
End of study	2.05 ± 0.46	1.98 ± 0.48	0.028
Percent diameter stenosis (%)			
Baseline	21.80 ± 7.8	21.80 ± 7.4	0.958
End of study	24.10 ± 9.8	25.70 ± 10.8	0.020

*p-values for Student's t test and for covariance analysis to compare treatment groups respectively at baseline and at the end of study

FIELD

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomised, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% Cl 0.75-1.05, p=0.16) and a significant 11% relative reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95-1.29], p=0.18) and 19% (HR 1.19, [0.90-1.57]; p=0.22) relative increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared with placebo.

ACCORD-Lipid

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomised placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate.

Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, p = 0.32; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 0.88 mmol/L) and highest tertile of TG (≥ 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, p = 0.03; absolute risk reduction: 4.95%). Another pre-specified subgroup analysis identified a statistically significant treatment-by-gender interaction (p = 0.01) indicating a possible treatment benefit of combination therapy in men (p=0.037) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy (p=0.069). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

Epidemiological studies have demonstrated a positive correlation between increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemias forms the rationale for treatment with fenofibrate. There is evidence that treatment with fibrates may reduce coronary heart disease events but fenofibrate has not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus overall.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Unlike that observed for FENOFIBRATE VIATRIS 160 mg tablets and 67 mg and 200 mg capsules, in which the absorption of fenofibrate is increased significantly when administered with food, the rate and extent of absorption of fenofibrate from FENOFIBRATE VIATRIS 48 mg and 145 mg tablets is not significantly affected by food. A food-effect study involving administration of the new 145 mg tablet formulation of fenofibrate to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_{max}) to fenofibric acid is not affected by food. Therefore, FENOFIBRATE VIATRIS 145 mg and 48 mg tablets may be taken without regard to meals.

The nanosized formulation of FENOFIBRATE VIATRIS 145 mg and FENOFIBRATE VIATRIS 160 mg are bioequivalent in respect of AUC and C_{max} under low fat fed conditions. The average C_{max} of FENOFIBRATE VIATRIS 145 mg is 15.5% higher than that from 160 mg tablets and its median T_{max} significantly shorter (2.9 and 3.7 hours for FENOFIBRATE VIATRIS 145 mg and 160 mg respectively).

Distribution and Metabolism

After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. Unchanged fenofibrate is not recovered in the plasma. Fenofibric acid, the major plasma metabolite, is highly bound to plasma albumin (more than 99%).

Peak plasma concentration occurs after a mean period of 2 to 4 hours following administration of 145 mg fenofibrate tablets. Kinetic studies after administration of repeated doses show the absence of accumulation of the product. The plasma half-life of elimination of fenofibric acid is approximately 20 hours.

Excretion

The product is mainly excreted in the urine: 70% in 24 hours and 88% in 6 days, at which time total excretion in urine and faeces reaches 93%. Fenofibrate is mainly excreted as fenofibric acid and its derived glucuronoconjugate. Fenofibric acid is not eliminated during haemodialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fenofibrate did not induce gene mutation in bacteria or mouse lymphoma cells in vitro, or chromosome aberration in CHO cells in vitro or rat bone marrow cells in vivo. Nor did it cause DNA damage in rat hepatocytes in vitro.

Carcinogenicity

The carcinogenic potential of fenofibrate was investigated in mice and rats. In two carcinogenicity studies in rats at dietary doses of 10, 45 and 200 mg/kg/day (24-month study) or 10 and 60 mg/kg/day (27-month study), the incidence of liver carcinomas and/or adenomas was increased at ≥45 mg/kg/day (≥4x the clinical exposure, based on AUC) in the 24-month study. Increased incidence of pancreatic acinar cell tumours (carcinomas and/or adenomas) occurred in males in both studies at ≥45 mg/kg/day and increased testicular Leydig cell tumours in both studies at ≥60 mg/kg/day (≥5x the clinical exposure, based on AUC). In two mouse studies at fenofibrate doses 10, 45 and 200 mg/kg/day (18-month study) or 10, 60 and 200 mg/kg/day (21-month study), the incidence of liver tumours (hepatocellular adenomas and/or carcinomas) was increased in the 18-month study at all doses (0.2x to 4.5x the maximum recommended clinical dose (MRCD) adjusted for body surface area (BSA)), and in the 21-month study at ≥60 mg/kg/day (1.4x the MRCD adjusted for BSA). Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

FENOFIBRATE VIATRIS 48 mg tablets also contain sucrose, hypromellose, sodium lauryl sulfate, lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, docusate sodium, magnesium stearate. The film coating for the tablets consists of polyvinyl alcohol, titanium dioxide, purified talc, lecithin and xanthan gum and indigo carmine aluminium lake, quinoline yellow aluminium lake and sunset yellow FCF aluminium lake as colouring agents.

FENOFIBRATE VIATRIS 145 mg tablets also contain sucrose, hypromellose, sodium lauryl sulfate, lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, docusate sodium, magnesium stearate. The film coating for the tablets consists of polyvinyl alcohol, titanium dioxide, purified talc, lecithin and xanthan gum.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

48 mg tablets: Packs of 60 in blister strip (PVC/PE/PVDC/Aluminium).

145 mg tablets: Packs of 30 tablets in blister strip (PVC/PE/PVDC/Aluminium).

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 230443 – FENOFIBRATE VIATRIS fenofibrate 145 mg tablet blister pack

AUST R 230444 – FENOFIBRATE VIATRIS fenofibrate 48 mg tablet blister pack

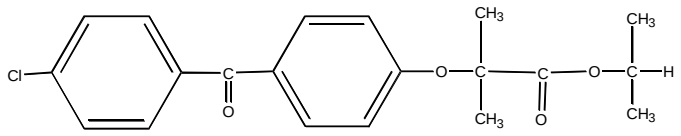
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Fenofibrate is a fibric acid derivative. Chemical name: 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester. The empirical formula is $C_{20}H_{21}O_4Cl$. MW: 360.83. Fenofibrate is a white solid powder, stable under ordinary conditions and practically insoluble in water. The melting point is 79-82°C.



CAS Number

49562-28-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

02/04/2016

10 DATE OF REVISION

02/12/2021

Summary Table of Changes

Section Changed	Summary of New Information
4, 5.2, 6.1	Update product name
6.5	Insert AUST R numbers
8	Update sponsor's details

FENOFIBRATE VIATRIS_pi\Dec21/00