PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINAL PRODUCT

LIPANTHYL 145 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 145 mg fenofibrate.

Excipients with known effect:

Each film-coated tablet contains sugar (132,00 mg lactose monohydrate and 145,00 mg sucrose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, oval, film-coated tablets engraved “145” on one side and the Fournier logo on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LIPANTHYL 145 mg is indicated as an adjunct to a diet and other non-medicinal treatment (e.g. exercise, weight reduction) for the following conditions:

- Severe hypertriglyceridaemia with or without low HDL cholesterol
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.
- Mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

LIPANTHYL 145 mg is indicated for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. LIPANTHYL 145 mg does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.

4.2 Posology and method of administration

The diet should be continued during the administration of LIPANTHYL 145 mg. Response to therapy should be monitored by determination of serum lipid levels. If an adequate lipid- lowering response has not been achieved after several months of treatment (e.g. 3 months), complementary or different therapeutic measures should be considered.

Posology:

Adults:

Recommended daily dose: 1 film-coated tablet (equivalent to 145 mg fenofibrate) daily.

Patients currently taking fenofibrate 200 mg or fenofibrate 160 mg can be changed to the LIPANTHYL 145 mg (1 film-coated tablet daily) without further dose adjustment.

Elderly patients (≥ 65 years old):

No dose adjustment is necessary. The usual dose is recommended except for decreased renal function with estimated glomerular filtration rate (eGFR) < 60 mL/min/1,73 m^2 (see “Patients with renal impairment”).

Patients with renal impairment:

Fenofibrate should not be used if severe renal impairment, defined as eGFR < 30 mL/min/1,73 m^2, is present.

If eGFR is between 30 and 59 mL/min/1,73 m^2, the daily dose should not exceed 100 mg fenofibrate (standard) or 67 mg micronised.

If, during follow-up, the eGFR decreases persistently to < 30 mL/min/1,73 m^2, fenofibrate should be discontinued.

Hepatic impairment:

LIPANTHYL 145 mg is not recommended for patients with hepatic impairment due to the lack of data.

Children and adolescents:

LIPANTHYL 145 mg should not be given to children under 18 years of age. The safety and efficacy of LIPANTHYL 145 mg have not been sufficiently established in children. No data are available.

Method of administration:

LIPANTHYL 145 mg may be given at any time of the day, with or without food (see section 5.2). The film-coated tablet should be swallowed whole with a glass of water.

4.3 Contraindications

- Hypersensitivity to the fenofibrate or to any of the excipients listed in section 6.1.
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality).
- Known gallbladder disease.
- Severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1,73 m^2).
- Chronic or acute pancreatitis.
- Known photo allergy or phototoxic reaction during treatment with fibrates or ketoprofen.

LIPANTHYL 145 mg should not be taken by patients allergic to peanuts, arachis oil, soya lecithin (3sn-phosphatidyl choline) or related products due to the risk of hypersensitivity reactions.

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidaemia:

Secondary causes of hypercholesterolaemia such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease or alcoholism should be adequately treated before LIPANTHYL 145 mg therapy is considered. Secondary causes of hypercholesterolaemia related to pharmacological treatment can be seen with diuretics, beta-blocking agents, oestrogens, progestogens, combined oral contraceptives, immunosuppressants and protease inhibitors. In these cases, it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic agents).

Liver:

Increases have been reported in transaminase levels in some patients whilst taking fenofibrate. In the majority of the observed cases, these elevations were temporary, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and regularly thereafter.

Patients displaying elevated transaminase levels should be closely monitored. Treatment should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than three times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus) and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Pancreas:

Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). In patients with severe hypertriglyceridaemia, this may be due to insufficient efficacy of the medicinal product, a direct drug effect or a secondary phenomenon mediated through cholelithiasis with obstruction of the common bile duct

Muscle:

Muscle toxicity including rare cases of rhabdomyolysis, with or without renal failure, has been reported with the administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in case of hypoalbuminaemia and previous renal insufficiency. Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or family history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at increased risk of developing rhabdomyolysis. For these patients, the benefits and risks of fenofibrate therapy should be carefully weighed up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in creatine phosphokinase (CPK) (levels exceeding five times the upper normal range). In such cases, the medicinal product should be stopped.

The risk of muscle toxicity may be elevated if this medicinal product is combined with another fibrate or with an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the combination of fenofibrate with an HMG-CoA reductase inhibitor or another fibrate should be reserved for patients with severe combined hyperlipidaemia and high cardiovascular risk without any history of muscular disease and with close monitoring of potential muscle toxicity.

Renal function:

LIPANTHYL 145 mg is contraindicated in severe renal impairment (see section 4.3).

LIPANTHYL 145 mg should be used with caution in patients with mild to moderate renal insufficiency. Dose adjustment is required in patients with an eGFR between 30 and 59 mL/min/1,73 m^2 (see section 4.2).

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable

over time with no evidence of continued increase with long-term therapy. A return to baseline values was observed following discontinuation of treatment.

During clinical trials, 10 % of patients had a creatinine increase from baseline greater than 30 µmol with co-administered fenofibrate and simvastatin versus 4,4 % with statin monotherapy. 0,3 % of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/L.

Treatment should be interrupted when the creatinine level is 50 % above the upper limit of normal. It is recommended that creatinine is measured during the first three months after initiation of treatment and periodically thereafter.

Excipients:

As LIPANTHYL 145 mg contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LIPANTHYL 145 mg

As LIPANTHYL 145 mg contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this LIPANTHYL 145.

LIPANTHYL 145 mg contains less than 1 mmol (23 mg) sodium per film-coated tablet, i.e. it is virtually “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants:

Fenofibrate may enhance the oral anticoagulant effect and thus may increase the 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 – whilst monitoring coagulation parameters (international normalised ratio (INR)).

Cyclosporin:

Isolated cases of severe albeit reversible, impairment of renal function have been reported during concomitant administration of fibrate-containing medicinal products and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate discontinued in the case of significant changes in diagnostic laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates:

The risk of serious muscle damage is increased if a fibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution, and patients monitored closely for signs of muscle damage (see section 4.4).

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. Either therapy should be discontinued if HDL cholesterol is too low.

Cytochrome P450 enzymes:

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. They are

weak inhibitors of CYP2C19 and CYP2A6, and moderate inhibitors of CYP2C9 at therapeutic concentrations.

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

LIPANTHYL 145 mg should not be administered to women who are pregnant or are breastfeeding.

Therefore, LIPANTHYL 145 mg should only be used during pregnancy after a careful benefit/risk assessment.

4.7 Effects on ability to drive and use machines

LIPANTHYL 145 mg has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse effects during fenofibrate therapy are digestive or gastrointestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n=2344) and post-marketing[a] with the frequencies indicated below:

MedDRA system organ class	**Common**	**Uncommon**	**Rare**	**Frequencies unknown**
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased	
Immune system disorders			Hypersensitivity	

Nervous system disorders		Headache		
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*		
Respiratory tract, thoracic and mediastinal disorders				Interstitial pulmonary diseases[a]
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*		
Hepatobiliary disorders	Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis	Jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic)[a]
Skin and subcutaneous tissue		Cutaneous hypersensitivity	Alopecia Photosensitivity	Severe cutaneous

disorders		(e.g. rashes, pruritus, urticaria)		reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)[a]
Musculoskeletal, connective tissue and bone disorders		Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness)		Rhabdomyolysis[a]
Reproductive system and breast disorders		Sexual dysfunction		
General disorders and administration site conditions				Fatigue[a]
Investigations	Blood homocysteine level increased**	Blood creatinine increased	Blood urea increased	

* In the FIELD study, a randomised placebo-controlled clinical trial performed in 9 795 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 same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0,7 % in the placebo group versus 1,1 % in the fenofibrate group; p = 0,022) and a statistically non-significant increase in deep vein thromboses [placebo 1 % (48/4 900 patients) versus fenofibrate 1,4 % (67/4 895 patients); p = 0,074].

** In the FIELD study, the average increase in blood homocysteine levels in treated patients was 6,5 µmol/L and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance is unclear.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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4.9 Overdose

Only isolated reports of fenofibrate overdose have been received to date. In the majority of cases no overdose symptoms were reported. There is no specific antidote. If an overdose is suspected, symptomatic treatment should be initiated and suitable supportive measures taken. Fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid-lowering agents/cholesterol and triglyceride-lowering preparations/fibrates

ATC code: C10AB05

Fenofibrate is a fibric acid derivative whose lipid-regulating effects in humans are mediated via activation of PPARα (peroxisome proliferator activated receptor type alpha).

Activation of PPARα increases the activity of lipoprotein lipase and reduces the production of apolipoprotein CIII. Via this mechanism, fenofibrate increases lipolysis and elimination of atherogenic, triglyceride-rich particles from the plasma. Activation of PPARα also induces an increase in the synthesis of apolipoproteins AI and AII.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomised placebo-controlled study in 5 518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Treatment with fenofibrate plus simvastatin did not show significant differences in the composite primary endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular deaths compared to simvastatin monotherapy (hazard ratio [HR] 0,92; 95% CI: 0,79 to 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 (≤ 34 mg/dL or 0,88 mmol/L) and highest tertile of TG (≥ 204 mg/dL or 2,3 mmol/L), fenofibrate plus simvastatin therapy demonstrated a 31 % relative risk reduction compared to simvastatin monotherapy for the composite primary outcome criterion (Hazard ratio [HR] 0,69;

95 % CI 0,49 to 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 endpoint in women treated with combination therapy compared to simvastatin monotherapy (p = 0,069). This was not observed in the above-mentioned 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.

Extravascular deposits of cholesterol (tendinous and tuberous xanthomas) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

5.2 Pharmacokinetic properties

LIPANTHYL 145 mg contains 145 mg of fenofibrate as nanoparticles in the form of a filmcoated tablet.

Absorption:

Maximum plasma concentrations (C_{max}) occur within 2 - 4 hours after oral administration. Plasma concentrations remain constant in any given individual following repeated administration.

Contrary to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticle formation is independent from food intake. Therefore, the medicinal product may be taken without regard to meals.

A study involving 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.

Distribution:

Fenofibric acid is strongly bound to plasma albumin (> 99 %).

Metabolism and excretion:

After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite, fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP3A4. No hepatic microsomal metabolism is involved.

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. Plasma clearance of fenofibric acid is unchanged in elderly patients.

Pharmacokinetic studies with single and repeated dosing have demonstrated that the active substance does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

The plasma elimination half-life of fenofibric acid is approximately 20 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Crospovidone

Docusate sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Silicified microcrystalline cellulose

Sucrose

Sodium laurilsulphate

Opadry OY-B-28920

Film-coating:

Opadry OY-B-28920 contains:

Polyvinyl alcohol

Soybean lecithin

Talc

Titanium dioxide (E171)

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C. Store in original container

6.5 Nature and contents of container

Lipanthyl 145 mg tablets are packaged in blister strips composed of a PVC base film, closed

with a hard-tempered aluminium foil.

Original pack size:

30 film coated tablets

100 film coated tablets

Not all pack sizes are marketed

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof, 1709

Republic of South Africa

8. REGISTRATION NUMBER

56/7.5/0113

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 2024

10. DATE OF REVISION OF THE TEXT

56/7.5/0113