SCHEDULING STATUS S3

1. NAME OF MEDICINE

LIPANTHYL 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE

Each hard capsule contains 200 mg fenofibrate (micronised).

Excipients with known effect:

Each hard capsule contains 101 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Number 1 hard gelatine capsule with orange cap and body, containing a whitish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Before starting treatment with LIPANTHYL 200 mg, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, or control of diabetes mellitus. When an appropriate diet has been followed but has not been sufficient, especially when the blood cholesterol remains elevated after the diet, and/or when there are associated risk factors, LIPANTHYL 200 mg is indicated for the reduction of triglycerides and cholesterol in the treatment of type IIa and IIb, type III and IV hyperlipoproteinaemias. It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has

detrimental, beneficial or no effects on the morbidity or mortality due to atherosclerosis or coronary heart disease. LIPANTHYL 200 mg therapy should be discontinued if a significant lowering in serum lipids is not obtained.

4.2 Posology and method of administration

The adult dosage is one capsule daily during one of the main meals. In elderly patients without renal impairment, the normal dose is recommended. Since it is less well absorbed from an empty stomach, LIPANTHYL 200 mg should always be taken with food. Individual adapted dietary measures should be instituted together with LIPANTHYL 200 mg treatment. Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows LIPANTHYL 200 mg treatment, but treatment should be discontinued if adequate response has not been achieved within three months.

Method of administration

LIPANTHYL 200 mg capsules should be swallowed whole during a meal.

4.3 Contraindications

- Hypersensitivity to fenofibrate or to any of the excipients listed in section 6.1.
- LIPANTHYL 200 mg should not be administered to women who are pregnant or are breastfeeding.
- It is also contraindicated in renal lithiasis and impaired liver or kidney function.

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidaemia

Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease,

pharmacological treatment, alcoholism, should be treated before LIPANTHYL 200 mg therapy is considered. Secondary cause of hypercholesterolemia related to pharmacological treatment can be seen with diuretics, β-blockers, estrogens, progestogens, combined oral contraceptives, immunosuppressives 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 medicines).

Liver function

Moderately elevated levels of serum transaminase may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminase should be monitored every three months during the first twelve months of treatment and thereafter periodically.

Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 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, LIPANTHYL 200 mg therapy should be discontinued.

Pancreas

Pancreatitis has been reported in patients taking fenofibrate (see section 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct medicine effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle

Muscle toxicity, including cases of rhabdomyolysis, with or without renal failure has been

reported with the use of administration of LIPANTHYL 200 mg. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of LIPANTHYL 200 mg 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 CPK (levels exceeding 5 times the normal range). In such cases treatment with LIPANTHYL 200 mg should be stopped. The risk of muscle toxicity may be increased if LIPANTHYL 200 mg is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of LIPANTHYL 200 mg with an 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 and a close monitoring of potential muscle toxicity.

Renal impairment

In renal dysfunction the dose of LIPANTHYL 200 mg may need to be reduced, depending on the rate of creatinine clearance. Use of a non-micronised fibrate is preferred in elderly patients with renal impairment where dosage reduction may be required.

Reversible elevations in serum creatinine have been reported in patients receiving LIPANTHYL 200 mg monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.

Treatment should be interrupted when creatinine level is 50 % above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

LIPANTHYL 200 mg contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LIPANTHYL 200 mg.

4.5 Interaction with other medicines and other forms of interaction

Oral anticoagulants

Fenofibrate, as in LIPANTHYL 200 mg, enhances oral anticoagulant effect and may increase the risk of bleeding. In patients receiving oral anticoagulant therapy, the dose of anticoagulant should be reduced by about one third at the commencement of treatment and then gradually adjusted if necessary.

HMG-CoA reductase inhibitors or other fibrates

The risk of serious muscle toxicity 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 toxicity (see section 4.4). There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.

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 the treatment with LIPANTHYL 200 mg stopped in the case of severe alteration of laboratory parameters.

Glitazones

Cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of LIPANTHYL 200 mg and glitazones. 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.

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 mild-to-moderate of CYP2C9 at therapeutic concentrations. Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised medicines with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these medicines is recommended.

Other

No proven clinical interactions of LIPANTHYL 200 mg and with other medicines have been reported, although *in vitro* interaction

studies suggest displacement of phenylbutazone from plasma protein binding sites. In common with other fibrates, LIPANTHYL 200 mg induces microsomal mixed-function oxidases involved in fatty-acid metabolism in rodents and may interact with medicines metabolised by these enzymes. Possible interactions with oral hypoglycaemic medicines should also be considered.

4.6 Fertility, pregnancy and lactation

LIPANTHYL 200 mg should not be administered to women who are pregnant or are breastfeeding.

4.7 Effects on ability to drive and use machines

LIPANTHYL 200 mg has no or negligible influence on the ability to drive a vehicle and use machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions during LIPANTHYL 200 mg therapy are digestive, gastric or intestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n = 2 344) with the below indicated frequencies:

MedDRA system organ class	**Common** **> 1/100 < 1/10**	**Uncommon** **> 1/1 000 < 1/100**	**Rare** **> 1/10 000 < 1/1 000**
Blood and lymphatic system disorders			Decreased haemoglobin, decreased white blood cell count
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache		
Ear and labyrinth disorders	Vertigo		

Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*	
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*	
Hepatobiliary disorders	Increased transaminases (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. rash, pruritus, urticaria)	Alopecia, photosensitivity reactions
Musculoskeletal, connective tissue and bone disorders		Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness), muscle cramps, myopathy, increased creatine	

		phosphokinase (CPK)	
Reproductive system and breast disorders		Sexual dysfunction	
Investigations	Increased blood homocysteine level **	Increased blood creatinine	Increased blood urea

* In the FIELD-study, a randomised placebo-controlled 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: 1,0 % [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 level in patients treated with fenofibrate was 6,5 µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.

In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during post-marketing use of LIPANTHYL 200 mg. A precise frequency cannot be estimated from the available data and is therefore classified as “not known”.

- Respiratory, thoracic and mediastinal disorders: interstitial lung disease
- Musculoskeletal, connective tissue and bone disorders: rhabdomyolysis

- Hepatobiliary disorders: jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic)
- Skin and subcutaneous tissue disorders: severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- General disorders and administration site conditions: fatigue.

Glucose tolerance should be monitored.

Gallstones have occasionally been reported during LIPANTHYL 200 mg treatment, but any causal relationship remains inconclusive.

Episodes of hepatitis have been reported less frequently.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LIPANTHYL 200 mg is important. It allows continued monitoring of the benefit/risk balance of LIPANTHYL 200 mg. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Only anecdotal cases of fenofibrate overdosage have been received. In most cases no overdose symptoms were reported.

No specific antidote is known. If overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.5 – Serum cholesterol reducers

Pharmacotherapeutic group: Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.

ATC code: C10 AB 05.

Fenofibrate reduces elevated cholesterol as well as elevated triglyceride levels in type lla and llb, type IV and diet-resistant type lll hyperlipidaemia. The reduction of cholesterol and triglyceride levels varies according to initial levels. The greatest reduction occurs in patients with major forms of hyperlipidaemia. The onset of the hypotriglyceridaemic effect precedes the hypocholesterolaemic effect of LIPANTHYL 200 mg. The maximum hypocholesterolaemic effect of LIPANTHYL 200 mg is obtained only after treatment of a period of at least three months.

5.2 Pharmacokinetic properties

Absorption: Maximum plasma concentrations (C_{max}) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. The absorption of fenofibrate is increased when administered with food.

Distribution: Fenofibric acid is strongly bound to plasma albumin (more than 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. Fenofibrate is excreted mainly in the urine. Practically all fenofibrate is eliminated

within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronoconjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified. Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that fenofibrate does not accumulate. Fenofibric acid is not eliminated during haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Pregelatinised starch

Sodium laurilsulfate

Crospovidone

Magnesium stearate.

Composition of the capsule shell:

Gelatine

Titanium dioxide (E171)

Red iron oxide (E172)

Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place and protect from light.

6.5 Nature and contents of container

Blister packs of 2 x 15 capsules.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

30/7.5/0494

9. DATE OF FIRST AUTHORISATION

18 June 1999

10. DATE OF REVISION OF TEXT

NAME AND ADDRESS OF MANUFACTURER

Recipharm Fontaine

Rue de Protes

21121 Fontaine les Dijon

France

Country	Product	Strength	Registration number	Scheduling status
Botswana	Lipanthyl 200	200 mg	Not on the current Blue Book	2
Mauritius	Lipanthyl	200 mg	R6130/02/14	Prescription
Namibia	Lipanthyl	200 mg	10/7.5/0333	NS2