Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipantil Micro 200mg capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200mg fenofibrate

Excipient: Lactose Monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Product imported from the UK:
Orange, hard gelatin capsules, size 1, containing a whitish powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lipantil Micro 200mg capsules, hard is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:
- Treatment of 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.

4.2 Posology and method of administration

Posology

Adults
In adults, the recommended initial dose is 200mg daily administered as 1 x 200mg capsule.
Lipantil Micro 200mg should always be taken with food, because it is less well absorbed from an empty stomach.
Dietary measures instituted before therapy should be continued.
Elderly patients
In elderly patients without renal impairment, the normal adult dose is recommended.
Patients with Renal Impairment
In renal dysfunction, the dosage may need to be reduced depending on the rate of creatinine clearance, for example:

Creatinine clearance (ml/min)	**Dosage***
20-60	Two 67mg capsules
10-20	One 67mg caplsule

*Lipantil Micro 67mg should be used in this case.

Hepatic disease
Patients with hepatic disease have not been studied.
Method of administration: Capsules should be swallowed whole with water

4.3 Contraindications

Lipantil® Micro 200 mg is contra-indicated in patients with:
- hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality e.g. persistent elevations in serum transaminases),
- severe liver or renal dysfunction,
- children (age below 18 years),
- hypersensitivity to the active substance or to any of the excipients,
- known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen,
- gallbladder disease,
- chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.

4.4 Special warnings and precautions for use

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 recommended if fenofibrate is combined with other drugs.

Liver function: Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminases should be monitored every three months during the first twelve months of treatment and thereafter periodically. Treatment should be discontinued if ASAT (SGOT) and ALAT (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 are 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.). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation resulting in the obstruction of the common bile duct.

Muscle: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. 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 fenofibrate should be stopped.

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, 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 muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

Renal function: In renal dysfunction, the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance (see Section 4.2). Dose reduction should be considered in elderly patients with impaired renal function. Treatment should be interrupted in case of an increase in creatinine levels> 50% ULN (upper limit of normal). It is recommended that creatinine is measured during the first three months after initiation of treatment and thereafter periodically (for dose recommendations, see section 4.2 Posology and method of administration).

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

This medicinal product contains lactose. Therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Oral Anti-coagulants
Fenofibrate enhances oral anti-coagulant effect and may increase risk of bleeding.
In patients receiving oral anti-coagulant therapy, the dose of anti-coagulant should be reduced by about one-third at the commencement of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. Therefore, this combination is not recommended.

Cyclosporin
Concomitant administration of fenofibrate (200mg once daily) and cyclosporin did not significantly alter steady-state pharmacokinetic parameters of cyclosporin in heart transplantation patients. However, some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA Reductase Inhibitors or Other Fibrates
The risk of serious muscle toxicity is increased if fenofibrate 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).

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.

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 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.

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 recommended if fenofibrate is combined with other drugs.
In vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. It is therefore recommended that fenofibrate should not be administered to pregnant women or to breast-feeding women.

4.7 Effects on ability to drive and use machines

Lipantil Micro 200 mg, capsule has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported ADRs during fenofibrate therapy are digestive, gastric or intestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n=2344) 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**	**Very rare <1/10,000 incl. isolated reports**	**Not known[a]** **(cannot be estimated from the available data)**
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased		
Immune system disorders			Hypersensitivity		
Nervous system disorders		Headache	Fatigue and vertigo		
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*			
Respiratory, thoracic and mediastinal disorders					Interstitial pneumopathies
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence) moderate in severity	Pancreatitis*			
Hepatobiliary disorders	Transaminases increased (see section 4.4)	Cholelithiasis	Hepatitis (see section 4.4)		Jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic, etc).
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. rashes, pruritus, urticaria)	Alopecia Photosensitivity reactions		
Musculoskeletal, connective tissue and bone disorders		Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)			Rhabdomyolysis
Reproductive system and breast disorders		Sexual dysfunction			
Investigations		Blood creatinine increased	Blood urea increased		

* In the FIELD-study, a randomized 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=0.0222) 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).

[a] In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of Lipantil Micro 200mg. 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.

4.9 Overdose

Only anecdotal cases of fenofibrate overdosage have been received. In the majority of 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

Pharmacotherapeutic group
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
ATC Code: C10 AB 05

The lipid-lowering properties of fenofibrate seen in clinical practice have been explained in vivo in transgenic mice and in human hepatocyte cultures by 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 Apoprotiens A-I, A-II and of HDL cholesterol.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) 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 the small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

During clinical trials with fenofibrate total cholesterol is reduced by 20 to 25%, triglycerides by 40 – 50% and HDL cholesterol is increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 30%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk.

Patients with raised levels of fibrinogen and Lp(a) have shown significant reductions in these measurements during clinical trials and fenofibrate.

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. However, the possible beneficial and adverse long-term consequences of fibrates used in the hyperlipidaemias are still the subject of scientific discussion.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. 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 (≤34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥204 mg/dl or 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.

Results of the Diabetes Atherosclerosis Intervention Study (DAIS) showed that fenofibrate significantly reduces the angiographic progression of focal coronary atherosclerosis in patients with type 2 diabetes and hyperlipoproteinaemia. DAIS was a double-blind, randomised, placebo-controlled study in 418 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, HDL cholesterol 1.03 mmol/L). Treatment with fenofibrate for an average of 38 months resulted in a significant reduction of the progression of the focal coronary artery lesions assessed by quantitative coronary angiography by 40%.

Regression of xanthomata has been observed during fenofibrate therapy.

In addition, fenofibrate has a uricosuric effect.

5.2 Pharmacokinetic properties

The absorption of fenofibrate in the gastrointestinal tract is increased when taken with food. Steady-state plasma concentration lies in the range of 10 to 15 μg/ml during a total daily dosage of 200mg of micronised fenofibrate.

After oral administration, fenofibrate is rapidly hydrolised 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%) and can displace antivitamin K compounds from the protein binding sites with a potential for increasing their anti-coagulant effect.

Peak plasma concentration occurs after a mean period of 5 hours following administration.
The plasma half-life of elimination of fenofibric acid is approximately 20 hours.
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 (9 to 11%) and its derived glucuronoconjugate.

Kinetic studies after administration of repeated doses show the absence of accumulation of the product.

Fenofibric acid is not eliminated during haemodialysis.

5.3 Preclinical safety data

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.
Studies on the mutagenicity of fenofibrate have been negative.
In rats and mice, liver tumours have been found at high dosages which are attributable to peroxisome proliferation. 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.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses. No sign of any effect on fertility has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients
Lactose Monohydrate
Magnesium Stearate
Pregelatinised maize starch
Sodium laurilsulfate
Crospovidone

Capsule Shell
Gelatin
Titanium dioxide (E171)
Ferrous oxide (E172)
Erythrosine (E127)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Pack sizes: 28 capsules in blister (PVC/Aluminium) contained in an over labelled outer carton

6.6 Special precautions for disposal and other handling

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

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/229/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 2009

10 DATE OF REVISION OF THE TEXT

August 2012