Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipantil Micro 67mg capsules**,** hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 67mg fenofibrate.

Excipients with known effect: Each capsule contains 33.8 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Yellow hard gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lipantil Micro 67mg 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

Response to therapy should be monitored by determination of serum lipid values. If an adequate response has not been achieved after several months (e.g. 3 months), complementary or different therapeutic measures should be considered.

Posology:

Adults

The recommended dose is 200mg daily administered as three capsules Lipantil Micro 67mg capsules.

The dose can be titrated up to 267mg daily administered as 4 capsules Lipantil Micro 67mg if required.

Special populations

Geriatric population:

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

Renal impairment:

Dosage reduction is required in patients with renal impairment (creatine clearance <60mL/min):

Creatinine clearance (ml/min)	Dosage
20 - 60	One 67mg capsules
10 - 20	None

In patients with severe renal dysfunction , fenofibrate should not be used (see section 4.3 Contra-indications)

Hepatic impairment
Lipantil Micro 67mg capsules is not recommended for use in patients with hepatic impairment due to the lack of data.
Paediatric population:

The safety and efficacy of fenofibrate in children have not yet been established. Only limited paediatric data are available (see section 5.1). Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years.

Method of administration: Capsules should be swallowed whole during a meal.

4.3 Contraindications

- hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality)
- known gallbladder disease
- severe renal dysfunction
- chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia
- known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidemia:
Secondary cause of hyperlipidemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is considered. 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).

Liver Function:
Increases in transaminase levels have been reported in some patients. It is recommended that transaminase levels are 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 therapyshould 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, 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 with obstruction of the common bile duct.

Muscle: Muscle toxicity, including rare cases of rhabdomyolysis, with or without renal failure 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. 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. 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. 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 HMG-CoA reductase inhibitor should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular diseaseand with a close monitoring of potential 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 Posology and method of administration). 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).

Excipients:

As this medicinal product contains lactose. Therefore patients with rare hereditary problems of galactose intolerance, 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. It is recommended that the dose of anti-coagulant is reduced by about one-third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Cyclosporin: 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 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).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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. Therefore, Lipantil Micro 67 mg should only be used during pregnancy after a careful benefit/risk assessment.

Lactation:

It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore fenofibrate should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Lipantil Micro 67 mg, 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**
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)*		
Gastrointestinal	Gastrointestinal signs and symptoms (abdominal	Pancreatitis*		

disorders	pain, nausea, vomiting, diarrhoea, flatulence)			
Hepatobiliary disorders	Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis	
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)		
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 = 0.022) 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 addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of Lipantil Micro 67mg. 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 multiforma, Stevens-Johnson syndrome, toxic epidermal necrolysis)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

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 an overdose is supsected, 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

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation Peroxisome Proliferator Activated Receptor type α (PPARα). Through activation of PPARα, 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 and A-II.

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 A-I and A-II.

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 for coronary heart disease.

During clinical trials with fenofibrate total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, 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 A-I, all of which are markers of atherogenic risk.

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 prespecified 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%.

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

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.

A uricosuric effect has been demonstrated for fenofibrate leading to average reductions in uric acid levels of approximately 25%.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.
Limited paediatric data are available. The effects of fenofibrate in dyslipidemic children have been studied in two small clinical trials and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving fenofibrate for 1 to 11 years. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of fenofibrate in dyslipidemic children.

Adverse events similar to those observed in adults have been reported in children: leucopenia, liver function test adnormal, rhabdomyolysis, renal failure, hepatitis, jaundice, myositis and rhabdomyolysis.

Overall, the safety and efficacy of fenofibrate in children and adolescents have not yet been established (see section 4.2)

5.2 Pharmacokinetic properties

Absorption:

Maximum plasma concentrations (Cmax) 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 administeredwith food.

Distribution:

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

Metabolism and excretion:

After oral administration, fenofibrate is rapidly hydrolised by esterases to the active metabolite fenofibric acid.

No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

The product 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 glucuronoconjugate.

In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

Kinetic studies following the administration a single dose and continuous treatment have demonstrated that the drug does not accumulate.
Fenofibric acid is not eliminated during haemodialysis.

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

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 (E 171)
Quinoline yellow (E 104)
Erythrosine (E 127).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Pack sizes: 28, 30, 90 and 100 capsules in blister (PVC/aluminium).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

BGP Products Ltd
Abbott House
Vanwall Business Park
Vanwall Road
Maidenhead SL6 4XE
UK

8 MARKETING AUTHORISATION NUMBER

PA2007/012/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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