SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lipantil® Micro 200 mg, capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg fenofibrate.
Excipients with known effect: each capsule contains:
-101 mg of lactose monohydrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ochre, hard gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lipantil® Micro 200mg 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

Dietary measures initiated before therapy should be continued. 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 200 mg daily administered as one capsule of Lipantil Micro 200mg.
The dose can be titrated up to 267 mg daily administered as one capsule of Lipantil Micro 267 mg or 4 capsules of Lipantil Micro 67 mg, if required. This maximum dose is not recommended in addition to a statin.

Special populations

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 < 60 mL/min/1.73 (see Patients with renal impairment).

Patients with renal impairment:
Fenofibrate should not be used if severe renal impairment, defined as eGFR <30 mL/min per 1.73 m^2, is present. If eGFR is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 100 mg standard or 67 mg micronized once daily. If, during follow-up, the eGFR decreases persistently to <30 mL/min per 1.73 m^2, fenofibrate should be discontinued.

Hepatic impairment:
Lipantil Micro 200 mg 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 and adolescents younger than 18 years has not been established. No data are available. 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 insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2),
- 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 causes 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. Secondary cause of hypercholesterolemia related to pharmacological treatment can be seen with diuretics, β-blocking agents, estrogens, progestogens, combined oral contraceptives, immunosuppressive agents 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 function:
As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 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, 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, 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 a 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 function:
Lipantil Micro 200 mg is contraindicated in severe renal impairment (see section 4.3).

Lipantil Micro 200 mg should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate is 30 to 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 for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.
During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 μmol/L 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 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.

Excipients:
As this medicinal product contains Lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

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.

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.

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 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
In common with other fibrates, fenofibrate induces microsomal mixed-function oxidases involved in fatty acid metabolism in rodents and may interact with drugs metabolised by these enzymes.

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 200 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.

Fertility: Reversible effects on fertility have been observed in animals (see section 5.3). There are no clinical data on fertility from the use of Lipantil Micro 200 mg.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

The most commonly reported ADRs during Lipantil 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		
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*		
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	
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 homocysteine level increased**	Blood creatinine increased	Blood urea increased	

* In the FIELD-study, a randomized 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 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 % [48/4900 patients] versus fenofibrate 1.4% [67/4895 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 postmarketing use of Lipantil. 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

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 directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

Lipantil Micro 200 is a formulation containing 200mg of micronised fenofibrate; the administration of this product results in effective plasma

concentrations identical to those obtained with 3 capsules of Lipantil Micro 67 containing 67mg of micronised fenofibrate.

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type α (PPARα). Through activation of PPARα, fenofibrate increases lipolysis and elimination of atherogenic 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.

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.

Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which epidemiological studies have correlated with a decrease in atherogenic risk. Apolipoprotein-A and apolipoprotein-B levels are altered in parallel with HDL and LDL and VLDL levels respectively.

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

Plasma uric acid levels are increased in approximately 20% of hyperlipidaemic patients, particularly in those with type IV disease.

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.

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.

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.

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 administered with 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 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 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 the drug does not accumulate.

Fenofibric acid is not eliminated during haemodialysis.

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

5.3 Preclinical safety data

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I -slow oxidative- myofibres) and cardiac degeneration, anaemia and decreased body weight were seen. No skeletal toxicity was noted at doses up to 30 mg/kg (approximately 17-time the exposure at the human maximum recommended dose (MRHD). No signs of cardiomyotoxicity were noted at an exposure about 3 times the exposure at MRHD. Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated for 3 months. No gastro-intestinal lesions were noted in that study at an exposure approximately 5 times the exposure at the MRHD.

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.

Reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat-dose toxicity study with fenofibric acid in young dogs. However no effects on fertility were detected in non-clinical reproductive toxicity studies conducted with fenofibrate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: lactose monohydrate, pregelatinised starch, sodium laurilsulfate, crospovidone and magnesium stearate.
Composition of the capsule shell: gelatin, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172).

6.2 Incompatibilities

No effect noted to date.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 30°C.

6.5 Nature and contents of container

Pack of 10,28,30 capsules in blisters (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

Viatris Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/00042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/03/2007

10 DATE OF REVISION OF THE TEXT

29/09/2025