Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipantil Supra 215 mg, film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 215.0 mg fenofibrate.
Excipients with known effect: each tablet contains:
- 134.4 mg of lactose monohydrate
- 2.28 mg of Sunset yellow lake (E110)
- 5.31 mg of Allura red AC lake (E129)
- 0.6 mg of Soybean lecithin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.
Orange-red, oblong, film-coatedtablet engraved “215” on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lipantil Supra 215mg 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.

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 initial dose is 160 mg daily administered as one Lipantil Supra 160mg tablet
The dose can be titrated up to 215 mg daily administered as one Lipantil Supra 215 mg tablet.
Patients currently taking one 267mg capsule can be changed to one Lipantil Supra 215 mg tablet without further dose adjustment.

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 m2, is present.
If eGFR is between 30 and 59 mL/min per 1.73 m2, 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 m2, fenofibrate should be discontinued.

Hepatic impairment:

Lipantil Supra 215 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:
Tablet should be swallowed whole during a meal.

4.3 Contraindications

- Hepatic insufficiency (including biliary cirrhosis and unexplained persistant liver function abnormality),
- Known gallbladder disease,
- Severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m2),
- 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

In addition, Lipantil Supra 215 mg should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions.

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidemia:
Secondary cause of hyperlipidemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephritic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is considered. For hyperlipidaemic patients taking estrogens 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 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 Contraindications and Undesirable effects). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with the obstruction of the common bile duct.

Muscle:
Muscle toxicity, including rare cases of rhabdomyolysis, with and without renal failure, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in case 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 case of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with an HMG-CoA reductase inhibitor should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity.

Renal function:
Lipantil Supra 215mg is contraindicated in severe renal impairment (see section 4.3).

Lipantil Supra 215mg 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 m2 (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.
Lipantil Supra 215 mg contains "Sunset yellow lake (E110)" and "Allura red AC lake (E129)"; these excipients may cause allergic reactions.
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 anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase 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 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 and 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 shown embryo toxic effects at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, Lipantil Supra 215mg film-coated tablet should only be used during pregnancy after a careful benefit/risk assessment.
Breast feeding:
It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the breastfed newborns/infants 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 Supra 215mg.

4.7 Effects on ability to drive and use machines

Lipantil Supra 215 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		
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 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 postmarketing use of Lipantil Supra 215 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 multiforma, 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 via HPRA Pharmacovigilance, Website: www.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 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 Triglycerides Reducers / Fibrates.
ATC code: C10 AB 05
Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα).
Through activation of PPARα, fenofibrate increases the 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 is 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.
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.

5.2 Pharmacokinetic properties

Lipantil Supra 215 mg is a film-coated tablet containing 215 mg of micronised fenofibrate.

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 administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate.Fenofibric acid is not eliminated by 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, anemia 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 sign 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 in carcinogenicity studies, which are attributable to peroxisome proliferation. These changes are specific to rodents and have not been observed in other species at comparable dose levels. 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

Tablet core:
Sodium laurilsulfate
Lactose monohydrate
Povidone
Crospovidone
Microcrystalline cellulose
Silica colloidal anhydrous
Sodium stearyl fumarate

Film-coating:
Opadry :
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Soybean lecithin
Xanthan gum
Sunset yellow lake (E110)
Allura red AC lake (E129)
Indigo carmine lake (E132)

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

Thermoformed blister strips (clear PVC/PE/PVDC sealed with aluminium complex) of 10 or 14 tablets each.
Boxes of 28, 30, 56 and 100 tablets.
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

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

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