Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipantil®Supra 160 mg, film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160.0 mg fenofibrate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

White, oblong, film-coated tablets engraved “160” on one side and “Fournier logo” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypercholesterolaemia and hypertriglyceridaemia alone or combined (types IIa, IIb, IV dyslipidaemias, as well as types III and V dyslipidaemias although only a few patients have been treated during clinical trials) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk factors.

The treatment of secondary hyperlipoproteinaemias is indicated if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).

Dietary measures initiated before therapy should be continued.

4.2 Posology and method of administration

Posology:

Adults: The recommended dose is one tablet containing 160 mg fenofibrate taken once daily. Patients currently taking one *Lipantil Micro 200 mg* capsule can be changed to one Lipantil Supra 160 mg tablet without further dose adjustment.

Elderly patients: The usual adult dose is recommended.

Patients with renal impairment: Dosage reduction is required in patients with renal impairment. The use of dosage forms containing a lower dose of active ingredient (67 mg micronised fenofibrate capsules or 100 mg standard fenofibrate capsules) is recommended in these patients.

Children: The use of the 160 mg dosage form is contraindicated in children.

Hepatic disease: Patients with hepatic disease have not been studied.

Dietary measures initiated before therapy should be continued.
If after several months of fenofibrate administration (e.g. 3 months) serum lipid levels have not been reduced

satisfactorily, complementary or different therapeutic measures should be considered.

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

4.3 Contraindications

- Hepatic insufficiency (including biliary cirrhosis),
- Renal insufficiency,
- Children,
- Hypersensitivity to fenofibrate or any component of this medication,
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen,
- Gallbladder disease.
- Chronic or acute pancreatitis with the exception of acture pancreatitis due to severe hypertriglyceridemia.

Use during pregnancy and lactation: *see section 4.6.*

Lipantil Supra 160 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

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 be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

Pancreatitis: 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 hypertriglyceridemia, 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.

For hyperlipidaemic patients taking estrogens or contraceptives containing oestrogens 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.

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 measurement may be considered during the first three months after initiation of treatment.

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. Therefore, this combination is not recommended.

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 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.).*

4.6 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. Therefore, Lipantil Supra 160mg film-coated tablet should only be used during pregnancy after a careful benefit/risk assessment.

There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Consequently, Lipantil Supra 160mg film-coated tablet should not be used in nursing mother.

4.7 Effects on ability to drive and use machines

No effect noted.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1,000); Very rare (<1/10,000), including isolated reports.

Gastrointestinal disorders:
Common: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity
Uncommon: Pancreatitis *

Hepato-biliary disorders:
Common: Moderately elevated levels of serum transaminases *(see Special precautions for use)*
Uncommon: Development of gallstones
Very rare: episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable *(see Special warnings)*

Skin and subcutaneous tissue disorders:
Uncommon: rashes, pruritus, urticaria or photosensitivity reactions
Rare: alopecia

Very rare: cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sunlamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal, connective tissue and bone disorders:
Rare: diffuse myalgia, myositis, muscular cramps and weakness
Very rare: rhabdomyolysis

Cardiovascular system
Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis) *.

Blood and lymphatic system disorders:
Rare: decrease in haemoglobin and leukocytes

Nervous system disorders:
Rare: sexual asthenia

Respiratory, thoracic and mediastinal disorders:
Very rare: interstitial pneumopathies

Investigation:
Uncommon: Increases in serum creatinine and urea.

* 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).

4.9 Overdose

No case of overdosage has been 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

Pharmacotherapeutic group: 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 atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

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 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 AI, all of which are markers of atherogenic risk.

Because of its significant effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus.

At the present time, no results of long-term controlled clinical trials are available to demonstrate the efficacy of fenofibrate in the primary or secondary prevention of atherosclerotic complications.

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.

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.

5.2 Pharmacokinetic properties

Lipantil Supra 160 mg is a film-coated tablet containing 160 mg of micronised fenofibrate and is suprabioavailable (larger bioavailability) compared to the previous formulations.

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%).

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

Metabolism and excretion: No unchanged fenofibrate can be detected in the plasma where the principal metabolite is fenofibric acid. 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 glucuronide conjugate. 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 by haemodialysis.

5.3 Preclinical safety data

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

Studies on 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

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

Composition of the coating
Opadry®: polyvinyl alcohol, titanium dioxide (E171), talc, soybean lecithin, xanthan gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 30^{o}C

6.5 Nature and contents of container

Thermoformed blister strips (PVC/PE/PVDC) of 10 or 14 tablets each.
Boxes of 10, 20, 28, 30, 50, 84, 90, 98 and 100 tablets.
Hospital pack sizes: 280 (10 x 28) and 300 (10 x 30) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Solvay Healthcare Limited
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West End
Southampton
SO18 3JD
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0108/030/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 September 2000

Date of last renewal: 04 November 2004

10 DATE OF REVISION OF THE TEXT

June 2007