NAME OF THE MEDICINAL PRODUCT
Fenofibrate (Lipanthyl NT) 145 mg, film-coated tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION
Fenofibrate (Lipanthyl NT) 145 mg: Each tablet contains 145.0 mg fenofibrate (nanoparticles).
Excipients with known effect: each tablet contains:
- 132.00 mg of Lactose monohydrate
- 145.00 mg of Sucrose
- 0.50 mg of Soybean lecithin

PHARMACEUTICAL FORM
Fenofibrate (Lipanthyl NT) 145 mg: White, oblong, film-coated tablets engraved “145” on one side and “Fournier logo” on the other side.

CLINICAL PARTICULARS
Therapeutic indications
Hypercholesterolemia and hypertriglyceridemia alone or combined (types IIa, IIb, IV dyslipidemias, as well as types III and V dyslipidemias) 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 such as hypertension and smoking.

The treatment of secondary hyperlipoproteinemias is indicated if the hyperlipoproteinemia persists despite effective treatment of the underlying disease (e.g. dyslipidemia in diabetes mellitus).

Appropriate dietary measures initiated before therapy should be continued.

Targeted indication:
Diabetic retinopathy: Fenofibrate (Lipanthyl NT) is indicated to reduce the progression of diabetic retinopathy in patients with type 2 diabetes.

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
Fenofibrate (Lipanthyl NT) 145 mg:
The recommended dose is one tablet containing 145 mg fenofibrate taken once daily. Patients currently taking one 200 mg capsule (or one 160 mg tablet) can be changed to one 145 mg fenofibrate tablet without further dose adjustment.

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. In mild to moderate chronic kidney disease, start with one capsule of 100 mg standard or 67 mg micronized once daily. In patients with severe chronic kidney disease, fenofibrate is not recommended.

**Hepatic impairment**
Fenofibrate (Lipanthyl NT) is not recommended for use in patients with hepatic impairment due to the lack of data.

**Pediatric population**
Fenofibrate (Lipanthyl NT) 145 mg:
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 pediatric subjects under 18 years.

**Method of administration:**
Fenofibrate (Lipanthyl NT) 145 mg: Film-coated tablet may be given at any time of the day, with or without food (see section Pharmacokinetic properties). Tablet should be swallowed whole with a glass of water.

**Contraindications**
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality)
- Known gallbladder disease
- Severe chronic kidney disease
- 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(s) or to any of the excipients listed in section List of excipients

In addition, Fenofibrate (Lipanthyl NT) 145 mg Film-coated tablet should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to risk of hypersensitivity reactions.

**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 hyperlipidemic patients taking estrogens or contraceptives containing estrogen it should be ascertained whether the hyperlipidemia is of primary or secondary nature (possible elevation of lipid values caused by oral estrogen).

**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 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 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 case of hypoalbuminemia 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 (level 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 HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity.

Renal function
Treatment should be interrupted in case of an increase in creatinine levels > 50% (of upper limit of normal). It is recommended that creatinine is measured during the first 3 months after initiation of treatment and thereafter periodically (for dose recommendations see section Posology and method of administration).

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

For 48 mg / 145mg fenofibrate tablets only:
As this medicinal product contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interactions 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 Special warnings and precautions for use).

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 metabolized drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

**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 Preclinical safety data). The potential risk for humans is unknown. Therefore, Fenofibrate (Lipanthyl NT) 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.

**Effects on the ability to drive and use machines**

Fenofibrate (Lipanthyl NT) has no or negligible influence on the ability to drive and use machines.

**Undesirable effects**

The most commonly reported ADRs during Fenofibrate (Lipanthyl NT) 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:

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Common $\geq 1/100$, &lt;1/10</th>
<th>Uncommon $\geq 1/1,000$, &lt;1/100</th>
<th>Rare $\geq 1/10,000$, &lt;1/1,000</th>
<th>Very rare $&lt;1/10,000$ incl. isolated reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Hemoglobin decreased</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>White blood cell count decreased</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache</td>
<td>Fatigue and vertigo</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Thromboembolism (pulmonary embolism, deep vein thrombosis)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhea, flatulence)</td>
<td></td>
<td>Pancreatitis*</td>
<td></td>
</tr>
</tbody>
</table>
**PHARMACOLOGICAL PROPERTIES**  
**Pharmacodynamic properties**

Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.  
ATC code: C10 AB 05  
Fenofibrate is a fibrac 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.

### Liver-related Side Effects

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th>Transaminases increased (see section Special warnings and precautions for use)</th>
<th>Cholelithiasis (see section Special warnings and precautions for use)</th>
<th>Hepatitis</th>
</tr>
</thead>
</table>

### Skin and Subcutaneous Tissue Disorders

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Cutaneous hypersensitivity (e.g. rashes, pruritus, urticaria)</th>
<th>Alopecia</th>
<th>Photosensitivity reactions</th>
</tr>
</thead>
</table>

### Musculoskeletal, Connective Tissue and Bone Disorders

<table>
<thead>
<tr>
<th>Musculoskeletal, connective tissue and bone disorders</th>
<th>Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)</th>
<th></th>
</tr>
</thead>
</table>

### Reproductive System and Breast Disorders

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
<th>Sexual dysfunction</th>
<th></th>
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</thead>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Blood creatinine increased</th>
<th>Blood urea increased</th>
</tr>
</thead>
</table>

*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 Fenofibrate (Lipanthyl NT). 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 choledolithiasis (e.g. cholecystitis, cholangitis, biliary colic).
- **Skin and Subcutaneous Tissue Disorders**: severe cutaneous reactions (e.g erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis)

### 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 hemodialysis.
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 hypercholesterolemic 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.

Pharmacokinetic properties

Fenofibrate (Lipanthyl NT) 145 mg, film-coated tablets contain 145 mg of fenofibrate nanoparticles.

Absorption: Maximum plasma concentrations (C_max) occur within 2 to 4 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. Contrarily to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticle formulation is independent from food intake. Therefore, Fenofibrate (Lipanthyl NT) 145 mg may be taken without regard to meals. A food-effect study involving administration of the new 145 mg tablet formulation of fenofibrate to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_max) to fenofibric acid is not affected by food. Absorption: Maximum plasma concentrations (C_max) 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 hydrolyzed 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 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 hemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

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.
PHARMACEUTICAL PARTICULARS

List of excipients

Core:
Sucrose
Lactose monohydrate
Silicified microcrystalline cellulose
Crospovidone, Hypromellose
Sodium lauril sulphate
Docusate sodium
Magnesium stearate

Coating:
Polyvinyl alcohol
Titanium dioxide (E 171)
Talc
Soybean lecithin
Xanthan gum

Incompatibilities
Not applicable.

Shelf-life
36 months

Special precautions for storage
Store at temperatures not exceeding 25°C

Nature and contents of container
Blister Pack x 10’s (Box of 30’s)

Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by
Fournier Laboratories Ireland Limited
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