SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thylip 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg fenofibrate.

Excipient(s) with known effect:
Each hard capsule contains
- 52 mg sugar spheres, which corresponds to 48 mg of sucrose
- parahydroxybenzoates: not more than 26 micrograms methyl parahydroxybenzoate (E218) and less than 2.6 micrograms propyl parahydroxybenzoate.
- not more than 8.3 micrograms sodium benzoate (E211)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Size 1 hard gelatine capsules, approximately 19 mm long and 7 mm wide, having a yellow cap and a clear transparent body, filled with white to off-white spherical pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] 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 levels.
- 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 one [Invented name] 200 mg capsule once daily.

Special populations
Elderly patients (≥65 years)
No dose adjustment is necessary. The usual dose is recommended, except for impaired renal function with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (see *Patients with renal impairment*).

Patients with renal impairment
Fenofibrate should not be used in patients with severe renal impairment, defined as eGFR <30 mL/min/1.73 m^2.
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 micronised fenofibrate once daily.
During follow-up, if the eGFR decreases persistently to <30 mL/min per 1.73 m^2, fenofibrate should be discontinued.

Hepatic impairment
[Invented name] 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 persons under 18 years.

Method of administration
The capsule 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 [eGFR] <30 mL/min/1.73 m^2),
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia,
- Known photo allergy 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 hyperlipidaemia
Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is considered. In patients with hyperlipidaemia and using oestrogens or oral contraceptives containing oestrogen, it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of blood lipid values caused by oral oestrogen use).

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 and ALT 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 from 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.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, cramps and muscular weakness and/or marked increases in creatinine phosphokinase levels (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 concomitant use of fenofibrate with an HMG-CoA reductase inhibitor should be reserved to patients with serious combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and a close monitoring of signs of muscle toxicity.

Renal function
[Invented name] is contraindicated in severe renal impairment (see section 4.3). [Invented name] should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated eGFR 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.
In 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

Sugar spheres
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Parahydroxybenzoates
This medicine contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Sodium benzoate
This medicine contains not more than 8.3 micrograms sodium benzoate (E211) in each capsule.

Sodium
This medicine contains less than 1 mmol (23 mg) sodium per capsule, 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 the risk of bleeding. It is recommended that the dose of anticoagulant therapy is reduced by about one-third at the beginning of the treatment and then gradually adjusted if necessary, according to INR (International Normalised Ratio) levels.

Cyclosporin
Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. Renal function in 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 in co-administration. If HDL cholesterol is too low, treatment with either of the medicines should be stopped.

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 window should be carefully monitored, and dose adjustment of these drugs may be necessary.

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 maternally toxic doses (see section 5.3). The potential risk for humans is unknown. [Invented name] 200 mg should only be used during pregnancy after a careful benefit/risk assessment.

Breastfeeding
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 [Invented name].

4.7 Effects on ability to drive and use machines

[Invented name] has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported undesirable effects 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
Blood and lymphatic system disorders			Haemoglobin decreased Leukocyte 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	Transaminase levels increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity reactions (e.g. rash, pruritus, urticaria)	Alopecia Photosensitivity reactions
Musculoskeletal and connective tissue 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 randomised 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 post-marketing use of [Invented name] 200 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: Serious cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).

- General disorders and/or 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 the national reporting system listed in Appendix V.

4.9 Overdose

Only anecdotal cases of overdosage have been reported. In most 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

Pharmacotherapeutic group: Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates
ATC code: C10AB05

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 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 the number of small dense LDL particles, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

In 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 patients with elevated cholesterol levels, LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol / HDL cholesterol, LDL cholesterol / HDL cholesterol, or Apo B / 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 it has 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 randomised 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 elevated levels of fibrinogen and Lp(a) have shown significant reductions in these parameters during fenofibrate therapy. Other inflammatory markers, such as C-reactive protein, are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to an average reduction 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 adrenaline.

5.2 Pharmacokinetic properties

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 hydrolysed 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 glucuronic acid conjugate.

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

Kinetic studies following the administration of a single dose or repeated administration have demonstrated that the drug does not accumulate.

Fenofibric acid is not eliminated during haemodialysis.

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

5.3 Preclinical safety data

In a three-month oral non-clinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscle degeneration (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 times 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 gastrointestinal tract occurred in dogs treated for 3 months. No gastrointestinal 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 effects. 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 studies conducted with fenofibrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sugar spheres
Hypromellose
Sodium laurilsulfate
Dimeticone
Octoxinol
Polysorbate 20
Propylene glycol (E1520)
Sodium benzoate (E211)
Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate
Simeticone
Cetostearyl alcohol
Macrogol cetostearyl ether
Talc

Capsule shell
Gelatine
Sodium laurilsulfate
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[Invented name] are packed in clear transparent PVC-Aluminium blister and are available in blister packs of 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

2care4 Generics ApS
Stenhuggervej 12-14
6710 Esbjerg V
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2023-12-15