SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FEGENOR 140 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fenofibrate..... 140.00 mg

Per one capsule.

Excipient with known effect: Each capsule contains 24.16 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

FEGENOR is indicated as a supplement to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:

- Treatment of a severe hypertriglyceridaemia with or without low HDL cholesterol level.
- 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 levels are not adequately controlled.

4.2. Posology and method of administration

The diet initiated before the treatment must be continued.

The response to the treatment must be monitored by determining the serum lipid concentrations.

If after several months (for example 3 months) of treatment the serum lipid concentrations have not sufficiently decreased, additional or different therapeutic measures must be considered.

Posology

This dosage is reserved exclusively for maintenance treatment, when the cholesterol level is stabilised. It is then possible to recommend a posology of 1 FEGENOR 140 mg capsule per day or 2 FEGENOR 67 mg capsules per day, provided that cholesterolaemia is checked every 3 months.

Return to a posology of 3 FEGENOR 67 mg capsules per day if the lipid values increase again.

Elderly subjects (≥ 65 years old)

No dosage adjustment is necessary. The usual dose is recommended, except in case of patients with renal impairment with an estimated glomerular filtration rate < 60 mL/min/1.73 m² (see Patients with renal impairment).

Patients with renal impairment

The fenofibrate should not be used in case of severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m²).

If the estimated glomerular filtration rate is between 30 and 59 mL/min/1.73 m², the dosage should not exceed 100 mg of standard fenofibrate or 67 mg of micronized fenofibrate once a day.

If during the follow-up the estimated glomerular filtration rate persistently decreases to < 30 mL/min/1.73 m², the fenofibrate treatment must be stopped.

Hepatic impairment

Due to the lack of data, the use of fenofibrate is not recommended in patients with hepatic impairment.

Pediatric population

The fenofibrate safety and efficacy in children and adolescents under 18 years of age have not been established. No data is available. Therefore, the use of fenofibrate is not recommended in children and adolescents under 18 years of age.

Method of administration

The capsule must be swallowed whole during a meal.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hepatic impairment (including biliary cirrhosis and persistent and unexplained liver function abnormalities).
- Known disease of the gallbladder.
- Severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1,73 m²).
- Known phototoxicity or photoallergy reaction during a treatment with fenofibrate or ketoprofen.
- Chronic or acute pancreatitis except acute pancreatitis due to severe hypertriglyceridaemia.
- In combination with the rosuvastatin at a dose of 40 mg (see sections 4.4 and 4.5).

4.4. Special warnings and precautions for use

Secondary causes of hyperlipidaemia

Before considering a treatment with fenofibrate, the secondary causes of hypercholesterolaemia, such as the unbalanced type 2 diabetes, the hypothyroidism, the nephrotic syndrome, the dysproteinaemia, the hepatic cholestasis, the alcoholism must be adequately treated.

A secondary hypercholesterolaemia with a pharmacological treatment may be encountered when taking diuretics, beta-blockers, estrogens, progestins, estrogen-progestin oral contraceptives, immunosuppressive agents, or protease inhibitors. In these cases, it should be ascertained whether the hyperlipidaemia is primary or secondary in nature (possible increase in lipid concentrations caused by the administration of these drugs).

Liver function

As with other lipid-lowering drugs, increased transaminase levels have been observed in the case of a fenofibrate treatment in some patients. In the majority of cases, these elevations were transient, minor, and asymptomatic. It is recommended to check the transaminase levels every 3 months during the first 12 months of treatment and then periodically. A particular attention will be paid to patients who develop increased transaminase levels, and the treatment should be discontinued in the event of increased aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) levels beyond 3 times the upper limit of the normal range. When symptoms indicating hepatitis appear (e.g. jaundice, pruritus), and that this diagnosis has been confirmed by laboratory tests, the treatment with fenofibrate should be stopped.

Pancreas

Pancreatitis has been reported in patients receiving fenofibrate (see sections 4.3 and 4.8). This could be linked to a lack of efficacy in patients with a severe hypertriglyceridaemia, or to a direct effect of the medicinal product, or even to a phenomenon secondary to the formation of lithiasis or bile sludge obstructing the bile duct.

Muscle

Muscle toxicity, including very rare cases of rhabdomyolysis, with or without renal impairment has been reported in case of administration of fibrates or other lipid lowering agents. It can occur with greater frequency in cases of hypoalbuminaemia and pre-existing renal impairment.

Patients with a risk for myopathy or rhabdomyolysis, including those over 70 years of age, or with a personal or family history of hereditary muscle disorders, or an impaired renal function, or a hypothyroidism, or with high consumption of alcohol, are at higher risk of rhabdomyolysis. For these patients, the benefit-risk balance of a fenofibrate treatment should be carefully assessed.

The muscle toxicity should be suspected in patients presenting diffuse myalgia, a myositis, muscle cramps and weakness, and/or marked increase in muscle CPK (levels exceeding 5 times the normal range). In such cases, the 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 muscle disease. Accordingly, co- prescribing fenofibrate with an HMG-CoA reductase inhibitor or another fibrate should be reserved for patients with a severe mixed dyslipidemia and a high cardiovascular risk with no history of muscle disease, and under close monitoring of signs of muscle toxicity. The combination with rosuvastatin at a dose of 40 mg is contraindicated (see sections 4.3 and 4.5).

Renal function

FEGENOR is contraindicated in severe renal impairment (see section 4.3).

FEGENOR should be used with caution in patients with mild to moderate renal impairment. The dosage should be adjusted in patients with an estimated glomerular filtration rate between 30 and 59 mL/min/1,73 m² (see section 4.2).

Reversible increases in serum creatinine levels have been reported in patients receiving fenofibrate in monotherapy or in combination with statins. The increases in serum creatinine were generally stable over time with no evidence of a continuous increase in levels in case of a long-term treatment and tended to return to their initial level after treatment discontinuation.

During clinical studies, 10% of patients had an increase in creatinine greater than 30 µmol/L in relation to its baseline when co-administered with fenofibrate and simvastatin versus 4.4% of patients receiving a statin in monotherapy. 0.3% of patients receiving the combination had a clinically relevant increase in creatinine to values > 200 µmol/L.

The treatment should be discontinued when the creatinine level is above 50% of the upper limit of the normal range. It is recommended to measure the creatinine level during the first 3 months after the initiation of a treatment and periodically thereafter.

Excipients

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 capsule, that is to say essentially 'sodium-free'.

4.5. Interactions with other medicinal products and other forms of interaction

+ Rosuvastatin at a dose of 40 mg

Risk of addition of side effects (dose-dependent) such as rhabdomyolysis. This combination is contraindicated (see sections 4.3 and 4.4).

+ HMG-CoA reductase inhibitors and other fibrates

The risk of serious muscle toxicity is increased if fenofibrate is used in combination with HMG-CoA reductase inhibitors or with other fibrates. This combination should be used with caution, under close monitoring for signs of muscle toxicity (see section 4.4)

+ **Ezetimibe**

Risk of biliary lithiasis by increased biliary excretion of cholesterol.

+ Oral anti-coagulants:

Fenofibrate potentiates the effect of oral anti-coagulants and may increase the risk of bleeding. It is recommended to reduce the dosage of anti-coagulants by a third at the start of treatment and, if necessary, to gradually readjust the dose according to the INR (International Normalized Ratio).

+ Ciclosporin

Severe but reversible cases of renal function impairment have been reported with concomitant administration of fenofibrate and ciclosporin. In these patients, the renal function should be carefully monitored and treatment with fenofibrate discontinued in the event of significant disturbances in biological parameters.

+ Glitazones

Paradoxical and reversible reduction in HDL-cholesterol cases have been reported with concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor the HDL-cholesterol levels if these two medicinal products are combined, and to stop one of the two treatments if the HDL-cholesterol level is too low.

+ Enzymes cytochrome P450

Studies *in vitro* on human liver microsomes showed that fenofibrate and acid fenofibric are not inhibitors of CYP 3A4, CYP 2D6, CYP 2E1 or CYP 1A2 isoforms of the cytochrome (CYP) P450; on the other hand, they are weak inhibitors of CYP 2C19 and CYP 2A6 and weak to moderate inhibitors of CYP 2C9, at therapeutic concentrations.

The patients co-administered with fenofibrate and drugs with a narrow therapeutic window metabolized by CYP 2C19, CYP 2A6, and especially by CYP 2C9 should be carefully monitored and, if necessary, the dosage adjustment of these drugs is recommended.

4.6. Fertility, pregnancy, and lactation

Pregnancy

No data is available on the use of fenofibrate in pregnant women.

The results of animal studies have not revealed any evidence of teratogenic effects. Embriotoxic effects were observed at doses corresponding to those of maternal toxicity (see section 5.3). The potential risk in humans therefore remains unknown.

Therefore, FEGENOR should only be used during pregnancy after a careful assessment of the benefit/risk ratio.

Breast-feeding

There is no information about the passage of fenofibrate and/or its metabolites into breast milk. The risk to 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). No clinical fertility data are available from the use of FEGENOR.

4.7. Effects on ability to drive and use machines

Fenofibrate has none or a negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

The most common undesirable effects reported during the treatment with fenofibrate are digestive, gastric, and intestinal disorders.

The following undesirable effects were observed during placebo-controlled clinical studies (n = 2344) and post-marketing studies[a] at the frequencies listed below:

MedDRA Systems Organs Classes	**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 cases**	**Not known[a] (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Decreased hemoglobin, decreased leucocytes		
Immune system disorders			Hypersensitivity		

Nervous system disorders		Headaches			
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis) *			
Respiratory, thoracic, and mediastinal disorders					Interstitial lung disease[a]
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pains, nauseas, vomiting, diarrhea, and flatulence)	Pancreatitis *			
Hepatobiliary disorders	Increased transaminases (see section 4.4)	Biliary lithiasis (see section 4.4)	Hepatitis		Jaundice, complications of biliary lithiasis[a] (cholecystitis, cholangitis, biliary colic)
Skin and subcutaneous tissue disorders		Skin hypersensitivity (e.g. rash, pruritus, hives)	Alopecia, photosensitivity reactions		Severe skin reactions, e.g. multiform erythema, Stevens-Johnson syndrome, toxic epidermal necrosis)
Musculoskeletal and connective tissue disorders		Muscle disorders (e.g. myalgia, myositis, muscle cramps and weakness)			Rhabdomyolysis [a]
Reproductive system and breast disorders		Sexual dysfunction			
General disorders and administration site conditions					Fatigue[a]
Investigations	Increased blood levels of homocysteine **	Increased serum creatinine	Increased uremia		

* In the FIELD study, a randomized, placebo-controlled study, carried out in 9,795 patients with type 2 diabetes, a statistically significant increase in cases of pancreatitis was observed in patients receiving fenofibrate compared to those receiving placebo (0.8% versus 0.5%; p = 0.031). In this same study, a statistically significant increase in the incidence of pulmonary embolism was reported (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022), as well as an increase statistically non-significant in deep vein thrombosis (placebo: 1.0% (48/4900 patients) versus fenofibrate 1.4% (67/4895 patients); p = 0.074).

** In the FIELD study, the mean increase in blood levels of homocysteine in patients treated with fenofibrate was 6.5 µmol/L and was reversible on discontinuation of treatment. The increased risk of venous thrombotic events may be related to increased homocysteine. The clinical relevance of this observation is not clear.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows a continuous 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: [French] National

Agency for Safety of Medicines and Healthcare Products (ANSM) and network of Regional Pharmacovigilance Centers – Internet site: www.signalement-sante.gouv.fr.

4.9. Overdose

Only isolated cases of fenofibrate overdose have been reported. In the majority of the cases, no symptoms have been reported.

No specific antidote is known. If an overdose is suspected, a symptomatic treatment as well as corrective therapeutic measures should be implemented. Fenofibrate is not hemodialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: hypocholesterolamiants and hypotriglyceridaemiant/fibrate, code ATC: C10AB05.

The fenofibrate is a derivative of the fenofibric acid whose reported effects on the lipid parameters in humans are explained by the activation of Peroxisome Proliferator Activated Receptor alpha (PPAR-α).

By activating the PPAR-α, fenofibrate increases the lipolysis and clearance of the triglyceride-rich atherogenic particles from the plasma by activating the lipoprotein lipase and by reducing the production of apoprotein C III. The activation of PPAR-α also leads to an increase in the synthesis of A I and A II apoproteins.

The above effects of fenofibrate on the lipoproteins lead to a decrease of the low-density fractions (VLDL and LDL) containing the apoprotein B and an increase of the high-density fractions (HDL) containing the A I and A II apoproteins.

In addition, by modulating the synthesis and the catabolism of the VLDL fractions, fenofibrate increases the LDL clearance and reduces the level of small and dense LDLs. The small and dense LDL levels are frequently increased in patients with a risk for coronary disease (Atherogenic Lipid Profile).

In the clinical studies with fenofibrate, the decrease in total cholesterol is 20 to 25%, the decrease in triglycerides is 40 to 55%, and the level of HDL cholesterol increases by 10 to 30%.

In hypercholesterolemic patients in whom the LDL cholesterol levels have decreased by 20 to 35%, the overall effect on cholesterol results in a decrease of the total cholesterol on the HDL cholesterol ratio, of the LDL cholesterol on the HDL cholesterol or the Apo B on the Apo A I, which are all 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.

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, nonfatal 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 pre-specified 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.

Extra-vascular cholesterol deposits (tendinous and tuberous xanthomas) can, under treatment with fenofibrate, be significantly reduced or even disappear completely.

Patients with elevated fibrinogen levels treated with fenofibrate showed a significant decrease of this parameter like those with elevated Lp(a) levels. Other markers of the inflammation, such as the C-Reactive Protein, are lowered during a treatment with fenofibrate.

The uricosuric effect of fenofibrate leading to an average decrease in uric acid of the order of 25% should be an additional benefit for dyslipidaemic patients with hyperuricaemia.

A platelet anti-aggregant effect of fenofibrate was demonstrated in animals and then in man by means of a clinical study. It is manifested by reduced platelet aggregation induced by ADP, arachidonic acid, and epinephrine.

5.2. Pharmacokinetic properties

Absorption

Maximal plasma concentration occurs 4 to 5 hours following the oral administration. For one individual, steady state levels are observed throughout continuous treatments.

The co-administration with food increases the absorption of fenofibrate.

Distribution

Fenofibric acid is highly bound to plasma albumin (over 99%).

Biotransformation

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to fenofibric acid, the active metabolite. Unchanged fenofibrate cannot be detected in serum. Fenofibrate is not a CYP 3A4 substrate. Hepatic microsomal metabolism is not involved.

Elimination

The product is mainly excreted in the urine. Practically all of the product is eliminated in 6 days. Fenofibrate is mainly excreted as fenofibric acid and its derived glucuroconjugate. In elderly patients, the apparent total plasma clearance is not altered.

Kinetic studies after single dose and continuous treatment show the absence of accumulation of the product. Fenofibric acid is not eliminated during haemodialysis.

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

5.3. Preclinical safety data

In a three-month oral non-clinical study in rats with fenofibric acid, the active metabolite of fenofibrate, toxicity was observed for the skeletal muscles (especially those rich in type I muscle fibers - oxidative with slow contraction) and cardiac degeneration, anemia, and decreased body weight. No skeletal toxicity was noted at doses up to 30 mg/kg (approximately 17 times the exposure at the maximum recommended human dose). No evidence of cardiomyotoxicity was observed at an exposure of approximately 3 times the exposure to the maximum recommended dose in humans. Reversible ulcers and erosions in the gastrointestinal tract have occurred in dogs treated for 3 months. No gastrointestinal injury was noted in this study at approximately 5 times the exposure at the maximum recommended human dose.

Mutagenicity studies with fenofibrate were negative. In rats and mice, hepatic tumors have been observed at high doses which have been attributed to a proliferation of peroxisomes. These manifestations are specific to small rodents and have not been observed in other animal species. This is of no consequence for therapeutic use in humans.

Studies in mice, rats and rabbits have shown no teratogenic effects. Embryotoxic effects have been observed at doses around those of maternal toxicity. Prolonged gestation period and difficulties during labor have been observed at high doses.

A reversible hypospermia, a testicular vacuolation, and an ovaries immaturity have been observed in young dogs in a repeat dose toxicity study with fenofibric acid. However, no effect on fertility has been detected in animal reproduction studies performed with fenofibrate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium laurilsulphate, lactose monohydrate, povidone K 30, croscarmellose sodium, sodium starch glycolate (type A), magnesium stearate.

Composition of the capsule shell: gelatine, titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25 °C.

6.5. Nature and contents of container

28, 30 or 90 capsules in blister packs (PVC/Aluminum).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PROVEPHARM
22 RUE MARC DONADILLE
13013 MARSEILLE

8. MARKETING AUTHORISATION NUMBERS

34009 357 600 2 9: 28 capsules in blisters packs (PVC/Aluminum)
34009 357 601 9 7: 30 capsules in blisters packs (PVC/Aluminum)
34009 373 027 1 5: 90 capsules in blisters packs (PVC/Aluminum)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: September 13, 2001

10. DATE OF REVISION OF THE TEXT

November 30, 2020

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS REGARDING PRESCRIPTION AND SUPPLY

List II.