ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FEGENOR 200 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fenofibrate..... 200.00 mg

Per one capsule

Excipient(s) with known effect: 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 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

Posology

In combination with the diet, this medicinal product is taken as long-term symptomatic treatment; its efficacy should be monitored periodically.

Fegenor 200 mg capsules must only be taken as one capsule per day during one of the main meals by patients requiring this form, which is equivalent to 3 Fegenor 67 mg capsules.

When the cholesterol level is normalised, it is recommended to reduce the dosage by using 2 Fegenor 67 mg capsules per day.

Method of administration

Oral use. Swallow the capsule in one dose per day, taken during one of the main meals of the day.

4.3. Contraindications

This medicine must never be prescribed in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- hepatic insufficiency,
- renal insufficiency (see section 4.4),
- known phototoxicity or photoallergy reactions during treatment with fenofibrate or a substance with a similar structure, particularly ketoprofen,
- in combination with **another fibrate** (see section 4.5),
- in children.

This medicine is generally contraindicated in combination with **HMG-CoA reductase inhibitors** (see section 4.5) as well as while breast-feeding (see section 4.6).

4.4. Special warnings and precautions for use

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with fibrates. It can occur with much greater frequency in cases of hypoalbuminaemia.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, painful muscle sensitivity and/or a marked increase in muscle CPK (levels exceeding 5 times the normal range): in such cases the treatment should be stopped.

Furthermore, the risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, (see section 4.5).

This medicinal product contains lactose. Patients with galactose intolerance, Lapp lactase deficiency or a glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.

If, after administration for a period of a few months (3 to 6 months), a satisfactory reduction of serum lipid concentrations is not obtained, additional or different therapeutic methods should be considered.

Generally transient increases have been reported in transaminase levels in some patients. The current state of knowledge appears to justify:

- systematic monitoring transaminase levels every 3 months during the first 12 months of treatment,
- discontinuing therapy if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range.

Where treatment is combined with oral anti-coagulants, increased monitoring of the prothrombin level, expressed as INR, is necessary (see section 4.5).

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

Contraindicated combinations

+ Other fibrates:

Increase risk of side effects involving rhabdomyolysis and pharmacodynamic antagonism between the two molecules.

Combinations not recommended

+ HMG-CoA reductase inhibitors:

Increased risk of side effects involving rhabdomyolysis.

Combinations requiring precautions for use

+ Oral anti-coagulants:

Increase in the effect of oral anticoagulants and risk of bleeding (by displacement of its plasma protein binding).

More frequent monitoring of prothrombin level and INR monitoring. Adjustment of oral anticoagulant dosage during treatment with fenofibrate and 8 days after discontinuation.

The same type of monitoring is essential when switching to another fibrate, as the degree of potentiation can vary from one product to another.

4.6. Fertility, pregnancy and lactation

Pregnancy

The results of animal studies have not revealed any evidence of teratogenic effects.

No malformation or foetotoxic effect has so far been observed in clinical use. However, monitoring pregnant women exposed to fenofibrate is insufficient to exclude all risks.

There is no indication for prescribing fibrates during pregnancy, except for severe hypertriglyceridaemia (> 10 g/L) inadequately corrected through diet and creating the risk of acute maternal pancreatitis.

Breast-feeding

There is no information about the passage of fenofibrate into breast milk. Consequently, prescribing is not recommended during breast-feeding

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Cases of muscle toxicity (diffuse myalgia, painful sensitivity, weakness) as well as exceptional and sometimes severe cases of rhabdomyolysis have been reported, as with other fibrates. They are frequently reversible on discontinuing treatment (see section 4.4).

Other less frequent and moderately intense side effects have also been reported:

- gastric or intestinal digestive disorders involving dyspepsia,
- increased transaminase levels (see section 4.4),
- skin reactions such as rashes, pruritus, urticaria or photosensitivity reactions have been reported rarely. In certain cases, even after several months of use without complications, skin photosensitisation can appear with erythema, papules, vesicles or eczema-like rashes on areas exposed to the sun or artificial UV light (UV lamps).

There are currently no controlled trials to assess the overall long-term side effects, more particularly the risk of biliary lithiasis.

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: [French] National agency for safety of medicines and healthcare products (ANSM) and network of Regional Pharmacovigilance Centres - Internet site: www.signalement-sante.gouv.fr.

4.9. Overdose

Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

The Fegenor capsule dosed with 200 mg of fenofibrate with high bioavailability makes it possible to achieve plasma concentrations identical to those obtained with 3 Fegenor 67 mg capsules.

Fenofibrate can lower cholesterolaemia from 20% to 25% and triglyceridaemia from 40% to 50%.

- The reduction of cholesterolaemia is due to lowering the low-density atherogenic fractions (VLDL and LDL). It improves the distribution of plasma cholesterol by reducing the total cholesterol/HDL cholesterol ratio, increased during atherogenic hyperlipidaemia.
- The relationship between hypercholesterolaemia and atherosclerosis is established, in the same way as the relationship between atherosclerosis and coronary risk. Low HDL levels are associated with increased coronary risk. Increased triglyceride levels are associated with an increase in vascular risk, but it can not be asserted that this relationship is independent. In addition, triglycerides could be implicated in the process of atherogenesis but also of thrombogenesis.
- Extra-vascular cholesterol deposits (tendinous and tuberous xanthomas) can, under effective prolonged treatment (significant reduction in cholesterolaemia), be significantly reduced or even disappear completely.
- An uricosuric effect has been demonstrated in hyperlipidaemic patients, leading to a moderate reduction of about 25% in uricaemia.

- Under fenofibrate, the increase in apolipoproteins A1 and the reduction in apolipoproteins B improve apo. A1/apo. B ratio, which can be considered as an atherogenic risk marker.
- 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 aggregation with ADP, arachidonic acid and epinephrine.
- By activating the Peroxysome Proliferator Activated Receptor alpha (PPAR-α), fenofibrate increases lipolysis and clearance of triglyceride-rich particles from the plasma by activating the lipoprotein lipase and by reducing the production of apoprotein C III.

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 2.3mmol/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.

5.2. Pharmacokinetic properties

Absorption

The unchanged compound is not recovered in the plasma. Fenofibric acid is the major plasma metabolite.

Maximal plasma concentration occurs after a mean period of 5 hours following dosing. Mean plasma concentration is 15 µg/mL for a daily dosage of 1 Fegenor 200 mg capsule or 3 Fegenor 67 mg capsules. For one individual, steady state levels are observed throughout continuous treatments.

Distribution

Fenofibric acid is highly bound to plasma albumin and can displace antivitamin K compounds from the protein binding sites and potentiate their anti-coagulant effect (see section 4.5).

Elimination

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

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.

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

5.3. Preclinical safety data

Not documented.

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), yellow iron oxide (E172), erythrosine (E127).

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 or 30 capsules in blister packs (PVC/Aluminium).

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, FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 353 491 4 9: 28 capsules in blisters packs (PVC/Aluminium).
- 34009 353 492 0 0: 30 capsules in blisters packs (PVC/Aluminium).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/02/2000

Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

04/2019

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List II.