SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FEPATIL 267 mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Fenofibrate ..... 267 mg

Excipients:
Lactose monohydrate (sourced from cow's milk) ..... 129 mg
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard gelatin capsule
Orange-ivory hard capsule filled with white or whitish granules.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
FEPATIL is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:
- Treatment of severe hypertriglyceridemia with or without low HDL cholesterol
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated

4.2. Posology and method of administration
Posology/frequency and duration of administration:
Dietary measures initiated before therapy should be continued. 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.

Adults: The recommended dose is 200 mg daily administered as one capsule. The dose can be titrated up to 267 mg FEPATIL hard capsule.

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

Additional information on special populations
Renal impairment:
In patients with renal impairment, the dose may need to be reduced according to creatinine clearance. Therefore, FEPATIL should not be used in patients with renal impairment.

Hepatic impairment:
Due to lack of clinical data, FEPATIL is not recommended for use in patients with hepatic impairment.

Pediatric 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 pediatric subjects under 18 years.

Geriatric population:
The usual adult dose is recommended for elderly patients without renal impairment.

4.3. Contraindications
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality)
- Known gallbladder disease
- Severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2)
- Chronic or acute pancreatitis other than acute pancreatitis due to severe hypertriglyceridemia
- Phototoxic reaction or known photosensitivity during treatment with fibrates or ketoprofen
- Hypersensitivity to fenofibrate or to any of the excipients (see Section 6.1)

4.4. Special warnings and precautions for use
Secondary causes of hyperlipidemia:
Secondary causes 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. Secondary cause of hypercholesterolemia related to pharmacological treatment can be seen with diuretics, β-blocking agents, estrogens, progestogens, combined oral contraceptives, immunosuppressive agents and protease inhibitors. In these cases it should be ascertained whether the hyperlipidemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic agents).

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 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 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 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 up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (creatine phosphokinase) (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 co-prescription of fenofibrate with a HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and a close monitoring of potential muscle toxicity.

Renal function:
FEPATIL is contraindicated in severe renal impairment (see section 4.3).

FEPATIL should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate 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.

During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 micromol/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 micromol/L.

Treatment should be interrupted when creatinine level is 50% above the upper limit of normal (ULN). It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter (for recommendations on dosage see section 4.2).

For hyperlipidaemic patients taking oestrogens or contraceptives containing oestrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

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

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. In patients receiving oral anti-coagulant therapy, the dose of anti-coagulant should be reduced by about one-third at the commencement of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Ciclosporin:

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. 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 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).
There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.

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

Other:
No proven clinical interactions of fenofibrate with other drugs have been reported, although in vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites. In common with other fibrates, fenofibrate induces microsomal mixed-function oxidases involved in fatty acid metabolism in rodents and may interact with drugs metabolised by these enzymes.

4.6. Pregnancy and lactation
General advice
Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)
No data is present.

Pregnancy
There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects were observed at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, FEPATIL should only be used during pregnancy after a careful benefit/risk assessment.

Lactation
It is unknown whether fenofibrate is excreted in human milk. A risk to the 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). There are no clinical data.

4.7. Effects on ability to drive and use machines
FEPATIL has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects
Fenofibrate is generally well tolerated.
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.

Adverse events are listed in the following order: 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), not known (cannot be estimated from the available data).

MedDRA system organ class	Common	Uncommon	Rare	Very rare, including isolated reports
Blood and lymphatic system disorders			Decrease in hemoglobin and leukocyte count	
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	Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis	
Skin and		Cutaneous	Alopecia	

subcutaneous tissue disorders		hypersensitivity (e.g. Rashes, pruritus, urticaria) **	Photosensitivity reactions	
Musculoskeletal, connective tissue and bone 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 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).

***Skin*: Reactions such as rashes, pruritus, urticaria or photosensitivity reactions; in individual cases (even after many months of uncomplicated use) cutaneous photosensitivity may occur with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sun lamp).

*** In the FIELD study the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 micromol/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 fenofibrate. 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)
-Vertigo
-Skin and subcutaneous tissue disorders: Severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
-General disorders and administration site conditions: Fatigue

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9. 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 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: Cardiovascular system / Lipid modifying agents / Fibrates
ATC Code: C10AB05

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of PPARα (Peroxisome Proliferator Activated Receptor type α). Through activation of PPARα, fenofibrate increases 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.

Because of its effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type II diabetes mellitus.

Epidemiological studies have demonstrated a positive correlation between increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemias forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long–term consequences of drugs used in the management of dyslipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of fenofibrate on cardiovascular morbidity and mortality is as yet unproven.

There is evidence that treatment with fibrates may reduce coronary heart disease events, but fibrates have not been proven to reduce all-cause mortality in primary and secondary prevention of cardiovascular disease.

Studies with fenofibrate consistently show decreases in levels of LDL–cholesterol. HDL–cholesterol levels are frequently increased. Triglyceride levels are also reduced decreased. This results in a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which has been correlated with a decrease in atherogenic risk in epidemiological studies. Apolipoprotein–A and apolipoprotein–B levels are altered in parallel with HDL and LDL and VLDL levels respectively.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.
Plasma uric acid levels are increased in approximately 20 % of hyperlipidaemic patients, particularly in those with type IV phenotype.

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 the 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

General Properties:

Absorption:

Maximum plasma concentrations (C_{max}) occur within 4-5 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. Mean plasma concentration is 15 µg / ml for a daily dosage of 200 mg of micronised fenofibrate.

Distribution:

Fenofibric acid is strongly bound to plasma albumin (more than 99%). It n displace antivitamin K compounds from the protein binding sites and potentiate their anticoagulant effect.

Biotransformation:

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.

Elimination:

The drug is excreted mainly in the urine: Almost all of the drug is eliminated in 6 days. 70 % in 24 hours and 88 % in 6 days, at which time total excretion in urine and faeces reaches 93 %. Fenofibrate is mainly excreted as fenofibric acid and its derived glucuroconjugate.

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

5.3. Preclinical safety data

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (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-time 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 gastro-intestinal tract occurred in dogs treated for 3 months. No gastro-intestinal lesions were noted in that study at an exposure approximately 5 times the exposure at the MRHD.

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 human.

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.

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 toxicity studies conducted with fenofibrate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (sourced from cow's milk)
Crospovidone
Pregelatinised starch
Sodium lauryl sulfate
Hydroxypropylmethyl cellulose, 3 cps
Magnesium stearate

Hard Gelatin Capsule:
Titanium dioxide
Iron oxide red
Iron oxide yellow
Gelatin (bovine origin)
Deionized water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 30°C. Store in the original package in order to protect from moisture.

6.5. Nature and contents of container

Blister made of transparent PVC and aluminum foil is used as the primary packaging material of our product. Blisters are packed in cardboard boxes. It is presented in a cardboard box with 30 capsules or 90 capsules and package leaflet.

6.6. Special precautions for disposal and other handling

No specific requirements.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2022/117

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 19.03.2022
Renewal of the authorization:

10.DATE OF REVISION OF THE TEXT