For the use of Registered Medical Practitioner or a Hospital only

1. NAME OF THE MEDICINAL PRODUCT

EP-Feno 145 mg Tablet

Fenofibrate Tablets 145mg

2. COMPOSITION:

Each tablet contains:

Fenofibrate (Nanonized)…….145 mg

Excipients: Lactose anhydrous, Hypromellose, Sodium Lauryl sulphate, Simethicone emulsion 30%, Croscarmellose sodium, Magnesium stearate.

3. PHARMACEUTICAL FORM

Tablet

EP-Feno 145 mg Tablet is available as white to off-white biconvex oblong tablet, 15.5 x 8.5 mm, embossed "F" on one side and "145" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications:

Hypercholesterolaemia and hypertriglyceridaemia alone or combined (type IIa, IIb, III, IV and V dyslipidaemias) 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 factors such as hypertension and smoking.

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

Dietary measures initiated before therapy should be continued.

EP Feno 145 mg Tablet is indicated for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. EP Feno does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.

4.2. Posology and method of administration

Posology:

Adults: 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.

For hyperlipidaemia indications, 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.

If a patient needs fenofibrate for both hyperlipidemia and diabetic retinopathy indications, only one tablet of fenofibrate 145 mg per day should be taken.

Special population

Geriatric Patients: In elderly patients, without renal impairment, the usual adult dose is recommended.

Renal impairment**:** Dosage reduction is required in patients with renal impairment.

In moderate chronic kidney disease (creatinine clearance 30 to 59 mL/min), and if a low dose is available, start with one capsule of 100 mg standard or 67 mg micronized once daily.

If no low dose is available, then fenofibrate is not recommended.

In patients with severe chronic kidney disease (creatinine clearance < 30ml/min), EP-Feno 145 mg Tablet is contraindicated.

If during follow-up the creatinine clearance decreases persistently to < 30 ml/min, treatment by EP Feno 145 mg Tablet should be terminated.

Hepatic impairment: EP-Feno 145 mg Tablet is not recommended for use in patients with hepatic impairment due to the lack of data.

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 paediatric subjects under 18 years.

Method of administration:

EP-Feno 145 mg tablet may be given at any time of the day, with or without food (see section 5.2 Pharmacokinetic properties). Tablet should be swallowed whole with a glass of water.

4.3. Contraindications:

- Hepatic insuffiency (including biliary cirrhosis and unexplained persistent liver function abnormalities),
- 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 6.1.

4.4. Special warning and precautions for use

Secondary cause of hypercholesterolemia:

Secondary cause of hypercholesterolemia, 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 initiated.

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

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 ASAT (SGOT) and ALAT (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), laboratory tests are to be conducted for verification and discontinuation of fenofibrate therapy may be considered.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate. 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 very rare cases of rhabdomyolysis, 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 old, 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 (levels exceeding 5 times the upper 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 (statins), especially in cases of pre-existing muscular disease. Consequently, the co- prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

Renal function: Treatment should be interrupted in case of an increase in creatinine levels > 50% and ULN (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 4.2 Posology and method of administration).

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

4.5. 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. Therefore, this combination is not recommended.

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 (for dose recommendations, see section 4.4 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 (GYP) 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.

4.6. Fertility, pregnancy and lactation

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 EP-Feno 145 mg tablet.

Pregnancy: There are no adequate and well controlled studies 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 5.3 Preclinical safety data). The potential risk for humans is unknown. Therefore, fenofibrate 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 in nursing mothers.

4.7. Effects on ability to drive and use machines

EP-Feno tablet 145 mg has no influence on the ability to drive and use machines.

4.8. Undesirable effects:

The most commonly reported ADRs during EP-Feno 145 mg Tablet 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:

Very common: ADR ≥ 1/10

- *Investigations*: Blood Homocysteine level increased***

Common: 1/100 ≤ ADR < 1/10

- *Gastrointestinal disorders*: Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhea, flatulence).
- *Hepato-biliary disorders*: transaminases increased (see section 4.4).

Uncommon: 1/1000 ≤ ADR < 1/100

- *Nervous system disorders*: Headache.
- *Vascular disorders:* Thromboembolism (pulmonary embolism, deep vein thrombosis)**
- *Gastrointestinal disorders:* Pancreatitis*
- *Hepatobiliary disorders:* Cholelithiasis (see section 4.4)
- *Skin and sub-cutaneous tissue disorders*: *cutaneous hypersensitivity (e.g.* rashes, pruritus, urticaria*).*
- *Musculoskeletal connective tissue and bone disorders:* Muscle disorders (e.g myalgia, myositis, muscular spasms and weakness).
- *Reproductive system and breast disorders:* Sexual dysfunction.
- *Investigations*: blood creatinine increased.

Rare: 1/10000 ≤ ADR <1/1000

- *Blood and lymphatic system disorders*: haemoglobin decreased, white blood cell count decreased.
- *Immune system disorders:* hypersensitivity.
- *Hepatobiliary disorders:* hepatitis.
- *Skin and sub-cutaneous tissue disorders:* alopecia, photosensitivity reactions.
- *Investigations:* 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).
**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 nonsignificant increase in deep vein thrombosis (placebo: 1.0 % [48/4900 patients] versus fenofibrate 1.4 % [67/4895 patients]; p = 0.074).
*** 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 reporting during clinical trials, the following side effects have been reported spontaneously during postmarketing use of EP-Feno 145 mg Tablet. 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: severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
Nervous system disorders: Fatigue

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 an 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
Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.
ATC code: C10 AB 05

Dyslipidaemia:
Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are medicated via activation of peroxisome proliferator activated receptor a (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.

The above stated effects of Fenofibrate on lipoprotein leads to a reduction in very low and low density fractions (VLDL & LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI &AII

In addition, through modulation of 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 hypercholesterolaemic 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.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

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 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.

<u>Diabetic Retinopathy:</u>

Several mechanisms have been proposed to explain the effects of fenofibrate in proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) in vitro and in rodent models. Fenofibrate was shown to reduce the retinal expression of VEGF, the major angiogenic factor in PDR and to reduce vascular permeability and apoptosis of retinal pigmented epithelium, which contributes to development of DME.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomized trial of 9795 patients with type 2 diabetes mellitus. Eligible patients were randomly assigned to receive fenofibrate 200 mg/day (n=4895) or matching placebo (n=4900). In a sub study of 1012 patients (ophthalmology sub study), standardized retinal photography was done and photographs graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses

were by intention to treat. In the ophthalmology sub study, the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups overall (46 [9·6%] patients on fenofibrate vs 57 [12·3%] on placebo; p=0·19) or in the subset of patients without pre-existing retinopathy (43 [11·4%] vs 43 [11·7%]; p=0·87). By contrast, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients vs 14 [14·6%]; p=0·004).

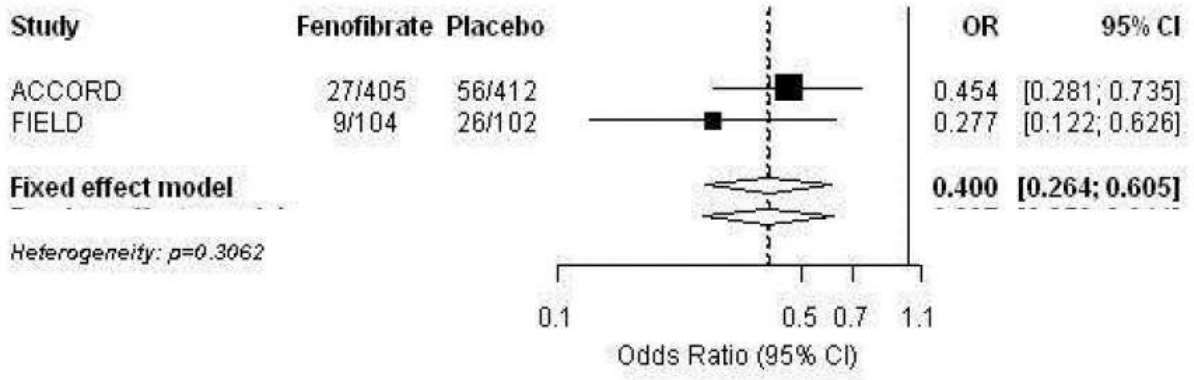
At each clinic visit, information concerning laser treatment for diabetic retinopathy—a prespecified tertiary endpoint of the main study—was gathered. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (164 [3·4%] patients on fenofibrate vs. 238 [4·9%] on placebo; hazard ratio [HR] 0·69, 95% CI 0·56–0·84; p=0·0002; absolute risk reduction 1·5% [0·7–2·3]). The need for such treatment was not affected by plasma lipid concentrations.

In a subgroup of 2856 participants of the ACCORD study, ACCORD Eye evaluated the effects of three interventions strategies, on the progression of diabetic retinopathy; intensive or standard treatment for glycaemia (target HbA1c <6.0% or 7.0 to 7.9%, respectively), dyslipidaemia (160 mg daily of fenofibrate plus simvastatin or placebo plus simvastatin) or systolic blood-pressure control (target, <120 or <140 mm Hg). Progression of diabetic retinopathy was defined at 4 years by 3 or more steps on the ETDRS scale (as assessed from seven-field stereoscopic fundus photographs) or the development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy.

The rate of progression of diabetic retinopathy was 6.5% with fenofibrate for intensive dyslipidaemia therapy, versus 10.2% with placebo (adjusted odds ratio, 0.60; 95% CI, 0.42 to 0.87; P = 0.006). It was concluded that intensive combination treatment of dyslipidaemia reduced the rate of progression of diabetic retinopathy.

An integrated analysis was performed from Patient individual Data from the FIELD study and the published information from ACCORD Eye publications. The combined primary endpoint of ACCORD Eye was applied to FIELD i.e.3-step ETDRS severity scale, photocoagulation or vitrectomy for proliferative diabetic retinopathy. The two studies were homogeneous (fixed effect model applicable) and showed an overall 60% reduction in the progression of diabetic retinopathy, OR: 0.40; 95% CI (0.26-0.61) for subjects with existing DR at baseline.

Figure 1. Progression of Diabetic Retinopathy (DR) in Subjects with DR at Baseline – Combined Analysis of FIELD PSP-DR and ACCORD Eye for ACCORD Eye Primary Endpoint



FIELD and ACCORD studies excluded patients with severe non-proliferative and proliferative diabetic retinopathy at baseline.

5.2. Pharmacokinetic properties

Metabolism and excretion:

EP-Feno 145 mg Tablet, contains 145 mg of fenofibrate nanoparticles

Absorption: Maximum plasma concentrations (Cmax) 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, EP-Feno 145 mg Tablet, 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 Cmax) to fenofibric acid is not affected by 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 CYP3A4. 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 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 haemodialysis.

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

5.3. Preclinical safety data

Acute toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

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, anemia and decreased body weight were seen at exposure levels ≥50- fold the human exposure for the skeletal toxicity and >15 fold for the cardiomyotoxicity.

Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated during 3 months at exposures approximately 7-fold the clinical AUC.

Studies on mutagenicity 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 effects on fertility were detected in non-clinical reproductive toxicity studies conducted with fenofibrate. However reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat-dose toxicity study with fenofibric acid in young dogs.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose anhydrous, Hypromellose, Sodium Lauryl sulphate, Simethicone emulsion 30%, Croscarmellose sodium, Magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

3 years

6.4. Special precautions for storage

Keep out of reach of children.

Protect from light and moisture.
Store below 30°C in a dry place

6.5. Nature and contents of container
Available as PVC/PVDC/Al blister pack of 3x10's.

6.6. Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by:
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