SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fenofibrate 160 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 160.0 mg fenofibrate.

Excipients with known effect:

Each film-coated tablet contains 301.2 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Fenofibrate are white to off-white, oval shaped, biconvex, film-coated tablets, debossed with “160” on one side and plain on the other side. They are about 18.50 mm in length and about 8.90 mm in width.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fenofibrate is indicated as an adjunct to diet or other non-pharmacological treatment (e.g. exercise, weight reduction) for the following diseases:

- severe hypertriglyceridaemia with or without low HDL cholesterol.
- 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

Dietary measures initiated before therapy should be continued. Response to therapy should be monitored by determination of serum lipid values. If after

several months of fenofibrate administration serum lipid levels have not been reduced satisfactorily, complementary or different therapeutic measures should be considered.

Posology

Adults
Recommended daily dose: One film-coated tablet (containing 160 mg fenofibrate) daily.
Patients taking fenofibrate 200 mg capsules (one capsule daily) can be changed to [product name] (one film-coated tablet daily) without further dose adjustment.

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

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

Hepatic impairment:
Fenofibrate 160 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 paediatric patients under 18 years.

Method of administration

The film-coated tablet should be swallowed whole during a meal with some liquid (e.g. a glass of water).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality).
- known gall bladder disease.

- severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min per 1,73 m2).
- 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

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidemia

Secondary cause of hypercholesteria, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease or alcoholism should be adequately treated before fenofibrate therapy is considered. Secondary cause of hypercholesteria 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 hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic agents).

Liver

As with other lipid lowering agents, increases have been reported in transaminase levels in some patients during treatment with fenofibrate. 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 hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the 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, as well as patients above 70 years of age, 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

those 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 creatinine phosphokinase CPK (levels exceeding 5 times the upper limit of 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 combination of fenofibrate with a HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined hyperlipidaemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity.

Renal function
Fenofibrate is contraindicated in severe renal impairment (see section 4.3).
Fenofibrate 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 µmol/L with co-administered fenofibrate and simvastatin versus 4.4 % with statin monotherapy. 0.3 % of patients receiving co-administration therapy had clinically relevant increases in creatinine to values > 200 µmol/L.
Treatment should be interrupted when the 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.

Fenofibrate 160 mg film-coated tablets contains lactose and sodium.
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 film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Fenofibrate may enhance oral anticoagulant effect and hence 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.

Ciclosporin
Some severe cases of reversible renal function impairment have been reported during concomitant administration of fibrate-containing medicines 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 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 (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 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 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

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 doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, Fenofibrate 160 mg should only be used during pregnancy after a careful benefit/risk assessment.

Breast-feeding

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 160 mg should not be used during breast-feeding.

Fertility

Reversible impairment of fertility was observed in animal testing (see section 5.3).

There is no clinical data available regarding the influence of Fenofibrate on fertility.

4.7 Effects on ability to drive and use machines

Fenofibrate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported ADRs during fenofibrate therapy are digestive or gastrointestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n=2,344) and post-marketing [a] with the below indicated frequencies:

The frequencies used in the following table are: common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), not known (frequency cannot be estimated from the available data).

MedDRA system organ class	**Common**	**Uncommon**	**Rare**	**Not known[a]**
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased	
Immune system disorders			Hypersensitivity	
Nervous system disorders		Headache		
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*		
Respiratory, thoracic and mediastinal disorders				Interstitial lung disease[a]
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Pancreatitis*		

	(abdominal pain, nausea, vomiting, diarrhoea, flatulence)			
Hepatobiliary disorders	Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis	Jaundice, Complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic)[a]
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. rashes, pruritus, urticaria)	Alopecia, Photosensitivity reactions	Severe cutaneous reactions (e.g erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)[a]
Musculoskeletal and connective tissue disorders		Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)		Rhabdomyolysis[a]
Reproductive system and breast disorders		Sexual dysfunction		
General disorders and administration site conditions				Fatigue [a]
Investigations	Blood homocysteine level increased**	Blood creatinine increased	Blood urea increased	

* In the FIELD-study, a randomized placebo-controlled clinical trial performed in 9,795 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 thrombosis (placebo 1 % [48/4,900 patients] versus fenofibrate 1.4 % [67/4,895 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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellow

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

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

Mechanism of action
Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of PPARα (Peroxisome Proliferator Activated Receptor type alpha).

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 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 AI and AII.

Pharmacodynamic effects

Patients with an increased CHD-risk often show an atherogenic lipoprotein phenotype, which is characterized with an increase of small dense LDL-particles. Through modulation of the synthesis and the catabolism of VLDL fractions fenofibrate increases the LDL clearance and reduces small dense LDL.

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 (LDL, HDL) 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.

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.

Clinical efficacy and safety

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) lipid trial was a randomized placebo-controlled study of 5,518 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 mono-therapy 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 mono-therapy 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 mono-therapy (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.

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.

5.2 Pharmacokinetic properties

Fenofibrate is a film-coated tablet containing 160 mg of micronised fenofibrate and is suprabioavailable (larger bioavailability) compared to the previous formulations.

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 (> 99 %).

Metabolism and elimination
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 CYP3A4. No hepatic microsomal metabolism is involved.

The active substance 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 glucuronide conjugate.

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

Pharmocokinetic studies following the administration of a single dose and continuous treatment have demonstrated that the active substance 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

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. 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 sign 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 tumors 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.

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

Tablet core:
Lactose monohydrate
Crospovidone (Type B)
Sodium laurilsulfate
Povidone K 30
Croscarmellose sodium
Silicified microcrystalline cellulose (comprising cellulose microcrystalline and silica, colloidal anhydrous)
Sodium stearyl fumarate

Film-coating:
Polyvinyl alcohol
Macrogol 4000
Talc
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Fenofibrate 160 mg Film-coated Tablets is available in blister packs containing 10, 20, 28, 30, 50, 84, 90, 98 and 100 film-coated tablets.

Hospital pack sizes: 280 and 300 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd.
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Crawley,
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RH10 9BG,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/04/2017

10 DATE OF REVISION OF THE TEXT

06/11/2020