SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fenofibrate 160 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fenofibrate 160mg

Excipients with known effect
Each Fenofibrate 160 mg tablet contains lactose monohydrate 238.45mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white oblong 15mm x 7mm tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fenofibrate 160 mg Tablets are indicated as an adjunct 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.
- 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

Posology:

Adults: The recommended dose is one tablet containing 160 mg fenofibrate taken once daily. Patients currently taking one fenofibrate 200mg capsule can be changed to one fenofibrate 160 mg tablet without further dose adjustment.

Elderly patients (≥ 65 years old): 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 m2 (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 m2, is present.
If eGFR is between 30 and 59 mL/min per 1.73 m2, the dose of Fenofibrate should not exceed 100mg standard or 67 mg micronized once daily.
If, during follow-up, the eGFR decreases persistently to <30 mL/min per 1.73 m2, Fenofibrate should be discontinued.

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 subjects under 18 years.

Hepatic disease: Patients with hepatic disease have not been studied.

Dietary measures initiated before therapy should be continued.

If after several months of fenofibrate administration (e.g. 3 months) serum lipid levels have not been reduced satisfactorily, complementary or different therapeutic measures should be considered.

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

4.3 Contraindications

- hepatic insufficiency (including biliary cirrhosis),
- severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m2),
- children,
- hypersensitivity to fenofibrate or any component of this medication,
- known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen,
- gall bladder disease.

Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia

Use during pregnancy and lactation: see section 4.6.

4.4 Special warnings and precautions for use

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 be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

Pancreatitis:
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 bilary tract stone or sludge formation, resulting in the 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 cases of hypoalbuminaemia and previous renal insufficiency. 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 normal range). In such cases treatment with fenofibrate should be stopped.

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.

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 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:
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 m2 (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 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 had clinically relevant increases in creatinine to values >200 µmol/L.
Treatment should be interrupted when 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.

Other warnings
For hyperlipidaemic patients taking oestrogens 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).
As fenofibrate 160 mg tablets 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 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

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. 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

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 and other fibrates:
The risk of serious muscle toxicity I increased if fenofibrate 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)

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.

4.6 Fertility, Pregnancy and lactation

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 160mg tablets should only be used after a careful benefit/risk assessment.
There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Consequently, fenofibrate 160mg tablets should not be used in nursing mothers.

4.7 Effects on ability to drive and use machines

No effect noted.

4.8. Undesirable Effects

The frequencies of adverse events are ranked according top the following: 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 including isolated reports

<u>Gastrointestinal</u>:
Common: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity
Uncommon: Pancreatitis *

Hepato-biliary disorders:
Common: Moderately elevated levels of serum transaminases (see Special Precautions for use).
Uncommon: Development of gallstones
Very rare: Episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable (see Special Warnings).

Cardiovascular system:
Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis*)

Skin and subcutaneous tissue disorder:
Uncommon: rashes, pruritus, urticaria or photosensitivity reactions.
Rare: alopecia

Very rare: cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin expose to sunlight or artificial light (e.g. sunlamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal, connective tissue and bone disorders:
Rare: diffuse myalgia, myositis, muscular cramps and weakness
Not known: rhabdomyolysis

Blood and lymphatic system disorders:
Rare: decrease in haemoglobin and leukocytes

Nervous system disorder:
Rare: sexual asthenia

Respiratory, thoracic and mediastinal disorders.
Not known: interstitial pneumopathies

Investigation
Uncommon: increases in serum creatinine and urea

* In the FIELD study, a randomised placebo controlled trial performed in 9795 patients with type II diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate verses patients receiving placebo. (0.8% versus 05% 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)

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/yellowcard

4.9 Overdose

No case of overdosage has been 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

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

In addition, through modulation of the 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.

Because of its significant effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus.

At the present time, no results of long-term controlled clinical trials are available to demonstrate the efficacy of fenofibrate in the primary or secondary prevention of atherosclerotic complications.

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.

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, 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 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 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 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

Fenofibrate 160 mg is a 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 (more than 99%).

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

Metabolism and excretion: No unchanged fenofibrate can be detected in the plasma where the principal metabolite is fenofibric acid. 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 glucuronide 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.

5.3 Preclinical safety data

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.
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 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 sign of any effect on fertility has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurilsulfate, lactose monohydrate, hypromellose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister strips (PVC/PVDC – Aluminium).
Boxes of 10, 20, 28, 30, 50, 84, 90, 98 and 100 tablets.
Hospital pack sizes: 280 and 300 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals Limited
T/A Genus Pharmaceuticals
Linthwaite,

Huddersfield,
HD7 5QH, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0204

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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