# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>12</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td></td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>13</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>20</td>
</tr>
<tr>
<td>Labelling</td>
<td>22</td>
</tr>
</tbody>
</table>
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Gentian Generics Limited a Marketing Authorisation for the medicinal product Fenofibrate 160 mg Tablets (PL 33217/0005) on 13 July 2011. This medicine is only available on prescription from your doctor.

Fenofibrate 160 mg Tablets are used, alongside a low-fat diet and other non-medical treatments (such as exercise and weight loss), to lower levels of fats in the blood. Fenofibrate 160 mg Tablets can be used in addition to other medicines (statins) in some circumstances when levels of fats in the blood are not controlled with a statin alone.

Fenofibrate 160 mg Tablets contain the active ingredient, fenofibrate, which belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the levels of fats (lipids), for example the fats known as triglycerides, in the blood.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Fenofibrate 160 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
FENOFLIBRATE 160 MG TABLETS
PL 33217/0005

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ........................................ Page 4
Pharmaceutical assessment .................. Page 5
Non-clinical assessment ....................... Page 8
Clinical assessment .......................... Page 9
Overall conclusions and risk assessment Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Gentian Generics Limited a Marketing Authorisation for the medicinal product Fenofibrate 160 mg Tablets (PL 33217/0005) on 13 July 2011. Fenofibrate 160 mg Tablets is a prescription-only medicine 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.

This application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Fenofibrate Fournier 100 mg capsule, hard (Laboratoires Fournier SA, France), which was first granted a marketing authorisation in France on 17 June 1987. The corresponding reference product in the UK is Supralip 160 mg film-coated tablets (Solvay Healthcare Limited, UK), which was first authorised in the UK on 22 September 2000.

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 A1 and AII. Fenofibrate has been found to reduce plasma triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) levels and to increase plasma high-density lipoprotein cholesterol (HDL-C) levels, although the latter may not be sustained long-term.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Fenofibrate 160 mg Tablets (Gentian Generics Limited, UK) versus the reference product Lipanthyl 160 mg Tablets (Laboratories Fournier SA, France) under fed conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Fenofibrate 160 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
**PHARMACEUTICAL ASSESSMENT**

**ACTIVE SUBSTANCE**

INN: Fenoﬁbrate  
Chemical Name: 1-methylethyl-2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate; propanoic acid, 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-1-methylethyl ester  
Molecular Formula: C_{20}H_{21}ClO_{4}  
Structure

![Structure of Fenoﬁbrate]

Molecular weight: 360.8 g/mol  
Appearance: A white or almost white powder, practically insoluble in water, very soluble in methylene chloride, slightly soluble in alcohol.

Fenoﬁbrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance fenoﬁbrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients sodium laurilsulfate, lactose monohydrate, hypromellose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has conﬁrmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has conﬁrmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modiﬁed organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Fenoﬁbrate Fournier 100 mg capsule, hard (Laboratoires Fournier SA, France).
Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future full-scale (commercial) batches.

**Control of Finished Product**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in polyvinylchloride/polvinylidene chloride/aluminium blisters. These are packed into cardboard cartons with patient information leaflets in pack sizes of 10, 20, 28, 30, 50, 84, 90, 98 and 100 tablets. Additionally, hospital pack sizes of 280 and 300 tablets are available.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with food.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically satisfactory.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of fenofibrate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of fenofibrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics
In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-period, two-way crossover study to compare the pharmacokinetics of the test product Fenofibrate 160 mg Tablets (Gentian Generics Limited, UK) versus the reference product Lipanthyl 160 mg Tablets (Laboratories Fournier SA, France) in healthy adult male subjects under fed conditions.

The subjects were given a single 160 mg dose of the test or reference product with 240ml of water within 5 minutes after completion of a high-fat breakfast. Blood samples were collected before and up to 96 after each administration. The washout period between the treatment arms was 21 days. The pharmacokinetic results are presented below. Please note, unchanged fenofibrate is not detectable in plasma following oral intake. Therefore, the active metabolite (fenofibric acid), which exerts the therapeutic effect of fenofibrate, was used to demonstrate bioequivalence.

Pharmacokinetic parameters (antilog of least square means, ratios and confidence intervals [CI]) of fenofibric acid (active metabolite)

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate 160 mg Tablet (Test)</th>
<th>Lipanthyl 160 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{inf} (ng h/ml)</td>
<td>142127±58310</td>
<td>146289±56350</td>
<td>96.32</td>
<td>92.30-100.51</td>
</tr>
<tr>
<td>AUC_{t-inf} (ng h/ml)</td>
<td>150278±73740</td>
<td>153168±67593</td>
<td>96.94</td>
<td>93.04-101.02</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>8690±1476</td>
<td>9429±1758</td>
<td>92.02</td>
<td>86.34-98.08</td>
</tr>
</tbody>
</table>

AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
AUC_{t-inf} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
Ratios and 90% CI calculated from ln-transformed data

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) defines the confidence limits as 80% to 125% for $C_{max}$ and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{t-inf}, AUC_{t-inf} and $C_{max}$ lie within the acceptable limits. Thus, the data support the claim that the test product Fenofibrate 160 mg Tablets (Gentian Generics Limited, UK) is bioequivalent to the reference product Lipanthyl 160 mg Tablets (Laboratories Fournier SA, France).

As the French product used in the bioequivalence study is considered identical to the UK reference product (Supralip 160 mg film-coated tablets), bioequivalence has also been shown between the test product and the UK reference product.
Efficacy
The efficacy of fenofibrate is well-known. No new efficacy data have been submitted and none are required for this type of application.

Safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Fenofibrate 160 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of fenofibrate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Fenofibrate 160 mg Tablets and the UK reference product under fed conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of fenofibrate is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fenofibrate is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
FENOFIBRATE 160 MG TABLETS
PL 33217/0005

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 01 April 2009.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 15 April 2009.
4. The applicant responded to the MHRA’s requests, providing further information on the clinical dossier 26 April 2010 and the quality dossier on 22 October 2009, 30 November 2010, 13 April 2011 and 16 June 2011.
5. The application was determined and granted on 13 July 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 160 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Fenofibrate 160 mg

Each Fenofibrate 160 mg tablet contains 238.45mg lactose monohydrate.
For a 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 200 mg capsule can be changed to one fenofibrate 160 mg tablet without further dose adjustment.

Elderly patients: The usual adult dose is recommended.

Patients with renal impairment: Dosage reduction is required in patients with renal impairment. The use of dosage forms containing a lower dose of active ingredient (67 mg micronised fenofibrate capsules or 100 mg standard fenofibrate capsules) is recommended in these patients.

Children: The use of the 160 mg dosage form is contraindicated in children.

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),
- renal insufficiency,
- 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 biliary 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 hypoaalbuminaemia 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.

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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Renal function:
Treatment should be interrupted in case of an increase in creatinine levels > 50% ULN (upper limit of normal).

It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.

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 is 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 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 160 mg 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 160 mg 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 to 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).

Gastrointestinal:
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 exposed 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 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)

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 fibrin 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 A1 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 A1 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 (Cmax) 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
Gentian Generics Limited
5th Floor, Castle Chambers
43 Castle Street
Liverpool
L2 9TL
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 33217/0005
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/07/2011

10 DATE OF REVISION OF THE TEXT
13/07/2011
UKPAR Fenofibrate 160 mg Tablets

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fenofibrate 160mg Tablets
(Fenofibrate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side-effects get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fenofibrate Tablets are and what they are used for
2. Before you take Fenofibrate Tablets
3. How to take Fenofibrate Tablets
4. Possible side-effects
5. How to store Fenofibrate Tablets
6. Further information

1. WHAT FENOFIBRATE TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Fenofibrate 160mg Tablets (hereafter referred to as Fenofibrate Tablets). Fenofibrate Tablets belong to a group of medicines, commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides. Fenofibrate Tablets are used, alongside a low fat diet and other non-medical treatments such as exercise and weight loss, to lower levels of fats in the blood. Fenofibrate Tablets can be used in addition to other medicines (statins) in some circumstances when levels of fats in the blood are not controlled with a statin alone.

2. BEFORE YOU TAKE FENOFIBRATE TABLETS

Do not take Fenofibrate Tablets if:
- you are allergic to fenofibrate or any of the other ingredients of Fenofibrate Tablets (see Section 6 'What Fenofibrate Tablets contain')
- you have a liver disorder
- you have a kidney disorder
- you have known allergic reactions to light during treatment with fenofibrate or ketoprofen (an anti-inflammatory drug)
- you have gallbladder disease
- you have inflammation of the pancreas.

Fenofibrate Tablets must not be used in children.

Take special care with Fenofibrate Tablets if:
- you or somebody in your family has had muscular disorders
- you have thyroid problems
- you drink a lot of alcohol.

You will have liver function tests before treatment and also at regular intervals during the first year of treatment. Your kidney function may also be checked by laboratory tests at the beginning of your treatment.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Take care when using any of the following medicines:
- blood thinners (anticoagulants) – an increased risk of bleeding can occur when fenofibrate is taken with these medicines
- ciclosporin – patients can encounter reversible kidney problems when fenofibrate is taken with ciclosporin
- statins or other ‘fibrate’ medicines – an increased chance of muscular disorders exists when fenofibrate is taken with statins or other ‘fibrate’ medicines
- contraceptives – oestrogen-containing contraceptives may interfere with the effects of fenofibrate.

Pregnancy and breast-feeding

The use of this medicine is not recommended in pregnant women as there is not sufficient experience of use during pregnancy. If you become pregnant during the treatment, you should stop taking the medicine and contact your doctor. This medicine should not be used whilst breast-feeding as it is not known whether the medicine is excreted in breast milk. Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

Fenofibrate Tablets will not affect your ability to drive or operate machinery.

Important information about some of the ingredients of Fenofibrate Tablets

This medicinal product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

3. HOW TO TAKE FENOFIBRATE TABLETS

You should continue on a low fat diet.
Always take Fenofibrate Tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Adults and the elderly
The usual dose is one tablet daily. The tablet should be swallowed whole together with a meal.
In addition to the diet, this medicine should be continued long-term and monitored regularly. To use this medicine appropriately, it is essential to undergo regular medical check-ups.

Children
Children should not be given Fenofibrate Tablets.
If you have the impression that the effect of Fenofibrate Tablets is too strong or too weak, talk to your doctor or pharmacist.

If you take more Fenofibrate Tablets than you should
If anyone has taken an overdose of Fenofibrate Tablets (that is more than the doctor has prescribed), seek medical help immediately, either by calling a doctor or going to the nearest hospital casualty department. Always take the labeled medicine container with you, even if there are no tablets left.

If you forget to take Fenofibrate Tablets
Do not take a double dose to make up for a forgotten tablet. If you forget to take a dose, don’t worry; just take your next tablet when it is due.

4. POSSIBLE SIDE-EFFECTS
Like all medicines, Fenofibrate Tablets can have side-effects, although not everyone gets them. You should contact your doctor if you experience severe or troublesome symptoms.

Tell your doctor immediately if you experience any of the following rare side-effects:
- muscle pain, muscle cramps or muscle weakness - symptoms of rhabdomyolysis, abnormal muscle breakdown which can lead to kidney problems
- yellowing of the skin or itching - symptoms of hepatitis or liver disease

Common side-effects (occurring in more than 1 in 100 patients) include:
- stomach pain
- nausea
- vomiting
- diarrhoea
- flatulence

Uncommon side-effects (occurring in more than 1 in 1,000 patients) include:
- rash
- itching
- urticaria (hives)
- gallstones
- inflammation of the pancreas
- blood clots in the leg causing redness or swelling (deep vein thrombosis)
- Sensitivity to light

Rare side-effects (occurring in more than 1 in 10,000 patients) include:
- hair loss
- muscle pain
- muscle inflammation
- muscle cramps
- muscle weakness
- reduced sex drive

Very rare side-effects (occurring in less than 1 in 10,000 patients) include:
- hepatitis
- skin reactions to light leading to redness, blisters, or swelling. This can occur any time after starting the medicine.

Not Known – frequency cannot be determined from the available data
- rhabdomyolysis
- lung disease

Fenofibrate can also affect the results of laboratory tests.

These include:
- Common: mild changes in liver enzymes
- Uncommon: changes in kidney function tests
- Rare: decreased levels of blood haemoglobin and white blood cells.

If any of the side-effects get serious or if you notice any side-effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE FENOFRIBRATE TABLETS
Keep out of the reach and sight of children.
No special precautions for storage.
Do not use Fenofibrate Tablets after the expiry date which is stated on the blister/carton. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION
What Fenofibrate Tablets contain
The active substance is fenofibrate.
The other ingredients are sodium laurylsulphate, lactose monohydrate, hypromellose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

What Fenofibrate Tablets look like and contents of the pack
Fenofibrate Tablets are white or off-white oblong 15mm x 7mm tablets and are available in packs of 28 tablets.

POM

PL 33217/0005 Fenofibrate 160mg Tablets

Marketing Authorisation Holder and Manufacturer:
Gentian Gaverica Ltd., 8th Floor, Castle Chambers, 63 Castle Street, Liverpool L2 9TL, UK.

This leaflet was last updated in June 2011.