FENOFRIBRATE MICRO 267MG CAPSULES  
PL 10622/0261

UKPAR

**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>13</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td></td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td></td>
</tr>
<tr>
<td>Labelling</td>
<td></td>
</tr>
</tbody>
</table>
FENOFIBRATE MICRO 267MG CAPSULES
PL 10622/0261

LAY SUMMARY

On 24th April 2009, the MHRA granted Pliva Pharma Limited a Marketing Authorisation (licences) for Fenofibrate Micro 267mg Capsules (PL 10622/0261).

Fenofibrate Micro 267mg Capsules contains fenofibrate, which is used to reduce high fat (lipid) levels in the blood. If untreated, these high levels of fat might cause problems later on leading to heart disease or other illnesses.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Fenofibrate Micro 267mg Capsules outweigh the risks; hence a Marketing Authorisation has been granted.
**FENOFIBRATE MICRO 267MG CAPSULES**  
**PL 10622/0261**

**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment (including statistical assessment)</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>11</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Fenofibrate Micro 267mg Capsules (PL 10622/0261) to Pliva Pharma Limited on 24th April 2009. This product is a prescription only medicine and is indicated in appropriate cases of dyslipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

Fenofibrate Micro 267mg Capsules also reduce elevated serum cholesterol and triglycerides and is of benefit in the treatment of severe dyslipidaemia.

This application for Fenofibrate Micro 267mg Capsules is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Lipantil Micro 267mg Capsules, first authorised to Fournier Pharmaceuticals Limited in February 1999, then underwent a change of ownership to Solvay Healthcare Limited in July 2007.

The product contains the active substance fenofibrate, which increases lipolysis and by activation, lipoprotein lipase facilitates elimination of triglyceride rich particles. It also reduces apoprotein CIII. The overall results include reduction in total cholesterol, LDL cholesterol, apolipoprotein B, total TGs (and VLDL) in plasma. Additionally, HDL cholesterol is increased marginally.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Benzocaine
INN: Fenofibrate
Chemical name: 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

Structure:

![Structure of Fenofibrate]

Physical form: White or almost white crystalline powder
Solubility: Practically insoluble in water
Very soluble in methylene chloride
Slightly soluble in alcohol
Molecular formula: C_{20}H_{21}ClO_{4}
Molecular weight: 360.8

Fenofibrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance fenofibrate from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance fenofibrate.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, pregelatinised starch, sodium lauryl sulphate, crospovidone, magnesium stearate, anhydrous colloidal silica. All the ingredients within the body of the capsule comply with their relevant European Pharmacopoeia monographs.
The capsule shell contains: gelatin, brilliant blue (E133), titanium dioxide (E171). Gelatin is the subject of a European Pharmacopoeia monograph. Brilliant blue (E133) and titanium dioxide (E171) comply with in-house specifications.

With the exception of gelatin and lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

**Product development**
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Lipantil Micro 267mg Capsules (Solvay Healthcare Limited, July 2007).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Lipantil Micro 267mg Capsules (Solvay Healthcare Limited).

The reference products used in the bioequivalence studies are qualitatively and quantitatively identical to the UK reference product.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three pilot-scale batches of finished product and the results appear satisfactory. The applicant has committed to perform process validation on future production-scale batches.

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

**Container-Closure System**
The product is packaged in polyvinylchloride and aluminium foil blister packs in sizes of 28 capsules.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with the European Pharmacopoeia monograph.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are ‘Do not store above 25°C.’ and ‘Store in orginal package.’
ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
This is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is 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
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Fenofibrate Micro 267mg Capsules was submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Lipantil Micro 267mg Capsules, first authorised to Fournier Pharmaceuticals Limited in February 1999, then underwent a change of ownership to Solvay Healthcare Limited in July 2007.

No new preclinical data have been supplied with this application and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included three bioequivalence studies:

A single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study comparing the pharmacokinetics of fenofibrate 267mg Capsules (Test) versus Lipanthyl 267mg Capsules (Reference) under fed conditions.

All subjects had an overnight fast of 10 hours followed by breakfast before dosing. Blood sampling was performed pre- and up to 120 hours post dose in each treatment period. There was a washout period of 14 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th></th>
<th>AUC$_{0-t}$ (ng/ml/h)</th>
<th>AUC$_{0-\infty}$ (ng/ml/h)</th>
<th>C$_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>222.067 ± 94.20</td>
<td>234.370 ± 97.52</td>
<td>13.074 ± 4.74</td>
</tr>
<tr>
<td>Reference</td>
<td>232.428 ± 97.27</td>
<td>243.691 ± 99.75</td>
<td>14.704 ± 5.44</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>0.8697-1.0245</td>
<td>0.8588-1.0216</td>
<td>0.8106-0.9886</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC$_{0-t}$ and C$_{\text{max}}$ for fenofibrate lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.
DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Fenofibrate Micro 267mg Capsules can be considered as generic medicinal products to the originator product.

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Fenofibrate Micro 267mg Capsules 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Fenofibrate Micro 267mg Capsules and the reference product Lipantil Micro 267mg Capsules (Solvay Healthcare Limited).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Lipantil Micro 267mg Capsules.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with fenofibrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 25&lt;sup&gt;th&lt;/sup&gt; November 2004. The MHRA also received a further response regarding the application on 29&lt;sup&gt;th&lt;/sup&gt; November 2005.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 29&lt;sup&gt;th&lt;/sup&gt; March 2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 26&lt;sup&gt;th&lt;/sup&gt; April 2006, 16&lt;sup&gt;th&lt;/sup&gt; September 2008 and 19&lt;sup&gt;th&lt;/sup&gt; February 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 13&lt;sup&gt;th&lt;/sup&gt; January, 21&lt;sup&gt;st&lt;/sup&gt; November 2008 and 18&lt;sup&gt;th&lt;/sup&gt; March 2009 for the quality sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 24&lt;sup&gt;th&lt;/sup&gt; April 2009.</td>
</tr>
</tbody>
</table>
# STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate Micro 267 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 267 mg micronized fenofibrate.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsules, hard
Blue/blue capsule size 0

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Fenofibrate Micro 267 reduces elevated serum cholesterol and triglycerides and is of benefit in the treatment of severe dyslipidaemia in patients in whom dietary measures alone have failed to produce an adequate response. Fenofibrate Micro 267 is indicated in appropriate cases of dyslipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

<table>
<thead>
<tr>
<th>Type</th>
<th>Major lipid elevated</th>
<th>Lipoproteins elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>Cholesterol</td>
<td>LDL</td>
</tr>
<tr>
<td>IIb</td>
<td>Cholesterol, triglycerides</td>
<td>LDL, VLDL</td>
</tr>
<tr>
<td>III (rare)</td>
<td>Cholesterol, triglycerides</td>
<td>IDL and chylomicron remnants</td>
</tr>
<tr>
<td>IV</td>
<td>Triglyceride</td>
<td>VLDL</td>
</tr>
<tr>
<td>V (rare)</td>
<td>Triglyceride</td>
<td>Chylomicrons, VLDL</td>
</tr>
</tbody>
</table>

Fenofibrate Micro 267 should only be used in patients in whom a full investigation has been performed to define their abnormality. Other risk factors, such as hypertension and smoking, may also require management.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults
In patients with severe dyslipidaemia, an increased dose of 267mg (Fenofibrate Micro 267) is recommended. Fenofibrate Micro 267 should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be instituted.

Children
This dosage is not recommended in children.

Elderly
In elderly patients without renal impairment, the normal adult dose is recommended.

Renal impairment
In renal dysfunction, the dosage may need to be reduced depending on the rate of creatinine clearance, for example:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>Fenofibrate 140 mg capsule</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Fenofibrate 67 mg capsule</td>
</tr>
</tbody>
</table>

4.3 CONTRAINDICATIONS
Fenofibrate Micro 267 is contra-indicated
- in children
- in patients with severe liver or renal dysfunction, gallbladder disease, biliary cirrhosis and
- in patients hypersensitive to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- In patients with 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

In renal impairment
In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance, (see section 4.2). Dose reduction should be considered in elderly patients with impaired renal function.

Transaminases
Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminases should be monitored every three months during the first twelve months of treatment. Treatment should be interrupted in the event of ALAT (SGPT) or ASAT (SGOT) elevations to more than 3 times the upper limit of the normal range or more than one hundred international units.

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 hypertriglyceridaemia, 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.

Myopathy
Patients with pre-disposing factors for rhabdomyolysis, including renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis.

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.

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 oestrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

Patients with rare hereditary problems of galactose intolerance the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

HMG-CoA reductase inhibitors or 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).

There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.
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.

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

4.6 PREGNANCY AND LACTATION
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.

There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. It is therefore recommended that Fenofibrate Micro 267 should not be administered to women who are pregnant or are breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No effect noted to date.

4.8 UNDESIRABLE EFFECTS
Fenofibrate is generally well tolerated. Adverse reactions observed during fenofibrate treatment are not very frequent; they are generally minor, transient and do not interfere with treatment.

The most commonly reported adverse reactions include:
Gastrointestinal: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity.
Uncommon: Pancreatitis*

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

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

Neurological disorders: Headache

General disorders: Fatigue

Disorders of the ear: Vertigo

Less frequently reported adverse reactions:
Liver: Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment (see also section 4.4). Episodes of hepatitis have been reported very rarely. 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). Development of gallstones has been reported.

Muscle: As with other lipid lowering agents, cases of muscle toxicity (diffuse myalgia, myositis, muscular cramps and weakness) and very rare cases of rhabdomyolysis have been reported. These effects are usually reversible when the drug is withdrawn (see Special Warnings).
In rare cases, the following effects are reported: Sexual asthenia and alopecia. Increases in serum creatinine and urea, which are generally slight, and also a slight decrease in haemoglobin and leukocytes may be observed.

Very rare cases of interstitial pneumopathies have been reported.

* In the FIELD-study, a randomized placebo-controlled trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; \( p = 0.031 \)). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; \( p = 0.022 \)) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0% [48/4900 patients] versus fenofibrate 1.4% [67/4895 patients]; \( p = 0.074 \)).

4.9 OVERDOSE

No case of overdosage has been reported. No specific antidote is known. If overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.

ATC code:C10 AB 05

Fenofibrate Micro 267 is a formulation containing 267 mg of micronised fenofibrate.

The lipid lowering properties of fenofibrate seen in clinical practice have been explained in vivo in transgenic mice and in human hepatocyte cultures by activation of Peroxisome Proliferator Activated Receptor type \( \alpha \) (PPAR\( \alpha \)). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apoprotein C-III. Activation of PPAR\( \alpha \) also induces an increase in the synthesis of Apoproteins A-I, A-II and of HDL cholesterol.

Epidemiological studies have demonstrated a positive correlation between increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemias forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long-term consequences of drugs used in the management of dyslipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate Micro 267 on cardiovascular morbidity and mortality is as yet unproven.

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

Regression of xanthomata has been observed during fenofibrate therapy.

Plasma uric acid levels are increased in approximately 20% of hyperlipidaemic patients, particularly in those with type IV phenotype. Fenofibrate Micro 267 has a uricosuric effect and is therefore of additional benefit in such patients.

Patients with raised levels of fibrinogen and Lp(a) have shown significant reductions in these measurements during clinical trials with fenofibrate.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The unchanged compound is not recovered in the plasma. Fenofibric acid is the major plasma metabolite. Peak plasma concentration occurs after a mean period of 5 hours following dosing.

Mean plasma concentration is 15 \( \mu \)g/ml for a daily dosage of 200 mg of micronised fenofibrate.
Steady state levels are observed throughout continuous treatments. Fenofibric acid is highly bound to plasma albumin: it can displace antivitamin K compounds from the protein binding sites and potentiate their anti-coagulant effect.

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

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

Kinetic studies after administration of repeated doses show the absence of accumulation of the product.

Fenofibric acid is not eliminated during 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**

Excipients: lactose monohydrate, pregelatinised starch, sodium lauryl sulphate, crospovidone, magnesium stearate, anhydrous colloidal silica.

Composition of the capsule shell: gelatin, brilliant blue (E133), titanium dioxide (E171).

**6.2 INCOMPATIBILITIES**
Not applicable.

**6.3 SHELF LIFE**
3 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**
Do not store above 25°C.
Store in the original package

**6.5 NATURE AND CONTENTS OF CONTAINER**
Pack of 28 capsules in blisters (PVC/Aluminium).

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**
Pliva Pharma Ltd.
Vision House – Bedford Road, Petersfield
Hampshire GU32 3QB
UK
8 MARKETING AUTHORISATION NUMBER(S)
   PL 10622/0261

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   24/04/2009

10 DATE OF REVISION OF THE TEXT
    24/04/2009
Fenofibrate Micro 267mg Capsules

The name of your medicine is Fenofibrate Micro 267mg Capsules, which will be called Fenofibrate Capsules throughout this leaflet.

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 gets 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 Capsules are and what they are used for
2. Before you take Fenofibrate Capsules
3. How to take Fenofibrate Capsules
4. Possible side effects
5. How to store Fenofibrate Capsules
6. Further information

What Fenofibrate Capsules are and what they are used for

Fenofibrate is a type of drug known as a fibrate, and is used to modify the lipid (fat) levels in the blood. If untreated, these high levels of fat might cause problems later on leading to heart disease or other illnesses.

Fenofibrate is used to reduce high fat (lipid) levels in the blood. The types of fats in the blood which are lowered by fenofibrate include triglycerides and cholesterol (known as low density and very low density lipoproteins).

Fenofibrate should only be used in patients who have not been able to control their blood lipid levels with a low fat diet, exercise and weight reduction.

2 Before you take Fenofibrate Capsules

Do not take Fenofibrate Capsules:
- if you are hypersensitive (allergic) to Fenofibrate, similar drugs or to any ingredient in Fenofibrate Capsules;
- if you have severe liver or kidney problems;
- if you have gall bladder disease;
- if you suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain);
- if you have had a side-effect of reacting to sunlight when taking other fibrates (for example bezafibrate, ciprofibrate or gemfibrozil) or ketoprofen;
- if you are pregnant or there is a possibility that you may become pregnant;
- if you are breast feeding;
- if you are under 18.

Take special care with Fenofibrate if you have:
- kidney disease or have a history of kidney disease;
- thyroid problems;
- alcohol problems (regularly drinking large amounts of alcohol);
- low levels of serum albumin (hypoalbuminaemia) a component of the blood;
- a muscular disease.

Taking other medicines

Please tell your doctor or pharmacist if you are taking any of the following medicines:
- anticoagulants (prevent clotting or thickening of the blood, for example warfarin);
- other fibrates which lower levels of fats in the blood (for example bezafibrate, ciprofibrate or gemfibrozil);
- statins which reduce the level of fats in the blood (for example atorvastatin, fluvastatin, pravastatin, or simvastatin);
- ciclosporin (used after organ transplants);
- phenylbutazone, a non-steroidal anti-inflammatory drug used to treat ankylosing spondylitis;
- oestrogens which are in medicines including HRT (hormone replacement therapy) and the pill.

Taking Fenofibrate capsules may increase the levels of certain enzymes in your blood (transaminases). Your doctor may decide to monitor this with blood tests every 3 months during the first year of treatment.

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

Pregnancy and breast-feeding

You should not take Fenofibrate Capsules while pregnant or breast-feeding unless your doctor tells you to.

Driving and using machines:

There are no data to suggest that fenofibrate affects ability to drive.

Important information about some of the ingredients of Fenofibrate Capsules

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

3 How to take Fenofibrate Capsules

Always take Fenofibrate Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Fenofibrate Capsules should always be taken with food and swallowed whole with a little water.

Adults and elderly patients

The usual dose of Fenofibrate Capsules is one capsule taken daily during a main meal.

This dose may be reduced (by your doctor) if you have kidney problems.

Children

Fenofibrate Capsules are not recommended for use in children.
If you have been on a diet (as recommended by your doctor) before starting to take Fenofibrate Capsules, you should continue the same diet.

If you suffer from high blood pressure, your doctor may advise you to start taking medication for this condition if you are not already doing so. Your doctor may also advise you to stop smoking if you are a smoker.

If you take more Fenofibrate Capsules than you should:
It is important to stick to the dose on the label of your medicine. If you or someone else should take too many Fenofibrate Capsules all together, contact your doctor, pharmacist or hospital emergency department immediately. Always take any capsules left over with you and also the box, as this will allow easier identification of the medicine.

If you forget to take your Fenofibrate Capsule:
If you forget to take a dose, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose if it is almost time for your next dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects
Like all medicines, Fenofibrate Capsules can have side effects, although not everybody gets them.

All medicines can cause allergic reactions, although serious allergic reactions are very rare. Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Contact your doctor as soon as possible and stop taking Fenofibrate if you develop any unexplained or persistent muscle pain, tenderness, weakness or cramps, especially if at the same time you feel unwell or have a high temperature. In very rare cases this can progress to become a serious and potentially life threatening condition, called rhabdomyolysis.

You should tell your doctor if you experience yellowing of the skin or the whites of the eyes (jaundice) or itching as this may be due to hepatitis (liver inflammation). Your doctor may need to carry out tests to check this.

Other side effects that most commonly occur include:
- Stomach and bowel problems such as abdominal pain, sickness, diarrhoea, and wind;
- Skin reactions such as itching and rashes, hives, sensitivity to sunlight or UV light (which can lead to redness, blistering or rashes);
- Dizziness, tiredness and headache.

Uncommon side effects:
- Inflammation of the pancreas (pancreatitis);
- Formation of blood clots in veins (deep vein thrombosis) and blockage of the lung arteries by blood clots (pulmonary embolism).

Rare side effects:
- Development of gallstones;
- A loss of interest in sex or an inability to perform sexually;
- Hair loss;
- A slight decrease in the level of a component in red blood cells (haemoglobin) in the blood;
- A slight decrease in the number of leucocytes (a type of white blood cells) in the blood;
- A slight increase in the levels of certain substances in the blood (serum transaminases, serum creatinine and urea).

Very rare side effects:
- Problems with the lungs known as interstitial pneumopathy;
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store Fenofibrate Capsules
Keep out of the reach and sight of children.

Do not store above 25°C. Store your capsules in the original packaging.

Do not use Fenofibrate Capsules after the expiry date which is stated on the 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 to protect the environment.

6 Further information

What Fenofibrate Capsules contain:
The active ingredient is fenofibrate in a micronised form. This form has very fine particles which can enter the bloodstream quickly.

Fenofibrate 267 mg Capsules also contain: lactose monohydrate, pregelatinised starch, sodium lauryl sulphate, crospovidone, magnesium stearate, anhydrous colloidal silica, gelatin, brilliant blue (E133), titanium dioxide (E171).

What Fenofibrate Capsules look like and contents of the pack:
Fenofibrate Capsules are blue capsules and are available in blister packs of 28 capsules.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
PLIVA Pharma Ltd., Vision House, Bedford Road, Petersfield, Hampshire, GU32 3Q8, United Kingdom

Manufacturer
PSI supply NV, Axxes Business Park, Guldenroepenpark 22 – Block C, 9820 Merelbeke, Belgium

Date of preparation: March 2009
PL 10622/0261
31404-P2
The capsules must be swallowed whole with some water and with food as directed by the physician. Read the package leaflet before use. Also contains lactose. For further information, please see the enclosed leaflet. Do not store above 25°C. Store in the original package. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder:
PLIVA Pharma Ltd
Vision House, Bedford Road
Peinsfield
Hampshire, GU32 3Q8
United Kingdom

POM
PL:10622/0261
61404-C1

Fenofibrate Micro 267mg Capsules
28 capsules

Fenofibrate Micro 267mg Capsules
Each capsule contains:
Active ingredient: 267mg fenofibrate (micronised)

28 capsules