FENOFIBRATE 67MG CAPSULES
PL 14894/0367, 70 AND 73

FENOFIBRATE 200MG CAPSULES
PL 14894/0368, 71 AND 74

FENOFIBRATE 267MG CAPSULES
PL 14894/0369, 72 AND 75

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PL 14894/0367, 70 AND 73

FENOFIBRATE 200MG CAPSULES
PL 14894/0368, 71 AND 74

FENOFIBRATE 267MG CAPSULES
PL 14894/0369, 72 AND 75

LAY SUMMARY

The MHRA granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Fenofibrate 67mg Capsules (PL 14894/0367, 70 and 73), Fenofibrate 200mg Capsules (PL 14894/0368, 71 and 74) and Fenofibrate 267mg Capsules (PL 14894/0369, 72, and 75) on 2nd January 2007. These are prescription only medicines (POM) which are indicated for the treatment of high blood fats (cholesterol/triglycerides).

Fenofibrate belongs to the class of medicines called fibrates. Fibrates help to reduce fats in the blood.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Fenofibrate Capsules outweigh the risks, hence Marketing Authorisations have been granted.
FENOFIBRATE 67MG CAPSULES
PL 14894/0367, 70 AND 73

FENOFIBRATE 200MG CAPSULES
PL 14894/0368, 71 AND 74

FENOFIBRATE 267MG CAPSULES
PL 14894/0369, 72 AND 75

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Fenofibrate 67mg Capsules (PL 14894/0367, 70 and 73), Fenofibrate 200mg Capsules (PL 14894/0368, 71 and 74) and Fenofibrate 267mg Capsules (PL 14894/0369, 72, and 75) to Ranbaxy UK Limited on 2nd January 2007. These products are prescription only medicines.

These are triplicate national abridged applications for three strengths of fenofibrate, submitted under article 10.1 of Directive 2001/83/EC as amended claiming to be a generic medicinal product of Lipantil® Micro 67mg and Lipantil® Micro 267mg which were authorised on 11/09/1997 and 03/02/1999 respectively as line extensions. The French reference product, Lipanthyl Micronise 200mg Gelule, has been used in the biostudy.

Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

Fenofibrate should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Fenofibrate

Chemical name 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate
CAS number 49562-28-9

Structure

Molecular formula C_{20}H_{21}ClO_{4}
Molecular weight 360.8
Chirality The substance has no optical activity
Physical form White or almost white crystalline powder
Solubility Practically insoluble in water
Very soluble in methylene chloride
Slightly soluble in alcohol
Polymorphism No polymorphs observed
Melting point 79-82°C

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active fenofibrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 5 years when stored in sealed polyethylene bags, which are placed in fibre drums.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely Sodium Lauryl Sulphate, Lactose monohydrate, Pregelatinised Starch, Crospovidone, Talc, Colloidal Anhydrous Silica, Magnesium Stearate, gelatine, Titanium Dioxide (E171) Shellac Glaze, Iron Oxide Black(E172), Lecithin Soya and water purified.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Shellac Glaze, Iron Oxide Black(E172) and Lecithin Soya which comply with in-house specifications. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate and magnesium stearate, none of the excipients used contain materials of animal or human origin. The manufacturer of lactose monohydrate has confirmed that this is sourced from milk from healthy animals under the same conditions as milk for human consumption. A satisfactory TSE declaration for magnesium stearate is provided.

There were no novel excipients used and no overages.

**Product development**

The applicant has provided a suitable product development rationale and data.

Satisfactory assay, impurity and dissolution data have been provided.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 have been provided for any working standards used.

**Container Closure System**
The capsules are packed in blisters consisting of clear transparent PVC film coated uniformly with PVdC on inner side with a backing of aluminium foil coated with heat seal lacquer on inner side. The blisters are packed in cartons. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions “Store in the original package” and “Do not store above 25 degree C” have been set, which is satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for generic medicinal product of reference products have been met with respect to qualitative and quantitative content of the active substance and pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.
1. **INTRODUCTION**
   Fenofibrate is an established treatment for hyperlipidaemia. It is a fibrate drug and an analogue of clofibrate.

   The original formulation was 100 or 400 mg/day. A micronised form was developed later of 67 or 267 mg/day. Micronisation increases oral bioavailability by about 50%.

2. **INDICATIONS**
   Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

<table>
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<tr>
<th>Type</th>
<th>Major lipid elevated</th>
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<tr>
<td>IIa</td>
<td>Cholesterol</td>
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<td>LDL 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 should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

3. **DOSE & DOSE SCHEDULE**
   **Adults** In adults, the recommended initial dose is 3 capsules taken daily in divided doses. Fenofibrate 67 mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

   The response to therapy should be monitored by determination of serum lipid values and the dosage may be altered within the range 2-4 capsules of Fenofibrate 67 mg daily.

   **Children**
   In children, the recommended dose is one capsule (67mg) micronised fenofibrate /
day / 20kg body weight.

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>Two 67mg capsules</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One 67mg capsule</td>
</tr>
</tbody>
</table>

4. CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics - General

The Clinical Expert Report reviews the published data on pharmacokinetics. Fenofibrate is a poorly soluble prodrug of its active metabolite, fenofibric acid. Oral absorption is about 30-50% and greatly increased by fat, being fat soluble and relatively insoluble in water. Although the SPC recommends intake with food, a low fat diet is also recommended. As stated in the Clinical Expert Report, food, especially a high fat meal, increased the bioavailability of fenofibrate. In one study the elimination half-life increased from 15 h to 26 h, high fat meal compared to a low fat meal.

Micronisation increases bioavailability, so that a daily dosage of 400 mg becomes approximately equivalent to 267 mg with the micronised form. Conversion to fenofibric acid is rapid by intestinal and plasma esterases. Fenofibric acid is highly protein bound.

4.2 Pharmacokinetics - Bioequivalence Studies

Two bioequivalence studies were carried out.

200mg strength:
The test product was Fenofibrate 200 mg capsules and the reference product Lipanthyl 200 mg Fenofibrate micronised capsules manufactured by Fournier Pharma, France. This was a cross over single dose randomised open label 2 period two treatment study with a 14 day wash out period. An HPLC method using an MS detection assay was used to measure fenofibric acid in plasma with a limit of quantitation of 50 ng/ml.

The applicant states that the study was in accordance with GCP principles.
Blood was sampled for 96 hours post dosing. A standardised breakfast was served 30 minutes before dosing with repeat meals at 4, 9, and 13 hours after dosing.
Table 1 - Fenofibric acid Pharmacokinetics, 200 mg, mean data, n = 31

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Agent, mean</th>
<th>Reference mean</th>
<th>Ratio 90% CI for log transformed</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{_max} μg/ml</td>
<td>11.8</td>
<td>11.1</td>
<td>1.04 (0.94-1.15)</td>
</tr>
<tr>
<td>T\text{_max} h</td>
<td>5.7</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>AUC\text{_α} μg.h/ml</td>
<td>222.9</td>
<td>222.5</td>
<td>0.99 (0.95-1.04)</td>
</tr>
</tbody>
</table>

267mg strength:
The test product was Fenofibrate 267 mg capsules and the reference product Lipantil micro capsules 267 mg Fenofibrate micronised capsules manufactured by Fournier Pharmaceutical UK. This was a cross over single dose randomised open label 2 period two treatment study with a 14 day wash out period. An HPLC method using an MS detection assay was used to measure fenofibric acid in plasma with a limit of detection of 0.061μg/ml.

The applicant states that the study was in accordance with GCP principles. Blood was sampled for 96 hours post dosing. A standardised breakfast was served 30 minutes before dosing with repeat meals at 4, 9, and 13 hours after dosing.

Table 2 - Fenofibric acid Pharmacokinetics, 267 mg, least square mean data, n = 26

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Agent, mean</th>
<th>Reference mean</th>
<th>Ratio 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{_max} μg/ml</td>
<td>16.8</td>
<td>16.4</td>
<td>101.1 (94.1-108.7)</td>
</tr>
<tr>
<td>T\text{_max} h</td>
<td>7.8</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>AUC\text{_α} μg.h/ml</td>
<td>341.2</td>
<td>324.3</td>
<td>105.1 (100.0-110.4)</td>
</tr>
</tbody>
</table>

Extrapolation of these data to the 67mg strength was accepted based on consideration of CHMP published criteria.

5. **EFFICACY**
No new data are presented and none are required for this application. There is a succinct and adequate overview of efficacy.

6. **SAFETY**
No new data are presented and none are required for these applications. The reference product is established and the main basis of the application depends upon the bioequivalence study.

7. **EXPERT REPORT**
A satisfactory expert report is provided by an appropriately qualified individual.

8. **SUMMARY OF PRODUCT CHARACTERISTICS**
Satisfactory.
9. PATIENT INFORMATION LEAFLET
   This is satisfactory.

10. LABELLING
    These are satisfactory.

11. RECOMMENDATION
    Marketing authorisations are recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Fenofibrate 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
No new data are presented and none are required for these applications.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Fenofibrate capsules is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
FENOFIBRATE 67MG CAPSULES  
PL 14894/0367, 70 AND 73

FENOFIBRATE 200MG CAPSULES  
PL 14894/0368, 71 AND 74

FENOFIBRATE 267MG CAPSULES  
PL 14894/0369, 72 AND 75

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 23rd December 2004</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 25th January 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 25th May 2005 and 15th August 2006</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information for the quality section 28th November 2005 and 11th November 2006</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on the 2nd January 2007</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 67 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 67 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
White cap/white body, self locked hard gelatin capsules of size ‘4’ imprinted with ‘FB67’ on cap
and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia
(Fredrickson classification types IIa, IIb, III, IV and V).

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Fenofibrate should only be used in patients whose disease is unresponsive to dietary control and in
whom a full investigation has been performed to define their abnormality, and where long-term
risks associated with their condition warrant treatment. Other risk factors, such as hypertension
and smoking, may also require management.

4.2 Posology and method of administration
Adults In adults, the recommended initial dose is 3 capsules taken daily in divided doses.
Fenofibrate 67 mg Capsules should always be taken with food, because it is less well absorbed
from an empty stomach. Dietary measures instituted before therapy should be continued.
The response to therapy should be monitored by determination of serum lipid
values and the dosage may be altered within the range 2-4 capsules of Fenofibrate
67 mg daily.

Children In children, the recommended dose is one capsule (67mg) micronised fenofibrate /
day / 20kg body weight.

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:
Creatinine clearance (ml/min) | Dosage
--- | ---
<60 | Two 67mg capsules
<20 | One 67mg capsule

### 4.3 Contraindications

Fenofibrate is contra-indicated 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.

See also section 4.6 (Pregnancy and lactation)

### 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. 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).

In children Only an hereditary disease (familial hyperlipidaemia) justifies early treatment, and the precise nature of the hyperlipidaemia must be determined by genetic and laboratory investigations. It is recommended to begin treatment with controlled dietary restrictions for a period of at least 3 months. Proceeding to medicinal treatment should only be considered after specialist advice and only in severe forms with clinical signs of atherosclerosis and/or xanthomata and/or in cases where patients suffer from atherosclerotic cardiovascular disease before the age of 40.
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 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.

**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.

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

ATC code: C10 AB 05

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

Fenofibrate 67 mg Capsules is a formulation containing 67mg 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 α (PPARα). 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 PPARα 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 hyperlipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate 67 mg Capsules 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 67 mg Capsules 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 15µg/ml for a daily dosage of 200mg of micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg Capsules.

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

Intragranular
Sodium lauryl sulphate
Lactose
Pregelatinised starch
Cros pivone

Extragranular
Cros pivone
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Antifoam DC1510

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blist strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 or 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0367

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Orange cap/orange body, self locked hard gelatin capsules of size ‘0’ imprinted with ‘FB200’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (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, triglyceride</td>
<td>LDL, VLDL</td>
</tr>
<tr>
<td>III</td>
<td>Cholesterol, triglyceride</td>
<td>LDL and Chylomicron Remnants</td>
</tr>
<tr>
<td>IV</td>
<td>Triglyceride</td>
<td>VLDL</td>
</tr>
<tr>
<td>V</td>
<td>Triglyceride</td>
<td>Chylomicrons, VLDL</td>
</tr>
</tbody>
</table>

Fenofibrate should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

4.2 Posology and method of administration
Adults The recommended initial dose is one capsule taken daily during a main meal. In elderly patients without renal impairment, the normal adult dose is recommended. Since it is less well absorbed from an empty stomach, Fenofibrate 200 mg Capsules should always be taken with food. Dietary restrictions instituted before therapy should be continued.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Fenofibrate 200 mg Capsules treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

4.3 Contraindications
Fenofibrate 200 mg Capsules is contra-indicated in children, in patients with severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal disorders and in patients hypersensitive to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
See also section 4.6 (Pregnancy and lactation)
4.4 Special warnings and precautions for use
Renal Impairment In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 200 mg Capsules (micronised fenofibrate) should be used, e.g. 2 capsules of Fenofibrate200 mg Capsules daily for creatinine clearance levels of <60 ml/min and 1 capsule of Fenofibrate 200 mg Capsules daily for creatinine clearance levels of <20 ml/min.
Use of Fenofibrate 200 mg Capsules is also to be preferred in elderly patients with renal impairment where dosage reduction may be required.
Serum 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. 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).

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.
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 200 mg Capsules 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
Adverse reactions observed during Fenofibrate Micro 200 treatment are not very frequent (2 - 4 % of cases): 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.

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.
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
ATC code:C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 200 mg Capsules is a formulation containing 200mg of micronised fenofibrate; the administration of this product results in effective plasma concentrations identical to those obtained with 3 capsules of Fenofibrate 67 mg Capsules containing 67mg 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 α (PPARα). 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 PPARα 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 abnormally increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemia forms the rationale for treatment with Fenofibrate Micro 200. However the possible beneficial and adverse long term consequences of drugs used in the management of dyslipidaemia are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate Micro 200 on cardiovascular morbidity and mortality is as yet unproven.
Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which epidemiological studies have correlated with a decrease in atherogenic risk. 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 disease. Fenofibrate 200 mg Capsules 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 15µg/ml for a daily dose of 200mg of micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg.
Steady state levels are observed throughout continuous treatments.
Fenofibric acid is highly bound to plasma albumin; it can displace antivitamin K compounds from protein binding sites and may potentiate their anti-coagulant effect.
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 the 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
Intragranular
Sodium lauryl sulphate
Lactose
Pregelatinised starch
Crospovidone

Extragranular
Crospovidone
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)
Sunset yellow FCF (E110)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Antifoam DC1510

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0368

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 267 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 267 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Ivory yellow cap/green body, self locked hard gelatin capsules of size ‘0 elongated’ imprinted with ‘FB267’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate 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 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>
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<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 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. The initial recommended dose is one capsule of Fenofibrate 267 mg Capsules taken daily with food. However, in patients with severe dyslipidaemia, an increased dose of 267mg (Fenofibrate 267 mg Capsules), is recommended. Fenofibrate 267 mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

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>One Fenofibrate Micro 140 mg capsule</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>One Fenofibrate Micro 67 mg capsule</td>
</tr>
</tbody>
</table>
4.3 **Contraindications**
Fenofibrate 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.
See also section 4.6 (Pregnancy and lactation)

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. 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).

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 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.

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.

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

ATC code:C10 AB 05

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

Fenofibrate 267 mg Capsules 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 267 mg Capsules 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. Fenofibrate267 mg Capsules 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 µg/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

- Intrgranular
  - Sodium lauryl sulphate
  - Lactose
  - Pregelatinised starch
  - Crospovidone
  - Extrgranular
  - Crospovidone
  - Pregelatinised starch
  - Talc
  - Colloidal anhydrous silica
  - Magnesium stearate

- Capsule
  - Gelatin
  - Titanium dioxide (E171)
  - FD & C blue No. 2 (E132)
  - Yellow iron oxide (E172)

- Printing Ink
  - Shellac glaze
  - Iron oxide black (E172)
  - Lecithin Soya
  - Simethicone

#### 6.2 Incompatibilities
Not applicable
6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0369

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 67 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 67 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
White cap/white body, self locked hard gelatin capsules of size ‘4’ imprinted with ‘FB67’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (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, triglyceride</td>
<td>LDL, VLDL</td>
</tr>
<tr>
<td>III (rare)</td>
<td>Cholesterol, triglyceride</td>
<td>LDL 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 should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

4.2 Posology and method of administration
Adults In adults, the recommended initial dose is 3 capsules taken daily in divided doses. Fenofibrate 67 mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

The response to therapy should be monitored by determination of serum lipid values and the dosage may be altered within the range 2-4 capsules of Fenofibrate 67 mg daily.

Children
In children, the recommended dose is one capsule (67mg) micronised fenofibrate / day / 20kg body weight.
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>Two 67mg capsules</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One 67mg capsule</td>
</tr>
</tbody>
</table>

4.3 Contraindications
Fenofibrate is contra-indicated 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.

See also section 4.6 (Pregnancy and lactation)

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. 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).
In children Only an hereditary disease (familial hyperlipidaemia) justifies early treatment, and the precise nature of the hyperlipidaemia must be determined by genetic and laboratory investigations. It is recommended to begin treatment with controlled dietary restrictions for a period of at least 3 months. Proceeding to medicinal treatment should only be considered after specialist advice and only in severe forms with clinical signs of atherosclerosis and/or xanthomata and/or in cases where patients suffer from atherosclerotic cardiovascular disease before the age of 40.

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 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.

**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.

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

**ATC code:** C10 AB 05

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

Fenofibrate 67 mg Capsules is a formulation containing 67mg 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 α (PPARα). 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 PPARα 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 hyperlipidaemias are still the subject of scientific
discussion. Therefore the presumptive beneficial effect of Fenofibrate 67 mg Capsules on
vascular 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 67 mg Capsules 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 15µg/ml for a daily dosage of 200mg of micronised fenofibrate,
equivalent to 3 capsules of Fenofibrate 67 mg Capsules.

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

Intragranular
Sodium lauryl sulphate
Lactose
Pregelatinised starch
Crospovidone

Extragranular
Crospovidone
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Antifoam DC1510

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blisters strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 or 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 14894/0370

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   02/01/2007

10 DATE OF REVISION OF THE TEXT
    02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Orange cap/orange body, self locked hard gelatin capsules of size ‘0’ imprinted with ‘FB200’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

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<td>Triglyceride</td>
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</tr>
</tbody>
</table>

Fenofibrate should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

4.2 Posology and method of administration
Adults The recommended initial dose is one capsule taken daily during a main meal. In elderly patients without renal impairment, the normal adult dose is recommended. Since it is less well absorbed from an empty stomach, Fenofibrate 200 mg Capsules should always be taken with food. Dietary restrictions instituted before therapy should be continued.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Fenofibrate 200 mg Capsules treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

4.3 Contraindications
Fenofibrate 200 mg Capsules is contra-indicated in children, in patients with severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal disorders and in patients hypersensitive to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
See also section 4.6 (Pregnancy and lactation)
4.4 Special warnings and precautions for use
Renal Impairment In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 200 mg Capsules (micronised fenofibrate) should be used, e.g. 2 capsules of Fenofibrate 200 mg Capsules daily for creatinine clearance levels of <60 ml/min and 1 capsule of Fenofibrate 200 mg Capsules daily for creatinine clearance levels of <20 ml/min.
Use of Fenofibrate 200 mg Capsules is also to be preferred in elderly patients with renal impairment where dosage reduction may be required.
Serum 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. 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).

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 200 mg Capsules 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

Adverse reactions observed during Fenofibrate Micro 200 treatment are not very frequent (2 - 4% of cases): 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.

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.
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
ATC code: C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 200 mg Capsules is a formulation containing 200mg of micronised fenofibrate; the administration of this product results in effective plasma concentrations identical to those obtained with 3 capsules of Fenofibrate 67 mg Capsules containing 67mg 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 α (PPARα). 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 PPARα 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 abnormally increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemia forms the rationale for treatment with Fenofibrate Micro 200. However the possible beneficial and adverse long term consequences of drugs used in the management of dyslipidaemia are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate Micro 200 on cardiovascular morbidity and mortality is as yet unproven. Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which epidemiological studies have correlated with a decrease in atherogenic risk. 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 disease. Fenofibrate 200 mg Capsules 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 15μg/ml for a daily dose of 200mg of micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg. Steady state levels are observed throughout continuous treatments. Fenofibric acid is highly bound to plasma albumin; it can displace antivitamin K compounds from protein binding sites and may potentiate their anti-coagulant effect. 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 the 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**
**Intragranular**
Sodium lauryl sulphate  
Lactose  
Pregelatinised starch  
Crospovidone

**Extragranular**
Crospovidone  
Pregelatinised starch  
Talc  
Colloidal anhydrous silica  
Magnesium stearate

**Capsule**
Gelatin  
Titanium dioxide (E171)  
Sunset yellow FCF (E110)

**Printing Ink**
Shellac glaze  
Iron oxide black (E172)  
Lecithin Soya  
Antifoam DC1510

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store in the original package. Do not store above 25°C.

6.5 **Nature and contents of container**
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0371

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 267 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 267 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Ivory yellow cap/green body, self locked hard gelatin capsules of size ‘0 elongated’ imprinted
with ‘FB267’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate 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 is indicated in appropriate cases of dyslipidaemia (Fredrickson
classification types IIa, IIb, III, IV and V).

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</tr>
<tr>
<td>IV</td>
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<td>VLDL</td>
</tr>
<tr>
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Fenofibrate 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 The initial recommended dose is one capsule of Fenofibrate 267 mg Capsules taken daily
with food. However, in patients with severe dyslipidaemia, an increased dose of 267mg
(Fenofibrate 267 mg Capsules), is recommended. Fenofibrate 267 mg Capsules should always be
taken with food, because it is less well absorbed from an empty stomach. Dietary measures
instituted before therapy should be continued.

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>One Fenofibrate Micro 140 mg capsule</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>One Fenofibrate Micro 67 mg capsule</td>
</tr>
</tbody>
</table>
4.3 Contraindications
Fenofibrate 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.
See also section 4.6 (Pregnancy and lactation)

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. 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).

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 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.

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.

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
ATC code:C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 267 mg Capsules 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 α (PPARα). 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 PPARα 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 267 mg Capsules 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. Fenofibrate267 mg Capsules 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 µg/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
Intragranular
Sodium lauryl sulphate
Lactose
Pregelatinised starch
Crospovidone

Extragranular
Crospovidone
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)
FD & C blue No. 2 (E132)
Yellow iron oxide (E172)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Simethicone

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years
6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0372

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 67 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 67 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
White cap/white body, self locked hard gelatin capsules of size ‘4’ imprinted with ‘FB67’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (Fredrickson classification types IIa, IIb, III, IV and V).

Type | Major lipid elevated | Lipoproteins elevated
---|---|---
IIa  | Cholesterol | LDL
IIb  | Cholesterol, triglyceride | LDL, VLDL
III (rare) | Cholesterol, triglyceride | LDL and Chylomicron Remnants
IV   | Triglyceride | VLDL
V (rare) | Triglyceride | Chylomicrons, VLDL

Fenofibrate should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

4.2 Posology and method of administration
Adults In adults, the recommended initial dose is 3 capsules taken daily in divided doses. Fenofibrate 67 mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

The response to therapy should be monitored by determination of serum lipid values and the dosage may be altered within the range 2-4 capsules of Fenofibrate 67 mg daily.

Children
In children, the recommended dose is one capsule (67mg) micronised fenofibrate / day / 20kg body weight.

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>Two 67mg capsules</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One 67mg capsule</td>
</tr>
</tbody>
</table>

4.3 Contraindications
Fenofibrate is contra-indicated 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.

See also section 4.6 (Pregnancy and lactation)

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. 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).

In children Only an hereditary disease (familial hyperlipidaemia) justifies early treatment, and the precise nature of the hyperlipidaemia must be determined by genetic and laboratory investigations.
It is recommended to begin treatment with controlled dietary restrictions for a period of at least 3 months. Proceeding to medicinal treatment should only be considered after specialist advice and only in severe forms with clinical signs of atherosclerosis and/or xanthomata and/or in cases where patients suffer from atherosclerotic cardiovascular disease before the age of 40.

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 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, diarrhea, and flatulence) moderate in severity.

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.

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

ATC code:C10 AB 05

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

Fenofibrate 67 mg Capsules is a formulation containing 67mg 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 α (PPARα). 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 PPARα 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 hyperlipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate 67 mg Capsules 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 67 mg Capsules 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 15µg/ml for a daily dosage of 200mg of micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg Capsules.

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

Intragranular

Sodium lauryl sulphate
Lactose
Pregelatinised starch
Crospondin

Extragranular

Crospondin
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Antifoam DC1510

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil

Pack size of 28 or 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0373

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Orange cap/orange body, self locked hard gelatin capsules of size ‘0’ imprinted with ‘FB200’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate reduces elevated serum cholesterol and triglyceride 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 is therefore indicated in appropriate cases of hyperlipidaemia (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, triglyceride</td>
<td>LDL, VLDL</td>
</tr>
<tr>
<td>III (rare)</td>
<td>Cholesterol, triglyceride</td>
<td>LDL 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 should only be used in patients whose disease is unresponsive to dietary control and in whom a full investigation has been performed to define their abnormality, and where long-term risks associated with their condition warrant treatment. Other risk factors, such as hypertension and smoking, may also require management.

4.2 Posology and method of administration
Adults The recommended initial dose is one capsule taken daily during a main meal. In elderly patients without renal impairment, the normal adult dose is recommended. Since it is less well absorbed from an empty stomach, Fenofibrate 200 mg Capsules should always be taken with food. Dietary restrictions instituted before therapy should be continued.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Fenofibrate 200 mg Capsules treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

4.3 Contraindications
Fenofibrate 200 mg Capsules is contra-indicated in children, in patients with severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal disorders and in patients hypersensitive to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
See also section 4.6 (Pregnancy and lactation)

4.4 Special warnings and precautions for use
Renal Impairment In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 200 mg Capsules
(micronised fenofibrate) should be used, e.g. 2 capsules of Fenofibrate 200 mg Capsules daily for creatinine clearance levels of <60 ml/min and 1 capsule of Fenofibrate 200 mg Capsules daily for creatinine clearance levels of <20 ml/min.

Use of Fenofibrate 200 mg Capsules is also to be preferred in elderly patients with renal impairment where dosage reduction may be required.

Serum 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. 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 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.

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).

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 200 mg Capsules 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
Adverse reactions observed during Fenofibrate Micro 200 treatment are not very frequent (2 -
4 % of cases): 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.

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.

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

ATC code: C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 200 mg Capsules is a formulation containing 200mg of micronised fenofibrate; the administration of this product results in effective plasma concentrations identical to those obtained with 3 capsules of Fenofibrate 67 mg Capsules containing 67mg 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 abnormally increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemia forms the rationale for treatment with Fenofibrate Micro 200. However the possible beneficial and adverse long term consequences of drugs used in the management of dyslipidaemia are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate Micro 200 on cardiovascular morbidity and mortality is as yet unproven.

Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which epidemiological studies have correlated with a decrease in atherogenic risk. 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 disease. Fenofibrate 200 mg Capsules 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 dose of 200mg of micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg.
Steady state levels are observed throughout continuous treatments.
Fenofibric acid is highly bound to plasma albumin; it can displace antivitamin K compounds from protein binding sites and may potentiate their anti-coagulant effect.
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 the 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

Intragranular
Sodium lauryl sulphate
Lactose
Pregelatinised starch
Crosopvidone

Extragranular
Crosopvidone
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Capsule
Gelatin
Titanium dioxide (E171)
Sunset yellow FCF (E110)

Printing Ink
Shellac glaze
Iron oxide black (E172)
Lecithin Soya
Antifoam DC1510

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
<table>
<thead>
<tr>
<th>8</th>
<th>MARKETING AUTHORISATION NUMBER(S)</th>
<th>PL 14894/0374</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION</td>
<td>02/01/2007</td>
</tr>
<tr>
<td>10</td>
<td>DATE OF REVISION OF THE TEXT</td>
<td>02/01/2007</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 267 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 267 mg fenofibrate.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Ivory yellow cap/green body, self locked hard gelatin capsules of size ‘0 elongated’ imprinted with ‘FB267’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate 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 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 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 The initial recommended dose is one capsule of Fenofibrate 267 mg Capsules taken daily with food. However, in patients with severe dyslipidaemia, an increased dose of 267mg (Fenofibrate 267 mg Capsules), is recommended. Fenofibrate 267 mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

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>One Fenofibrate Micro 140 mg capsule</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>One Fenofibrate Micro 67 mg capsule</td>
</tr>
</tbody>
</table>
4.3 Contraindications
Fenofibrate 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.
See also section 4.6 (Pregnancy and lactation)

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. 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 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.
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).

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.
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 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.

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.
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
ATC code:C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 267 mg Capsules 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 a (PPARα). 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 PPARα 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 267 mg Capsules 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. Fenofibrate267 mg Capsules 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 µg/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

Intragranular
- Sodium lauryl sulphate
- Lactose
- Pregelatinised starch
- Crospovidone

Extragranular
- Crospovidone
- Pregelatinised starch
- Talc
- Colloidal anhydrous silica
- Magnesium stearate

Capsule
- Gelatin
- Titanium dioxide (E171)
- FD & C blue No. 2 (E132)
- Yellow iron oxide (E172)

Printing Ink
- Shellac glaze
- Iron oxide black (E172)
- Lecithin Soya
- Simethicone

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 28 Tablets.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
95 Park Lane, Mayfair
London
W1K 7TE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0375

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
02/01/2007
PATIENT INFORMATION LEAFLET

FENOFIBRATE 67 mg CAPSULES
FENOFIBRATE 200 mg CAPSULES
FENOFIBRATE 267 mg CAPSULES

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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Fenofibrate Capsules are and what are they used for.
2. Before you take Fenofibrate Capsules.
3. How to take Fenofibrate Capsules.
4. Possible side effects.
5. Storing Fenofibrate Capsules.

The name of the medicine is Fenofibrate 67 mg, 200 mg and 267 mg capsules (referred to as Fenofibrate capsules or Fenofibrate throughout this leaflet). Fenofibrate capsules are available in three strengths:
- 67 mg, 200 mg or 267 mg.

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

The active ingredient is Fenofibrate.
Fenofibrate 67 mg Capsules are white cap/white body imprinted with “FB67” on cap and body containing white to off-white granular powder.
Fenofibrate 200 mg Capsules are orange cap/orange body imprinted with “FB200” on cap and body containing white to off-white granular powder.
Fenofibrate 267 mg Capsules are ivory yellow cap/white body imprinted with “FB267” on cap and body containing white to off-white granular powder.
Each tablet contains the active ingredient: fenofibrate.

Each tablet also contains the following inactive ingredients: lactose monohydrate, magnesium stearate, gelatin and titanium dioxide (E171).
The black printing ink contains shellac glaze, iron oxide black and lecithin soya.
The 67 mg capsules also contain antifoam DC1510 in the printing ink.
The 200 mg capsules also contain sunset yellow FCF (E110) and antifoam DC1510.
The 267 mg capsules also contain FD & C Blue No. 2 (E102), yellow iron oxide (E172) and talc.
Fenofibrate capsules are available in pack sizes of 28 capsules.
Fenofibrate belongs to the class of medicines called fibrates - lipid reducing agents that lower triglyceride reducing.
Fenofibrate capsules are used for one or more of the following:
- Treatment of high blood fats (cholesterol/triglycerides).
You will have had a blood test that shows you have raised levels of cholesterol/triglycerides or both.
You will initially be told about diet changes by your doctor.
If these diet changes are not enough to reduce the fats in the blood then your doctor will advise you to commence this medication.

Marketing Authorisation Holder: Ranbaxy (UK) Ltd., 95 Park Lane, Marylebone, London W1K 7TE.
Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co Tipperary, Republic of Ireland.

2. BEFORE YOU TAKE FENOFIBRATE CAPSULES

Do not take Fenofibrate Capsules if any of the following apply to you.
- You have previously had an allergic reaction to fenofibrate or any of the ingredients listed above.
- An allergic reaction can include rash, hives, itching, swelling of face/eyes/ears/feet or breathing difficulties.
- You have been sensitive to or had an allergy to the sunlight whilst taking drugs such as interferons or anti-inflammatory drugs (e.g. ibuprofen).
- You are under 18 years of age.
- You have severe kidney or liver problems (including biliary cirrhosis).
- You have a problem with your gallbladder.
- You have had a problem with your gallbladder.
- You have kidney problems: your doctor will start you on a lower dose.
- You have or may have previously had pancreatitis (inflammation of the pancreas).
- You have hypothyroidism (low thyroid function).
Please consult your doctor if any of the above were applicable to you in the past.

Pregnancy and Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Taking other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but bought/obtained without a prescription. You should especially be aware and notify your doctor if you are taking:
- You are already taking drugs to lower your lipids (fat).
- You are taking oestrogens e.g. HRT or oral
contraceptive pills.
- You are taking anticoagulants (drugs that "thin" the blood) e.g. warfarin
- You are taking cyclosporin
- You are taking any drugs for depression e.g. MAOIs (monoamine oxidase inhibitors)
- You are on treatment for diabetes e.g. sulphonylurea, metformin, insulin
You should avoid drinking alcohol with fenofibrate as this increases the risk of muscle problems.

Important Information about some of the ingredients of Fenofibrate Capsules
Your medicine contains an inactive ingredient called 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.
Your medicine also contains small amounts of inactive ingredients called sunset yellow (E 110) and FD & C Blue (E 132) which are found in the 200 mg and 267 mg tablets respectively. These are colouring agents and can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

3. HOW TO TAKE FENOFRIBRATE CAPSULES
Take your medicine as instructed by your doctor. Do not take more than the doctor told you to. Check the label carefully for how much to take and how often to take. Your pharmacist or doctor can help if you are not sure.
The standard doses for fenofibrate are:
67mg capsules: The recommended initial dose is three 67mg capsules in divided doses, with food.
200mg and 267mg capsules: The recommended dose is one 200mg capsule taken once daily, with food. In patients with very high lipids your doctor may recommend an increased dose of 267mg daily. This should be taken with food.
Do not change your dose unless told by your doctor.
The response to therapy should be monitored by regular blood tests.
Swallow the capsule(s) whole with a glass of water. The capsules should be taken with or after food to help you remember to take your medicine, try to get into the habit of taking it at the same time each day.
Take your capsules as directed and for as long as directed; do not stop them, even if you feel better, as otherwise the symptoms may return.
If you have the impression that the effect of Fenofibrate Capsules is too strong or too weak, talk to your doctor or pharmacist.
If you forget to take Fenofibrate Capsules at the right time, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.
If you have taken more Fenofibrate Capsules than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some capsules with you so your doctor will know what you have taken.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Fenofibrate Capsules can have side effects.
If any of the following happen, stop taking Fenofibrate Capsules and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Rashes, hives, itching, chest constriction, shortness of breath or swelling of face, lips, hands/feet, fainting, high temperature
These are very serious side effects. If you have them you may have had a serious allergic reaction or other type of reaction to Fenofibrate. You may need urgent medical attention or hospitalization.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- Chest pain, difficulty with breathing
- Severe muscle pains, cramps or weakness in muscles
Tell your doctor if you notice any of the following:
- Abdominal pains, nausea, vomiting, diarrhoea or increased flatulence
- Skin rashes, itching, hives or reactions to sunlight leading to redness, blistering and lumpiness of the skin. You should take care to avoid sun exposure and avoid artificial light e.g. sun lamps,
- Headache, fatigue, dizziness or vertigo
- Lack of sexual drive
- Hair loss - rare
There may be changes in certain laboratory tests (your doctor may require you to have blood tests at intervals)
- Liver blood tests, rarely fenofibrate can cause inflammation of the liver and pancreas, and gallstones. Tell your doctor if you notice any yellowing of the skin or abdominal pain
- Kidney blood tests and anaemia or reduction in white blood cells may occur. These are usually mild and resolve on stopping the drug.
Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

5. STORING FENOFRIBRATE CAPSULES
Do not store above 25°C. Store in the original package.
Keep out of the reach and sight of children.
Do not take after the expiry date on the label.
If your doctor tells you to stop taking the capsules, please take them back to the pharmacist.

This leaflet was prepared in August 2005.
Labelling

Braille translation is
fenofibrate
≠67 mg
capsules
Each capsule contains, as the active ingredient:
Fenofibrate 67 mg. The capsules also contain lactose.
Use as directed by a physician.
For oral use only.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Braille translation is

fenofibrate

≠200 mg

capsules

fenofibrate

≠200 mg

capsules
Each capsule contains, as the active ingredient:
Fenofibrate 200 mg. The capsules also contain lactose and sunset yellow FCF (E110).

For oral use only. Use as directed by a physician.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Each capsule contains, as the active ingredient:
Fenofibrate 267 mg. The capsules also contain lactose
and sunset yellow PCE (E110).
For oral use only. Use as directed by a physician.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Braille translation is

fenofibrate
≠67 mg
capsules
Braille translation is

fenofibrate
≠200 mg
capsules
UKPAR Fenofibrate 67mg, 200mg, and 267mg Capsules

Each capsule contains, as the active ingredient:
Fenofibrate 200 mg. The capsules also contain lactose
and sunset yellow FCF (E110).
For oral use only. Use as directed by a physician.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Braille translation is

fenofibrate
267 mg
capsules
Each capsule contains, as the active ingredient:
Fenofibrate 267 mg. The capsules also contain lactose and sunset yellow FCF (E110).
For oral use only. Use as directed by a physician.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Braille translation is:

fenofibrate
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Each capsule contains, as the active ingredient:
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Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
UKPAR Fenofibrate 67mg, 200mg, and 267mg Capsules

Press the capsule through foil from the other side.

Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule

MA Holder: Ranbaxy (UK) Limited

Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule

Press the capsule through foil from the other side.

Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule
Fenofibrate 200mg Capsule

MA Holder: Ranbaxy (UK) Limited

Braille translation is

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Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Braille translation is

fenofibrate

≠267 mg

capsules
Each capsule contains, as the active ingredient:
Fenofibrate 267 mg. The capsules also contain lactose and sunset yellow FCF (E110).

For oral use only. Use as directed by a physician.
Do not exceed the stated dose.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
FENOFIBRATE 67MG CAPSULES
PL 14894/0367, 70 AND 73

FENOFIBRATE 200MG CAPSULES
PL 14894/0368, 71 AND 74

FENOFIBRATE 267MG CAPSULES
PL 14894/0369, 72 AND 75

STEPS TAKEN AFTER AUTHORISATION

The following table lists non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

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<td>Approved 09/02/2007</td>
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<td>12/02/2007</td>
<td>Type II</td>
<td>To include a bioequivalence study for Fenofibrate 267mg Capsules</td>
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<td>Type IB</td>
<td>To add a pack size of 90 capsules for Fenofibrate 67mg</td>
<td>Approved 03/04/2007</td>
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<tr>
<td>24/08/2007</td>
<td>Type IA</td>
<td>To update TSE Certificate of suitability for magnesium stearate</td>
<td>Approved 27/09/2007</td>
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<td>Type IA</td>
<td>To change the printing ink.</td>
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<td>10/02/2008</td>
<td>Type IA</td>
<td>To update the SPC following an Article 31 referral for Fenofibrate 200mg and 267mg Capsules (PL 14894/0368-0369)</td>
<td>Approved 04/05/2011</td>
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Annex 1

Variation applications to update SmPC sections 4.1 (Therapeutic indications) and 5.1 (Pharmacodynamics) were submitted for Fenofibrate 200mg and 267mg Capsules (PL 14894/0368-0369) following an Article 31 referral for the active substance. In addition, section 2 (Qualitative and quantitative) of the SmPCs for these products was amended to add the term 'micronised' and a minor typographical correction was made to section 4.4 of the SmPCs. Changes were made to the Patient Information Leaflet (PIL) for these products as a consequence of the SmPC updates.

These variations were approved on 4 May 2011 and the following updated SmPCs and PILs have been incorporated into these Marketing Authorisations.
SUMMARY OF PRODUCT CHARACTERISTICS
1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg micronised fenofibrate.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Hard Capsule
Orange cap/orange body, self locked hard gelatin capsules of size ‘0’
imprinted with ‘FB200’ on cap and body containing white to off white
granular powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Fenofibrate is 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
Adults The recommended initial dose is one capsule taken daily during a main
meal. In elderly patients without renal impairment, the normal adult dose is
recommended. Since it is less well absorbed from an empty stomach,
Fenofibrate 200 mg Capsules should always be taken with food. Dietary
restrictions instituted before therapy should be continued.
Response to therapy should be monitored by determination of serum lipid
values. Rapid reduction of serum lipid levels usually follows Fenofibrate 200
mg Capsules treatment, but treatment should be discontinued if an adequate
response has not been achieved within three months.

4.3 Contraindications
Fenofibrate 200 mg Capsules is contra-indicated in children, in patients with
severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal
disorders and in patients hypersensitive to fenofibrate or any component of
this medication, known photoallergy or phototoxic reaction during treatment
with fibrates or ketoprofen.
See also section 4.6 (Pregnancy and lactation)
4.4 Special warnings and precautions for use

Renal Impairment In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 67 mg Capsules (micronised fenofibrate) should be used, e.g. 2 Fenofibrate 67 mg Capsules daily for creatinine clearance levels of <60 ml/min and 1 Fenofibrate 67 mg Capsule daily for creatinine clearance levels of <20 ml/min.

Use of Fenofibrate 200 mg Capsules is also to be preferred in elderly patients with renal impairment where dosage reduction may be required.

Serum 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. 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).

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 200 mg Capsules 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
Adverse reactions observed during Fenofibrate Micro 200 treatment are not very frequent (2 - 4% of cases): 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.

**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.

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
ATC code: C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 200 mg Capsules is a formulation containing 200mg of micronised fenofibrate; the administration of this product results in effective plasma concentrations identical to those obtained with 3 capsules of 67mg 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 α (PPARα). 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 PPARα 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 abnormally increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemia forms the rationale for treatment with Fenofibrate Micro 200. However the possible beneficial and adverse long term consequences of drugs used in the management of dyslipidaemia are still the subject of scientific discussion. Therefore the presumptive beneficial effect of Fenofibrate Micro 200 on cardiovascular morbidity and mortality is as yet unproven.
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.

Studies with fenofibrate on lipoprotein fractions show decreases in levels of
LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased.
LDL and VLDL triglycerides are reduced. The overall effect is a decrease in
the ratio of low and very low density lipoproteins to high density lipoproteins,
which epidemiological studies have correlated with a decrease in atherogenic
risk. 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 disease.
Fenofibrate 200 mg Capsules 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 15µg/ml for a daily dose of 200mg of
micronised fenofibrate, equivalent to 3 capsules of Fenofibrate 67 mg.
Steady state levels are observed throughout continuous treatments.

Fenofibric acid is highly bound to plasma albumin; it can displace antivitamin K compounds from protein binding sites and may potentiate their anticoagulant effect.

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 the 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.

Embrotoxic 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

**Intragranular**
- Sodium lauryl sulphate
- Lactose
- Pregelatinised starch
- Crospovidone

**Extragranular**
- Crospovidone
- Pregelatinised starch
- Talc
- Colloidal anhydrous silica
- Magnesium stearate

**Capsule**
- Gelatin
- Titanium dioxide (E171)
- Sunset yellow FCF (E110)
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil

Pack size of 10, 14, 20, 28, 30, 56, 60 or 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement

7 Marketing authorisation holder
Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0368

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
04/05/2011
PL 14894/0369:

1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 267mg Capsules

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

3 PHARMACEUTICAL FORM
Hard Capsule
Ivory yellow cap/green body, self locked hard gelatin capsules of size ‘0 elongated’ imprinted with ‘FB267’ on cap and body containing white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fenofibrate is 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
Adults: The initial recommended dose is one capsule of Fenofibrate 267mg Capsules taken daily with food. However, in patients with severe dyslipidaemia, an increased dose of 267mg (Fenofibrate 267mg Capsules), is recommended. Fenofibrate 267mg Capsules should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.
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>
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<th>Creatinine clearance (ml/min)</th>
<th>Dosage</th>
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<tr>
<td>&lt;60</td>
<td>One Fenofibrate Micro 140mg capsule</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One Fenofibrate Micro 67mg capsule</td>
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4.3 Contraindications
Fenofibrate is contra-indicated in children, in patients with severe liver or renal dysfunction, gallbladder disease, biliary cirrhosis and in patients
hypoallergenic to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.

See also section 4.6 (Pregnancy and lactation)

4.4 Special warnings and precautions for use

Renal Impairment: In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 67mg Capsules (micronised fenofibrate) should be used, e.g. 2 Fenofibrate 67mg Capsules daily for creatinine clearance levels of <60ml/min and 1 Fenofibrate 67mg Capsule daily for creatinine clearance levels of <20ml/min.

Use of Fenofibrate 267mg Capsules is also to be preferred in elderly patients with renal impairment where dosage reduction may be required.

Serum 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. 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).

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 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.
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.

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
ATC code: C10 AB 05
Serum Lipid Reducing Agents/Cholesterol and Triglyceride Reducers/Fibrates.
Fenofibrate 267mg Capsules is a formulation containing 267mg of micronised fenofibrate; the administration of this product results in effective plasma concentrations identical to those obtained with 3 capsules of 67mg 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 α (PPARα). 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 PPARα 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 abnormally increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemia forms the rationale for treatment with Fenofibrate Micro 267. However the possible beneficial and adverse long term consequences of drugs used in the management of dyslipidaemia 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.
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 (≤34mg/dl or 0.88 mmol/L) and highest tertile of TG (≥204mg/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.

Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low density lipoproteins to high density lipoproteins, which epidemiological studies have correlated with a decrease in atherogenic risk. 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 disease. Fenofibrate 267mg Capsules 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. Fenofibrin acid is the major plasma metabolite. Peak plasma concentration occurs after a mean period of 5 hours following dosing.

Mean plasma concentration is 15µg/ml for a daily dosage of 200mg 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

Intragranular
- Sodium lauryl sulphate
- Lactose
- Pregelatinised starch
- Crospovidone

Extragranular
- Crospovidone
- Pregelatinised starch
- Talc
- Colloidal anhydrous silica
- Magnesium stearate

Capsule
- Gelatin
- Titanium dioxide (E171)
- FD & C blue No. 2 (E132)
- Yellow iron oxide (E172)

Printing Ink
- Shellac glaze
Iron oxide black
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package
Do not store above 25°C

6.5 Nature and contents of container
Blister strip of clear transparent PVC film coated with PVdC on the inner side with a backing of aluminium foil
Pack size of 10, 14, 20, 28, 30, 56, 60 or 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement

7 MARKETING AUTHORITYHOLDER
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom

8 MARKETING AUTHORITYNUMBER(S)
PL 14894/0369

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
02/01/2007

10 DATE OF REVISION OF THE TEXT
04/05/2011
PACKAGE LEAFLET: INFORMATION FOR THE USER

FENOFRIBRATE 200 mg CAPSULES
FENOFRIBRATE 267 mg CAPSULES

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

1. WHAT FENOFRIBRATE CAPSULES ARE AND WHAT THEY ARE USED FOR

Fenofibrate belongs to a group of medicines, commonly known as fibrate. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.
Fenofibrate is 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 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 FENOFRIBRATE CAPSULES

Do not take Fenofibrate Capsules if any of the following apply to you:
- If you have previously had an allergic reaction to Fenofibrate or any of the ingredients listed in section 6 (an allergic reaction can include rash, hives, itching, swelling of face/lips/tongue or breathing difficulties)
- If you have been sensitive to or had an allergy to the sunlight whilst taking drugs such as fibrate or anti-inflammatory drugs (e.g. ketoprofen)
- If you are under 18 years of age
- If you have severe kidney or liver problems (including cirrhosis)
- If you have a problem with your gallbladder
- If you are pregnant, breast-feeding, or planning to get pregnant

Take special care with Fenofibrate Capsules:
Please tell your doctor:
- If you have kidney problems (your doctor may need to start you on a lower dose)
- If you have pancreatitis (inflammation of the pancreas)
- If you have hypothyroidism (low thyroid function)
- If you have liver problems
- If you or your family have had muscle problems
- If you have problems with certain proteins in your blood
- If you are over 70 years of age

Please tell your doctor if any of the above was applicable to you in the past.

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. You should especially be aware and notify your doctor if you:

- are already taking drugs to lower your lipids (fats). Example drugs known as "statins" or other "fibrotics",
- are taking oestrogens e.g. HRT or oral contraceptive pills
- are taking anticoagulants (drugs that "thin" the blood) e.g. warfarin
- are taking cyclosporine (an immunosuppressant)

**Taking Fenofibrate Capsules with food and drink**
The capsules should be taken with or after food.

**You should avoid drinking alcohol with Fenofibrate as this increases the risk of muscle problems.**

**Pregnancy and breast-feeding**
Tell your doctor if you are, you think you might be or are planning to become pregnant.
Fenofibrate Capsules must not be taken if you are pregnant or are breast feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

**Important information about some of the ingredients of Fenofibrate**
Your medicine contains an inactive ingredient called 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.
Your medicine also contains small amounts of inactive ingredients called sunset yellow (E 110) and FD & C blue (E 132) which are found in the 200 mg and 267 mg capsules respectively. These are colouring agents and can cause allergic reactions.

3. **HOW TO TAKE** Fenofibrate Capsules

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage:**

**The usual doses for Fenofibrate are:**

- **200mg and 267mg capsules:** The recommended dose is one 200mg capsule taken once daily, with food. In patients with very high lipids your doctor may recommend an increased dose of 267mg daily.
Do not change your dose without instruction to do so by your doctor.
The response to treatment will be monitored by regular blood tests to check levels of fats in your blood. Your dose may be altered according to your response. Blood tests will also be done to check your liver function and, if necessary, your kidney function.

**Methods and route of administration**

- Swallow the capsule(s) whole with a glass of water.
- The capsules should be taken with or after food.
- To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.
If you have the impression that the effect of Fenofibrate Capsules is too strong or too weak, talk to your doctor or pharmacist.

**If you take more Fenofibrate Capsules than you should**

If you have taken more Fenofibrate Capsules than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some capsules with you so your doctor will know what you have taken.
If you forget to take Fenofibrate Capsules
If you forget to take your medicine at the right time, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Fenofibrate Capsules
Take your capsules as directed and for as long as directed; do not stop them, even if you feel better, as otherwise the symptoms may return.
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 cause side effects, although not everybody gets them.

Very serious side effects
The following are very serious side effects. If you have them you may have had a serious allergic reaction or other type of reaction to Fenofibrate Capsules. You may need urgent medical attention or hospitalisation: stop taking Fenofibrate Capsules and tell your doctor immediately or go to the casualty department at your nearest hospital if you notice the following effects:
- Rashes, hives, itching, chest constriction, shortness of breath, swelling of face, lips, hands/feet, fainting, high temperature

Serious side effects
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
Uncommonly reported: (affects 1 to 10 users in 1,000)
- Unexplained muscle pain, tenderness, or weakness, especially if accompanied by a fever or flu-like symptoms or pink or “tea coloured” urine; these may be early symptoms of muscle problem. Fenofibrate capsules may affect your muscles (muscle toxicity), and very rarely, may cause severe form of muscle toxicity known as rhabdomyolysis.
- Raised level of various liver enzymes in the blood.
- Indigestion, flatulence, gas, nausea, vomiting and/ or feeling of bloating and discomfort especially after eating food which has high fat content. You may have developed gallstones if you have these symptoms.
- Severe abdominal pain, with nausea and vomiting; these may be signs of inflammation of the pancreas.
Very rarely reported: (affects less than 1 user in 10,000)
- Yellowing of the skin or eyes, abdominal pain, itching, unexplained fatigue, dark coloured urine or pale coloured stools. These may be signs of liver problems.

Other side effects
Tell your doctor if you notice any of the following:
Very commonly reported (affects more than 1 user in 10)
- Abdominal pain, nausea, vomiting, diarrhoea or increased flatulence
- Skin rashes, itching
- Hives or reactions to sunlight leading to redness, blistering and lumpiness of the skin. You should take care to avoid sun exposure and avoid artificial light e.g. sunbeds
- Headache, fatigue, dizziness or vertigo
Rarely reported: (affects 1 to 10 users in 10,000)
- Lack of sexual drive
- Hair loss
- Slight increase in blood levels of substances normally excreted by the kidneys (urea and creatinine)
- Decrease in haemoglobin (oxygen carrying pigment in the blood) and decrease in white blood cells.
Very rarely reported: (affects less than 1 user in 10,000)
- Chronic disease of the lung tissue

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 use Fenofibrate Capsules after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Do not store above 25°C. Store in the original package.
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
- Each capsule contains 200mg or 267mg of the active substance Fenofibrate.
- The other ingredients are sodium lauryl sulphate, lactose, pregelatinised starch, crospovidone, talc, colloidal anhydrous silica, magnesium stearate, gelatin and titanium dioxide (E171).
- The black printing ink contains shellac glaze, iron oxide black and propylene glycol.
- The 200 mg capsules also contain sunset yellow FCF (E110).
- The 267 mg capsules also contain FD & C blue No. 2 (E132) and yellow iron oxide (E172).

What Fenofibrate Capsules look like and the contents of the pack
Fenofibrate capsules are available in pack sizes of 10, 14, 20, 28, 30, 56, 60 and 90 capsules. Not all pack sizes may be marketed.
Fenofibrate 200 mg Capsules are orange cap/orange body imprinted with “FB200” on cap and body containing white to off-white granular powder.
Fenofibrate 267 mg Capsules are ivory yellow cap/green body imprinted with “FB267” on cap and body containing white to off-white granular powder.

Marketing Authorisation Holder
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Manufacturer
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