Public Assessment Report

Decentralised Procedure

Fenofibrate 67mg and 200mg Capsules
Fenofibrate

UK/H/1565/01-02/DC

UK licence no: PL 00289/1158-9

Applicant: Teva UK Limited
LAY SUMMARY

On the 3\textsuperscript{rd} February 2010 the MHRA granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Fenofibrate 67mg and 200mg Capsules. These are prescription-only medicines (POM).

Fenofibrate belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood, for example, the fats known as triglycerides. Fenofibrate 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.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Fenofibrate 67mg and 200mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
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**Module 1**

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<tr>
<th><strong>Product Name</strong></th>
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<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
<td>Fenofibrate</td>
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<td><strong>Form</strong></td>
<td>Hard Capsules, 67 mg and 200 mg</td>
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<tr>
<td><strong>Strength</strong></td>
<td>67mg and 200mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Teva UK Limited</td>
</tr>
<tr>
<td></td>
<td>Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG, UK</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>CY, DE, EL, HU, PL (67 mg)</td>
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<td>UK/H/1565/01-02/DC</td>
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<td><strong>Timetable</strong></td>
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</tbody>
</table>
Module 2

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 a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Hard-gelatin capsule
Hard-gelatin capsule with opaque yellow cap and body, filled with white to off-white powder, with small agglomerates, imprinted FM67 on both cap and body

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.

4.2 Posology and method of administration
For oral administration

Adults

In adults, the recommended initial dose is three 67 mg capsules taken daily in divided doses.

Fenofibrate 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. The dosage may be altered within the range of two to four 67 mg capsules daily. Rapid reduction of serum lipid levels usually follows fenofibrate treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

Children

In children, the recommended dose is 67 mg micronised fenofibrate/day/20 kg body weight. The use of the 200 mg dosage form is contraindicated in children (see section 4.3).

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:

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<th>Creatinine clearance (ml/min)</th>
<th>Dosage</th>
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</thead>
<tbody>
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<td>Two 67 mg capsules</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>Dosage</td>
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<td>------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One 67 mg capsule</td>
</tr>
</tbody>
</table>

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

### 4.3 Contraindications
- Hypersensitivity to fenofibrate or to any of the excipients
- Severe liver or renal dysfunction
- Gallbladder disease
- Biliary cirrhosis
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia

### 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.

**Liver function**

Increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increases in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

**Pancreatitis**

Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

**Myopathy**

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be stopped.

Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

The risk of muscle toxicity may be increased if fenofibrate 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).

**Renal function**

Treatment should be interrupted in case of an increase in creatinine levels > 50% ULN (upper limit of normal). It is recommended that creatinine measurement be considered during the first three months after initiation of treatment.

**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 the 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).

**Ciclosporin**

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

**4.6 Pregnancy and lactation**

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, fenofibrate should only be used during pregnancy after a careful benefit/risk assessment.

There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Consequently it should not be used in nursing mothers.

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

Estimated frequencies of events are ranked according to the following convention: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≤1/10,000), not known (cannot be estimated from the available data).

**Investigations**

**Rare:** Increases in serum creatinine and urea, which are generally slight
Blood and lymphatic system disorders
Rare: Slight decrease in haemoglobin and leukocytes

Nervous system disorders
Rare: Headache, sexual asthenia

Ear and labyrinth disorders
Rare: Vertigo

Respiratory, thoracic and mediastinal disorders
Very rare: Interstitial pneumopathies

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

Skin and subcutaneous tissue disorders
Uncommon: Reactions such as rashes, pruritus, urticaria or photosensitivity reactions
Rare: Alopecia
Very rare: Cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sun lamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal and connective tissue disorders
Rare: Muscle toxicity (diffuse myalgia, myositis, muscular cramps and weakness)
Very rare: Rhabdomyolysis.

Vascular disorders
Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis)*

General disorders
Rare: Fatigue

Hepatobiliary disorders
Common: Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment (see section 4.4). Uncommon: Development of gallstones has been reported. Very rare: 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 section 4.4).

* In the FIELD-study, a randomised placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0% [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients]; p = 0.074).

4.9 Overdose
No case of overdose has been reported. No specific antidote is known. If overdose is suspected, symptomatic treatment and appropriate supportive measures should be instituted as required. Fenofibrate cannot be eliminated by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic classification: Lipid-modifying agents, plain; fibrates
ATC code: C10A B05
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 dyslipidaemia forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long-term consequences of agents used in the hyperlipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of fenofibrate on cardiovascular morbidity and mortality is as yet unproven.

Studies with fenofibrate consistently show decreases in levels of LDL-cholesterol and VLDL-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 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.

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.

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.

The mean plasma concentration is 15 microgrammes/ml for a daily dosage of 200 mg of micronised fenofibrate, equivalent to three 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 protein binding sites and may 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 glucuron conjugate.

Kinetic studies after administration of repeated doses show the absence of accumulation of the product.
Fenofibrate 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
Capsule contents
Sodium laurilsulfate
Povidone (K-25)
Maize Starch, pregelatinised
Crosopovidone (Type A)
Croscarmellose sodium
Sodium starch glycolate (potato origin)
Colloidal silica anhydrous
Sodium stearyl fumarate

Capsule shell
Gelatin
Titanium dioxide (E171)
Quinoline yellow
Iron oxide yellow (E172)
Edible Printing ink containing shellac, iron oxide black, propylene glycol.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package in order to protect from light. Keep the blister in the outer carton.

6.5 Nature and contents of container
Transparent PVC/PVdC – Aluminium blister packs:
Pack sizes of 1, 28, 30, 50, 60, 84, 90 or 100 hard-gelatin capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
<p>| | |</p>
<table>
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<td>9</td>
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<tr>
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<td>DATE OF REVISION OF THE TEXT 03/02/2010</td>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
Fenofibrate 200mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200mg fenofibrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Hard-gelatin capsule
Hard-gelatin capsule with opaque red-orange cap and body, filled with white to off-white powder, with small agglomerates, imprinted FM200 on both cap and body

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.

4.2 Posology and method of administration
For oral administration
For doses not realisable/practicable with this strength, other strengths and pharmaceutical forms are available.

Adults
In adults, the recommended initial dose is one 200 mg capsule taken daily during a main meal.

Fenofibrate 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. Rapid reduction of serum lipid levels usually follows fenofibrate treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

Children
In children, the recommended dose is 67 mg micronised fenofibrate/day/20 kg body weight. The use of the 200 mg dosage form is contraindicated in children (see section 4.3).

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 67 mg capsules</td>
</tr>
<tr>
<td>&lt;20</td>
<td>One 67 mg capsule</td>
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Hepatic disease
Patients with hepatic disease have not been studied.

4.3 Contraindications
Hypersensitivity to fenofibrate or to any of the excipients
Severe liver or renal dysfunction
Gallbladder disease
Biliary cirrhosis
Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia
Children (see section 4.2)

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.

Liver function

Increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increases in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Myopathy

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be stopped.

Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

The risk of muscle toxicity may be increased if fenofibrate 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).

Renal function

Treatment should be interrupted in case of an increase in creatinine levels> 50% ULN (upper limit of normal).
It is recommended that creatinine measurement be considered during the first three months after initiation of treatment.
**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 the 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).

**Ciclosporin**

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

4.6 **Pregnancy and lactation**

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, fenofibrate should only be used during pregnancy after a careful benefit/risk assessment.

There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Consequently it should not be used in nursing mothers.

4.7 **Effects on ability to drive and use machines**

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

4.8 **Undesirable effects**

Estimated frequencies of events are ranked according to the following convention: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

**Investigations**

Rare: Increases in serum creatinine and urea, which are generally slight

**Blood and lymphatic system disorders**

Rare: Slight decrease in haemoglobin and leukocytes

**Nervous system disorders**

Rare: Headache, sexual asthenia

**Ear and labyrinth disorders**

Rare: Vertigo

**Respiratory, thoracic and mediastinal disorders**

Very rare: Interstitial pneumopathies
Gastrointestinal disorders
Common: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity
Uncommon: Pancreatitis*

Skin and subcutaneous tissue disorders
Uncommon: Reactions such as rashes, pruritus, urticaria or photosensitivity reactions
Rare: Alopecia
Very rare: Cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sun lamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal and connective tissue disorders
Rare: Muscle toxicity (diffuse myalgia, myositis, muscular cramps and weakness)
Very rare: Rhabdomyolysis.

Vascular disorders
Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis)*

General disorders
Rare: Fatigue

Hepatobiliary disorders
Common: Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment (see section 4.4).
Uncommon: Development of gallstones has been reported.
Very rare: 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 section 4.4).

* In the FIELD-study, a randomised placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0 % [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients]; p = 0.074).

4.9 Overdose
No case of overdose has been reported. No specific antidote is known. If overdose is suspected, symptomatic treatment and appropriate supportive measures should be instituted as required. Fenofibrate cannot be eliminated by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic classification: Lipid-modifying agents, plain; fibrates
ATC code: C10A B05

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 dyslipidaemia forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long-term consequences of agents used in the hyperlipidaemias are still the subject of scientific discussion. Therefore the presumptive beneficial effect of fenofibrate on cardiovascular morbidity and mortality is as yet unproven.
Studies with fenofibrate consistently show decreases in levels of LDL-cholesterol and
VLDL-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 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.

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.

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.

The mean plasma concentration is 15 microgrammes/ml for a daily dosage of 200 mg of micronised
fenofibrate, equivalent to three 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
protein binding sites and may 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

Capsule contents
Sodium laurilsulfate
Povidone (K-25)
Maize Starch, pregelatinised
Crosnopvidone (Type A)
Croscarmellose sodium
Sodium starch glycolate (potato origin)
Colloidal silica anhydrous
Sodium stearyl fumarate

Capsule shell
Gelatin
Titanium dioxide (E171)
Allura red AC
Edible Printing ink containing shellac, iron oxide black, propylene glycol.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package in order to protect from light. Keep the blisters in the outer carton.

6.5 Nature and contents of container
Transparent PVC/PVdC – Aluminium blister packs:
Pack sizes of 1, 20, 28, 30, 50, 60, 90, 100 or 300 (10 x 30) hard-gelatin capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1159

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/02/2010

10 DATE OF REVISION OF THE TEXT
03/02/2010
Module 3

FENOFRIBRATE
67 mg CAPSULES

PACKAGE LEAFLET INFORMATION FOR THE PATIENT

Read all of this leaflet carefully before you start taking this medicine.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you. Do not pass it on to others, it may harm them, even if their symptoms are the same as yours.

• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

WHAT FENOFRIBRATE 67 mg CAPSULES IS AND WHAT IT IS USED FOR

Fenofibrate belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood, for example the fats known as triglycerides.

Fenofibrate 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.

BEFORE YOU TAKE FENOFRIBRATE 67 mg CAPSULES

Do NOT take Fenofibrate
• If you are allergic (hypersensitive) to fenofibrate or any of the other ingredients of this medicine.

• If you have known photo-allergy (allergic reaction caused by sunlight or exposure to UV light) or phototoxic reactions (damage to skin caused by exposure to sunlight or UV light) during treatment with fibrates (lipid-modifying medicines) or ketoprofen (an anti-inflammatory medicine).

• If you suffer from liver, kidney or gallbladder disease.

• If you suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain).

Take special care with Fenofibrate

Talk to your doctor or pharmacist:
• If you are over 70 years old.

• If you or a blood relative have or have had muscle disease.

• If you have impaired kidney function.

• If you have an underactive thyroid gland (hypothyroidism).

• If you have a high alcohol intake.

• If you are already taking another fibrate or a statin (another type of lipid-modifying medicine), or if you are taking oral contraceptives (the pill).

These factors may put you at increased risk for muscle problems during treatment with fenofibrate. You should contact your doctor immediately if you experience unexplained muscle pain, muscle tenderness or muscle weakness. This is because in rare cases, muscle problems due to fenofibrate can be serious.

Your doctor may order regular blood tests to monitor your liver and kidney function.

Pancreatitis (inflammation of the pancreas leading to abdominal pain) sometimes occurs in patients taking fenofibrate, please refer to “DON’T take Fenofibrate” above, and “4. Possible side effects” below.

In children, fenofibrate should only be used after specialist advice and genetic and laboratory tests to treat severe hereditary disease.

TAKING OTHER MEDICINES

Tell your doctor or pharmacist if you are taking any of the following:
• Anti-coagulants to thin your blood (e.g. warfarin): the risk of bleeding could be increased.

• Opioids, an immunosuppressant: your kidney function could be affected.

• Statins or fibrates, which are other lipid-modifying medicines: the risk of muscle problems could be increased (see “Take special care with Fenofibrate” above).

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

Taking Fenofibrate with food and drink

You should take Fenofibrate during a meal, as it won’t work as well if you take it on an empty stomach.

A high cholesterol level in your blood (hypercholesterolaemia) requires that you take special care, even if the high cholesterol level does not affect the way you feel. You should follow the dietary recommendations given by your doctor while taking this medicine.

Pregnancy and breastfeeding

Tell your doctor if you are, you think you might be, or are planning to become pregnant. As there is not enough experience with use of Fenofibrate during pregnancy, you should use Fenofibrate only if your doctor considers it absolutely necessary. It is not known whether the fenofibrate passes into breast-milk. Therefore, you should not use Fenofibrate if you are breastfeeding.

Driving and using machines

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

HOW TO TAKE FENOFRIBRATE 67 mg CAPSULES

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

The usual initial dose is one capsule three times a day for adults, including the elderly, your doctor may reduce your dose to two capsules a day or increase to four capsules a day depending on how you respond to treatment.

If you have impaired kidney function

Your doctor will prescribe a lower dose.

Other strengths and pharmaceutical forms of fenofibrate are available for doses not realistic/practicable with this medicinal product.
Children
The dose for children is lower than the adult dose. Your doctor will work out the correct dose depending on the child's body weight.
Ask your doctor or pharmacist if you would like more details. Other strengths and pharmaceutical forms of fenofibrate are available for doses not realisable/practicable with this medicinal product.

Method of administration
Oral use.
Swallow the capsules whole with water. It is important to take the capsules with food, as they won't work as well if your stomach is empty.
To treat your raised blood cholesterol levels, you must follow the dietary recommendations given to you by your doctor while taking this medicine.

Duration of treatment
Do not forget that for fenofibrate to be effective, it needs to be taken very regularly, and for as long as your doctor has recommended, even if this duration is a very long time. Do not stop taking this medicine unless your doctor has told you to.
If you take more Fenofibrate than you should, you should contact your nearest hospital casualty department or tell your doctor immediately.
If you forget to take Fenofibrate, you should contact your nearest hospital casualty department or tell your doctor immediately.

Possible side effects
Like all medicines, Fenofibrate can cause side effects; although not everybody gets them.
The following side effects are important and will require immediate action if you experience them. You should stop taking Fenofibrate and see your doctor immediately if the following symptoms occur.
Very rare side effects affecting fewer than 1 in 10,000 patients:
• Muscle wasting or inflammation and tenderness that may progress to become a serious, potentially life-threatening condition (called 'myositis').
Rare side effects affecting fewer than 1 in 1000 patients:
• Muscle weakness or pain.
The following side effects have also been reported.
Common (occur in more than 1 in 100 patients):
• Digestive disorders such as abdominal pain, nausea (feeling sick), vomiting (being sick), diarrhoea, flatulence
• Alterations in blood test results that show how your liver is working.
Uncommon (occur in fewer than 1 in 100 patients):
• Pancreatitis (inflammation of the pancreas leading to abdominal pain)
• Skin rashes, itching, hives, photosensitivity reactions (sensitivity to sunlight, sunlamps or sunbeds)
• Blood clots in the veins (deep vein thrombosis) or in the arteries of the lung (pulmonary embolism)
• Gallstones.
Rare (occur in fewer than 1 in 1000 patients):
• Alterations in blood test results that show how your kidneys are working
• Reduced levels of haemoglobin (oxygen-carrying pigment in blood) and white blood cells
• Headache, dizziness, reduced sex drive, tiredness
• Hair loss.
Very rare (occur in fewer than 1 in 10,000 patients):
• Chronic lung disease causing breathlessness (interstitial pneumonitis)
• Inflammation of the liver (hepatitis), which may produce jaundice (yellowing of the skin and whites of the eyes), abdominal pain and itching.
If any of the side effects gets serious, or if you notice any effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE FENOFIBRATE 67 mg CAPSULES
• Keep out of the reach and sight of children.
• Do not use Fenofibrate after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
• Store in the original package in order to protect from light. Keep the blister in the outer carton.
• 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 67 mg Capsules contain
• The active substance is fenofibrate. One hard gelatin capsule contains 67 mg fenofibrate.
• The other ingredients are sodium laurylsulfate, povidone, pregelatinised maize starch, crospovidone, croscarmellose sodium, sodium starch glycolate (potato origin), colloidal silica anhydrous and sodium stearyl fumarate. The capsule shells contain gelatin, titanium dioxide (E171), quinoline yellow and iron oxide yellow (E172) and edible printing ink containing shellac, iron oxide black, polyethylene glycol glycol.
What Fenofibrate 67 mg Capsules look like and contents of the pack
• Hard gelatin capsule: Hard gelatin capsule with opaque yellow cap and body, filled with white to off-white powder, with small agglomerates, imprinted FM67 on both cap and body
• Pack sizes of 1, 28, 30, 60, 80, 90 or 100 hard gelatin capsules.
• Not all pack sizes may be marketed.
Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne, BN22 9AG
This leaflet was last revised in January 2010.
PL 00286/1158
87791-A
160 x 223
PAR Fenofibrate 67mg and 200mg Capsules

UK/H/1565/01-02/DC

FENOFLIBRATE
200 mg CAPSULES

PACKAGE LEAFLET INFORMATION FOR THE USER

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 200 mg Capsules is and what it is used for
2. Before you take Fenofibrate 200 mg Capsules
3. How to take Fenofibrate 200 mg Capsules
4. Possible side effects
5. Handling
6. Further information

1 WHAT FENOFLIBRATE 200 mg CAPSULES IS AND WHAT IT IS USED FOR

Fenofibrate belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood, for example the fats known as triglycerides.

Fenofibrate 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.

2 BEFORE YOU TAKE FENOFLIBRATE 200 mg CAPSULES

Do NOT take Fenofibrate
- If you are allergic (hypersensitive) to fenofibrate or any of the other ingredients of this medicine
- If you have known photo-allergy (allergic reaction caused by sunlight or exposure to UV light) or phototoxic reactions (damage to skin caused by exposure to sunlight or UV light) during treatment with fibrates (lipid-modifying medicines) or ketoprofen (an anti-inflammatory medicine)
- If you suffer from liver, kidney or gallbladder disease
- If you suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain). Fenofibrate 200 mg Capsules must not be given to children.

Take special care with Fenofibrate
- Talk to your doctor or pharmacist:
  - If you are over 70 years old
  - If you or a blood relative have or have had muscle disease
  - If you have impaired kidney function
  - If you have an underactive thyroid gland (hypothyroidism)
  - If you have a high alcohol intake
  - If you are already taking another fibrate or a statin (another type of lipid-modifying medicine), or if you are taking oral contraceptives (‘the pill’).

These factors may put you at increased risk for muscle problems during treatment with fenofibrate. You should contact your doctor immediately if you experience unexplained muscle pain, muscle tenderness or muscle weakness. This is because in rare cases, muscle problems due to fenofibrate can be serious.

Your doctor may order regular blood tests to monitor your liver and kidney function.

Pancreatitis (inflammation of the pancreas leading to abdominal pain) sometimes occurs in patients taking fenofibrate; please refer to ‘Do NOT take Fenofibrate’ above, and ‘4. Possible side effects’ below.

In children, fenofibrate should only be used after specialist advice and genetic and laboratory tests to treat severe hereditary disease.

Taking other medicines
Tell your doctor or pharmacist if you are taking any of the following:
- Anti-coagulants to thin your blood (e.g. warfarin): the risk of bleeding could be increased
- Glitazones, an immunosuppressant: your kidney function could be affected
- Statins or fibrates, which are other lipid-modifying medicines: the risk of muscle problems could be increased (see ‘Take special care with Fenofibrate’ above).

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

Taking Fenofibrate with food and drink
You should take Fenofibrate during a meal, as it won’t work as well if you take it on an empty stomach.

A high cholesterol level in your blood (hypercholesterolaemia) requires that you take special care, even if the high cholesterol level does not affect the way you feel. You should follow the dietary recommendations given by your doctor while taking this medicine.

Pregnancy and breastfeeding
Tell your doctor if you are, you think you might be or are planning to become pregnant. As there is not enough experience with use of Fenofibrate during pregnancy, you should use Fenofibrate only if your doctor considers it absolutely necessary. It is not known whether the fenofibrate passes into breast milk. Therefore, you should not use Fenofibrate if you are breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicines.

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

3 HOW TO TAKE FENOFLIBRATE 200 mg CAPSULES

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

The usual dose is one capsule a day for adults, including the elderly.

If you have impaired kidney function
Your doctor will prescribe a lower dose. Other strengths and pharmaceutical forms of fenofibrate are available for doses not realisable/practicable with this medicinal product.

20
Children
The dose for children is lower than the adult dose. Your doctor will work out the correct dose depending on the child’s body weight. Ask your doctor or pharmacist if you would like more details. Other strengths and pharmaceutical forms of fenofibrate are available for doses not realisable/practicable with this medicinal product.

Method of administration
Oral use.
Swallow the capsules whole with water. It is important to take the capsules with food, as they won’t work as well if your stomach is empty.
To treat your raised blood cholesterol levels, you must follow the dietary recommendations given to you by your doctor while taking this medicine.

Duration of treatment
Do not forget that for fenofibrate to be effective, it needs to be taken very regularly, and for as long as your doctor has recommended, even if this duration is a very long time. Do not stop taking this medicine unless your doctor has told you to.
If you take more Fenofibrate than you should
If you accidentally take too many capsules, or you think that a child has swallowed any, contact your nearest hospital casualty department or tell your doctor immediately.
If you forget to take Fenofibrate
If you forget to take Fenofibrate, take it with your next meal, unless it is time to take your next dose; do not take a double dose to make up for a forgotten one.
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 can cause side effects, although not everybody gets them.
The following side effects are important and will require immediate action if you experience them. You should stop taking Fenofibrate and see your doctor immediately if the following symptoms occur:

Very rare side effects affecting fewer than 1 in 10,000 patients:
- Muscle wasting or inflammation and tenderness that may progress to become a serious, potentially life-threatening condition (called ‘rhabdomyolysis’).

Rare side effects affecting fewer than 1 in 1,000 patients:
- Muscle weakness or pain.
The following side effects have also been reported.

Common (occur in more than 1 in 100 patients):
- Digestive disorders such as abdominal pain, nausea (feeling sick), vomiting (being sick), diarrhoea, flatulence
- Alterations in blood test results that show how your liver is working.

Uncommon (occur in fewer than 1 in 100 patients):
- Pancreatitis (inflammation of the pancreas leading to abdominal pain)
- Skin rashes, itching, hives, photosensitivity reactions (sensitivity to sunlight, sunlamps or sunbeds)
- Blood clots in the veins (deep vein thrombosis) or in the arteries of the lung (pulmonary embolism)
- Gallstones.

Rare (occur in fewer than 1 in 1,000 patients):
- Alterations in blood test results that show how your kidneys are working
- Reduced levels of haemoglobin (oxygen-carrying pigment in blood) and white blood cells
- Headache, dizziness, reduced sex drive, tiredness
- Hair loss.

Very rare (occur in fewer than 1 in 10,000 patients):
- Chronic lung disease causing breathlessness (interstitial pneumonitis)
- Inflammation of the liver (hepatitis), which may produce jaundice (yellowing of the skin and whites of the eyes), abdominal pain and itching.

If any of the side effects gets serious, or if you notice any effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FENOFRIBRATE 200 mg CAPSULES

- Keep out of the reach and sight of children.
- Do not use Fenofibrate after the expiry date which is stated on the carton and blister after EXP the expiry date refers to the last day of that month.
- Store in the original package in order to protect from light. Keep the blister in the outer carton.
- 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 200 mg Capsules contain:
- The active substance is fenofibrate. One hard-gelatin capsule contains 200 mg fenofibrate.
- The other ingredients are sodium lauryl sulphate, povidone, pregelatinised maize starch, crospovidone, croscarmellose sodium, sodium starch glycolate (potato origin), colloidal silica anhydrous and sodium stearyl fumarate.
The capsule shells contain gelatin, titanium dioxide (E171), ferric red AC and edible printing ink containing shellac, iron oxide black, propylene glycol.

What Fenofibrate 200 mg Capsules look like and contents of the pack:
- Hard-gelatin capsule: Hard-gelatin capsule with opaque red-orange cap and body, filled with white to off-white powder, with small agglomerates. Imprinted FM200 on both cap and body
- 200 mg: Pack sizes of 1, 20, 28, 30, 50, 60, 90, 100 or 100 (10 x 10) hard-gelatin capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
TEVA UK Limited, Eastbourne, BN22 9AG.
This leaflet was last revised in January 2010.
PL 00289/1159
88028-A
160 x 323
Module 4

Labelling
PAR Fenofibrate 67mg and 200mg Capsules

UK/H/1565/01-02/DC
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Fenofibrate 67mg and 200mg Capsules in the treatment of dyslipidaemia, is approvable.

These are abridged applications submitted according to Art 10(1) of Directive 2001/83/EC, as amended, of the Decentralised Procedure (DCP) for generic applications. Fenofibrate was first licensed in the UK over 10 years ago. The reference medicinal product authorised for not less than 6/10 years in the EEA is the UK product Lipantil® Micro authorised to Fournier Pharmaceuticals Ltd on 11th September 1997. The licence is now held by Solvay Healthcare UK. The reference product used in the bioequivalence study that supports this application was Lipanthyl 200®M, lot 76148, Laboratoires Fournier SA, France.

The applicant, TEVA (UK) Ltd, has applied through the Decentralised Procedure with the UK acting as reference member state (RMS) and with the following CMS:

UK/H/1565/01/DC (67 mg): CY, DE, EL, HU, PL

UK/H/1565/02/DC (200 mg): BG, CY, DE, EL, ES, HU, IT, PL, SK

Fenofibrate, a fibric acid derivative, is used to reduce low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase high-density lipoprotein (HDL)-cholesterol, in the management of hyperlipidaemias.

The submitted dossier is of an acceptable standard.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
### ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Fenofibrate 67mg, 200mg Capsules</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Fenofibrate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>C10A B05</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Hard gelatin capsules, 67mg, 200mg</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Member States Concerned</td>
<td>UK/H/1565/01/DC (67 mg): CY, DE, EL, HU, PL</td>
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<td></td>
<td>UK/H/1565/02/DC (200 mg): BG, CY, DE, EL, ES, HU, IT, PL, SK</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/1158-9</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG</td>
</tr>
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</table>
II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: fenofibrate

Chemical Name: 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

Structure:

Molecular Formula: $C_{20}H_{21}ClO_4$

Molecular Weight: 360.8

Appearance: A white or almost white crystalline powder, practically insoluble in water, very soluble in methylene chloride, slightly soluble in alcohol.

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

Other ingredients
Other ingredients consist of the pharmaceutical excipients colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulfate, sodium stearyl fumarate, sodium starch glycolate, titanium dioxide E171, Quinoline yellow E104, Allura red (E129), Gelatin, Yellow Iron Oxide E172, crospovidone Type A, Opacode S-1-27794 Black, Tekprint SW-9008 Black Ink, Pregelatinised maize starch, Povidone K25, Shellac, Iron Oxide Black 17269 and Propylene Glycol.

All excipients comply with their respective European Pharmacopoeia monographs except Opacode S-1-27794 Black and Tekprint SW-9008 Black Ink which comply with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Confirmation has been provided that the hard gelatin capsule is the only excipient of animal origin included in these drug products. Suitable assurances concerning the satisfactory TSE status of the gelatin used by Capsugel in the manufacture of these hard shell capsules have been provided.

Pharmaceutical Development
Suitable pharmaceutical development data have been provided for these applications.

The aim of the pharmaceutical development was to obtain immediate-release capsules with identical qualitative/quantitative composition with respect to the active ingredient, and bioequivalent to the brand leader Lipanthyl® capsules.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

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

Container-Closure System
The finished product is packed in PVC/ PVdC/Aluminium blister packs.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set for the unopened product, with the storage instructions ‘Store in the original package’, ‘Keep container in the outer carton’ and ‘Protect from light’.
Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

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

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

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

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

III. PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of fenofibrate are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

IV. CLINICAL ASPECTS
Pharmacokinetics
Fenofibrate is a well known active substance and the pharmacokinetic characteristics have been studied in the past. The applicant has submitted a bioequivalence study in support of claims of essential similarity.
Bioequivalence study
An open-label, single dose, randomised, two-period, two-sequence, two-treatment, crossover comparative bioavailability study between the test generic product, Fenofibrate 200 mg Capsules (B/No K-33363) and the reference product, Lipanthyl® 200 mg capsules from Fournier SA in France (B/No: 76148), was conducted in healthy subjects under fed conditions. Thirty-six subjects were dosed in Period I but only thirty-one subjects completed the study and were analysed. The washout period was 14 days between the two administrations. Blood samples were taken pre-dose, and at half hourly intervals between the first and seventh hours, then at 8, 10, 12, 24, 48, 72 and 96 hours post-dose.

The French reference product is considered to be equivalent to the UK reference product, Lipantil®.

The plasma concentration of fenofibric acid was measured by HPLC/UV. The stated assay range of the system used was 50.06 to 20021.00 ng/mL Further analytical and pharmaceutical details are available in the accompanying Quality Assessment Report.

Pre-defined bioequivalence acceptance criteria
The protocol defines acceptance criteria of 0.8 – 1.25 for AUC and 0.7 – 1.43 for Cmax.

The order of product administration was generated by a randomisation scheme shown on module 5 of the submitted dossier.

Acceptance criteria of 0.8 – 1.25 for AUC is satisfactory. Acceptance criteria of 0.7 – 1.43 for Cmax is not acceptable but this point will be demoted since the applicant returned figures for Cmax that were within 0.8 – 1.25. The randomisation scheme appears random and balanced for sequence.

Protocol
Subjects were admitted to the research facility and were fasted overnight for at least 10hrs and 30mins. Subjects were required to consume completely a high-fat, high-calorie breakfast prior to drug administration.

The SPC states: “Method of administration: the tablet should be swallowed whole during a meal” and “The absorption of fenofibrate is increased when administered with food.” A bioequivalence study in the fed state is therefore acceptable. The schedule of blood collection is adequate for AUCt > 80% of AUCinf. The sampling frequency around Tmax was adequate for accurate Cmax estimation. The washout period of 14 days is adequate to avoid carry-over. There were “zero baseline plasma levels” at the start of period 2. Individual and aggregated concentration-time profiles have been inspected. The inter-individual variations displayed are consistent with known data. The plasma concentration – time curves are acceptable. All points are acceptable.

Protocol deviations are shown in module 5 of the submitted dossier. Most were minor deviations in blood sampling time. 2 deviations were dietary indiscretions before or after drug administration. One individual returned an incomplete urinalysis result. None of the deviations resulted in exclusion from the final statistical analysis.
The qualified investigator judged that deviations were unlikely to affect the conclusions of the study.

The management of protocol deviations is acceptable.

**Safety**
Safety was evaluated in a descriptive manner only. Adverse events (29 in total) are described and safety data is displayed in module 5 of the submitted dossier. Events were judged by a qualified or medical investigator and classified according to COSTART terms. Most issues were regarded as “mild” or “moderate” and most were considered to be “unrelated”, “unlikely to be related” or “possibly related” to drug administration. All had resolved within the timeframe of the study except for one instance of “pain at the injection site”, one instance of “oedema at the injection site” and one case of “hypochromic anaemia” that was “unlikely to be related” to drug administration. One subject reported “burning on urination” that resolved with antibiotic treatment.

The safety issues reported were similar in the test and reference product arms of the study and are consistent with known data on fenofibrate.

**Bio-analytical results**
Method of data analysis: AUC and Cmax were calculated by statistical analysis of a parametric ANOVA model of log-transformed data. Tmax was calculated by a non-parametric method.
The method of data analysis is acceptable.

<table>
<thead>
<tr>
<th>Analyte: fenofibric acid</th>
<th>Test</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>11.9</td>
<td>11.7</td>
</tr>
<tr>
<td>AUC$_{t}$ (mg.h/L)</td>
<td>198</td>
<td>197</td>
</tr>
<tr>
<td>AUC$_\infty$ (mg.h/L)</td>
<td>204</td>
<td>202</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>5.65</td>
<td>5.37</td>
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The unchanged compound is not recovered in the plasma. Fenofibric acid is the major plasma metabolite. The UK SPC states that the peak plasma concentration occurs “within 5 hours”.

The Cmax for fenofibrate is reported in: Dollery C (Ed) Therapeutic Drugs 2nd edition (1999) published by Churchill Livingstone Edinburgh (UK). According to Dollery, 300mg fenofibrate (non-micronised) given orally results in Cmax = 6 – 9.5mg/L. Micronised fenofibrate results in increased bioavailability of (about) 50%. On that basis, the results reported by the applicant are credible.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals (results are shown to 2 decimal points):

<table>
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<tr>
<th>Fenofibric acid test/reference ratio %, 90% confidence intervals</th>
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<tbody>
<tr>
<td>Cmax (ng/mL)</td>
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<tr>
<td>101.72, 96.90 – 106.76</td>
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<tr>
<td>AUC$_{t}$</td>
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<tr>
<td>100.28, 98.07 – 102.54</td>
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The 90% confidence intervals for test/reference ratio lie within the acceptance criteria of 80 – 125. This is acceptable.

The applicant has submitted results that are consistent with bioequivalence of the 200mg presentations of the test and reference products in the fed state. The results of study 40224 with the 200mg formulation (as described in this assessment report) may be extrapolated to other strength in this application (67mg).

**Pharmacodynamics**
New data are not submitted. New data are not required for generic medicinal products provided bioequivalence has been satisfactorily demonstrated.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.

**Expert Reports**
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.

**Conclusion**
The medical assessor recommended that marketing authorisation was granted for this product.

**Module 1 – Administrative information**

*MAA forms*
The MAA form is medically satisfactory.

*SPC, PIL, Labels*
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Conclusion**
The medical assessor recommended that marketing authorisation was granted for this product.

**V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Fenofibrate 67mg and 200mg 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 an application of this type.

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Fenofibrate 160mg Film-coated Tablets and their respective reference products. As the 67mg and 200mg products meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength can be extrapolated to the 67mg strength capsules also.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and Labelling are satisfactory and consistent with those for the reference product.

**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 is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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