Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Fenofibrate 160mg Film-coated Tablets

Fenofibrate

UK/H/1566/01/DC

UK licence no: PL 00289/1161

Applicant: Teva UK Limited

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On the 21st January 2010 the MHRA granted Teva UK Limited a Marketing Authorisation (licence) for the medicinal product Fenofibrate 160mg Film-coated Tablets. This is a prescription-only medicine (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 this application and it was, therefore, judged that the benefits of taking Fenofibrate 160mg Film-coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Fenofibrate 160 mg Film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Fenofibrate
Form	Film-Coated Tablet
Strength	160mg
MA Holder	Teva UK Limited Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG, UK
RMS	UK
CMS	BG, CY, CZ, DE, EL, ES, PL, RO, SI, SK
Procedure Number	UK/H/1566/01/DC
Timetable	Day 210 – 10th January 2010

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

[Fenofibrate 160mg Film-coated Tablets and associated names]

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 160 mg of fenofibrate.

Excipients

Each film-coated tablet contains 212 mg of lactose monohydrate..
Each film-coated tablet contains 0.45 mg of soya lecithin.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off-white, oval-shaped film-coated tablet, debossed "93" on one side and "7331" on the other.

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

Posology

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

Elderly patients
The usual adult dose is recommended.

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

Children
The use of the 160 mg dosage form is contraindicated in children (see section 4.3).

Hepatic disease
Patients with hepatic disease have not been studied.

Dietary measures initiated before therapy should be continued.

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

Method of administration

The tablet should be swallowed whole during a meal.

4.3 Contraindications

- Hypersensitivity to fenofibrate or to any of the excipients,

- Hypersensitivity to peanut or arachis oil or soya lecithin or related products,
- Known photo-allergy or phototoxic reaction during treatment with fibrates or ketoprofen,
- Hepatic insufficiency (including biliary cirrhosis),
- Renal insufficiency,
- Gallbladder disease,
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia,
- Children.

4.4 Special warnings and precautions for use

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 hypertriglyceridemia, a direct effect of the substance, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Muscle

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of 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 the substance is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

For hyperlipidaemic patients taking oestrogens or contraceptives containing oestrogens it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

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.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Fenofibrate enhances the effect of oral anticoagulants and may increase the risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. Therefore, this combination is not recommended.

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 treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates

The risk of serious muscle toxicity is increased if fenofibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity (see section 4.4).

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

The frequencies of adverse events are ranked according to the following convention:
Very common (≥1/10)
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

Uncommon: Increases in serum creatinine and urea.

Blood and lymphatic system disorders

Rare: Decrease in haemoglobin and leukocytes

Nervous system disorders

Rare: Sexual asthenia

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:	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. sunlamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal, connective tissue and bone disorders

Rare:	Diffuse myalgia, myositis, muscular cramps and weakness
Very rare:	Rhabdomyolysis

Vascular disorders

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

Hepato-biliary disorders

Common:	Moderately elevated levels of serum transaminases (see section 4.4)
Uncommon:	Development of gallstones
Very rare:	Episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable (see section 4.4).

* In the FIELD study, a randomized 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

Symptoms

No case of overdose has been reported.

Treatment

No specific antidote is known. If an 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 group: Fibrates
ATC code:C10A B05

Fenofibrate is a fibric acid derivative whose lipid-modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα).
Through activation of PPARα, fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

The above-stated effects of fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII.

In addition, through modulation of the synthesis and catabolism of VLDL fractions fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the

atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease. During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk. Because of its significant effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus.

At the present time, no results of long-term controlled clinical trials are available to demonstrate the efficacy of fenofibrate in the primary or secondary prevention of atherosclerotic complications. Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.

5.2 Pharmacokinetic properties

This medicinal product contains 160 mg of micronised fenofibrate and is suprabioavailable (larger bioavailability) compared to the previous formulations.

Absorption

Maximum plasma concentrations (C_{max}) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

The absorption of fenofibrate is increased when administered with food.

Distribution

Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Plasma half-life

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

Metabolism and excretion

No unchanged fenofibrate can be detected in the plasma where the principal metabolite is fenofibric acid. It is excreted mainly in the urine. Practically all the substance is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the substance does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

5.3 Preclinical safety data

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in humans.

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

Core:
Cellulose microcrystalline
Povidone K-30
Povidone K-25
Croscarmellose sodium
Crospovidone
Sodium starch glycolate (type A)
Sodium laurilsulfate
Lactose monohydrate
Silica colloidal anhydrous
Sodium stearyl fumarate

Film-coating :
Opadry AMB White OY-B-28920 containing:
Polyvinyl alcohol, part-hydrolyzed
Titanium dioxide (E171)
Talc
Lecithin (soya)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging. Keep the blisters in the outer carton.

6.5 Nature and contents of container

Transparent PVC/PVdC – aluminium blister:
1, 10, 14, 15, 28, 30, 50, 56, 60, 84, 90 and 100 film-coated tablets.
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 00289/1161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2010

10 DATE OF REVISION OF THE TEXT

21/01/2010

Module 3

FENOFIBRATE 160 mg FILM-COATED TABLETS

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 160 mg FILM-COATED TABLETS 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 FENOFIBRATE 160 mg FILM-COATED TABLETS

Do NOT take Fenofibrate
- If you are allergic (hypersensitive) to fenofibrate or any of the other ingredients of this medicine
- If you are allergic (hypersensitive) to peanut or soya or related products (see 'Important information about some of the ingredients of Fenofibrate', below)
- 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 or kidney disease or gallbladder disease
- If you suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain).

Fenofibrate 160 mg Film-Coated Tablets 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).

Using other medicines

Tell your doctor or pharmacist if you are using any of the following:
- Anti-coagulants to thin your blood (e.g. warfarin): the risk of bleeding could be increased
- Ciclosporin, an immuno-suppressant: 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 using or have recently used 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 levels 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 breast-feeding

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 breast-feeding.

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

Driving and using machines

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

Important information about some of the ingredients of Fenofibrate

This medicine contains **soya lecithin.** If you are allergic to peanut or soya, do not use this medicinal product (see 'Do not take Fenofibrate' above).
This medicine contains a sugar 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.

3 HOW TO TAKE FENOFIBRATE 160 mg FILM-COATED TABLETS

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 tablet a day for adults, including the elderly.
If you are currently taking one 200 mg fenofibrate capsule, you can change to one tablet of Fenofibrate 160 mg Film-coated Tablets.

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.

Children

This medicinal product must not be given to children.

Method of administration

Oral use.

Swallow the tablets whole with water. It is important to take the tablets 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 tablets, 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 nearly 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.

Contact your doctor immediately if you experience unexplained muscle pain, muscle tenderness or muscle cramps or weakness. These side effects are rare (occurring in fewer than 1 in 1,000 patients) but they can sometimes be serious. Very rarely (in fewer than 1 in 10,000 patients), muscle breakdown may occur (see 'Take special care with Fenofibrate', in section 2 above).

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 of liver function.

Uncommon (occur in fewer than 1 in 100 patients):

- Alterations in blood test results of kidney function
- 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):

- Reduced levels of haemoglobin (oxygen-carrying pigment in blood) and white blood cells
- Reduced sex drive
- Hair loss.

Very rare (occur in fewer than 1 in 10,000 patients):

- Chronic disease of the lung tissues (interstitial pneumopathy)
- Photosensitivity reactions (sensitivity to sunlight, sunlamps or sunbeds) with redness, raised boils or solid swelling
- 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 160 mg FILM-COATED TABLETS

- **Keep out of the reach and sight of children.**
- Do not store above 25°C. 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 packaging. Keep the blisters 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 160 mg Film-Coated Tablets contains

- The active substance is fenofibrate.
- The other ingredients are microcrystalline cellulose, povidone K-30, povidone K-25, croscarmellose sodium, crospovidone, sodium starch glycolate (type A), sodium laurilsulfate, lactose monohydrate, colloidal silica anhydrous, sodium stearyl fumarate, polyvinyl alcohol part-hydrolyzed, titanium dioxide (E171), talc, soya lecithin and xanthan gum.

What Fenofibrate 160 mg Film-Coated Tablets looks like and contents of the pack

- Film-coated tablet: white to off-white, oval-shaped film-coated tablet, debossed "93" on one side and "7331" on the other.
- Fenofibrate 160 mg Film-coated Tablets are available in pack sizes of 1, 10, 14, 15, 28, 30, 50, 56, 60, 84, 90 & 100 film-coated tablets.
  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.

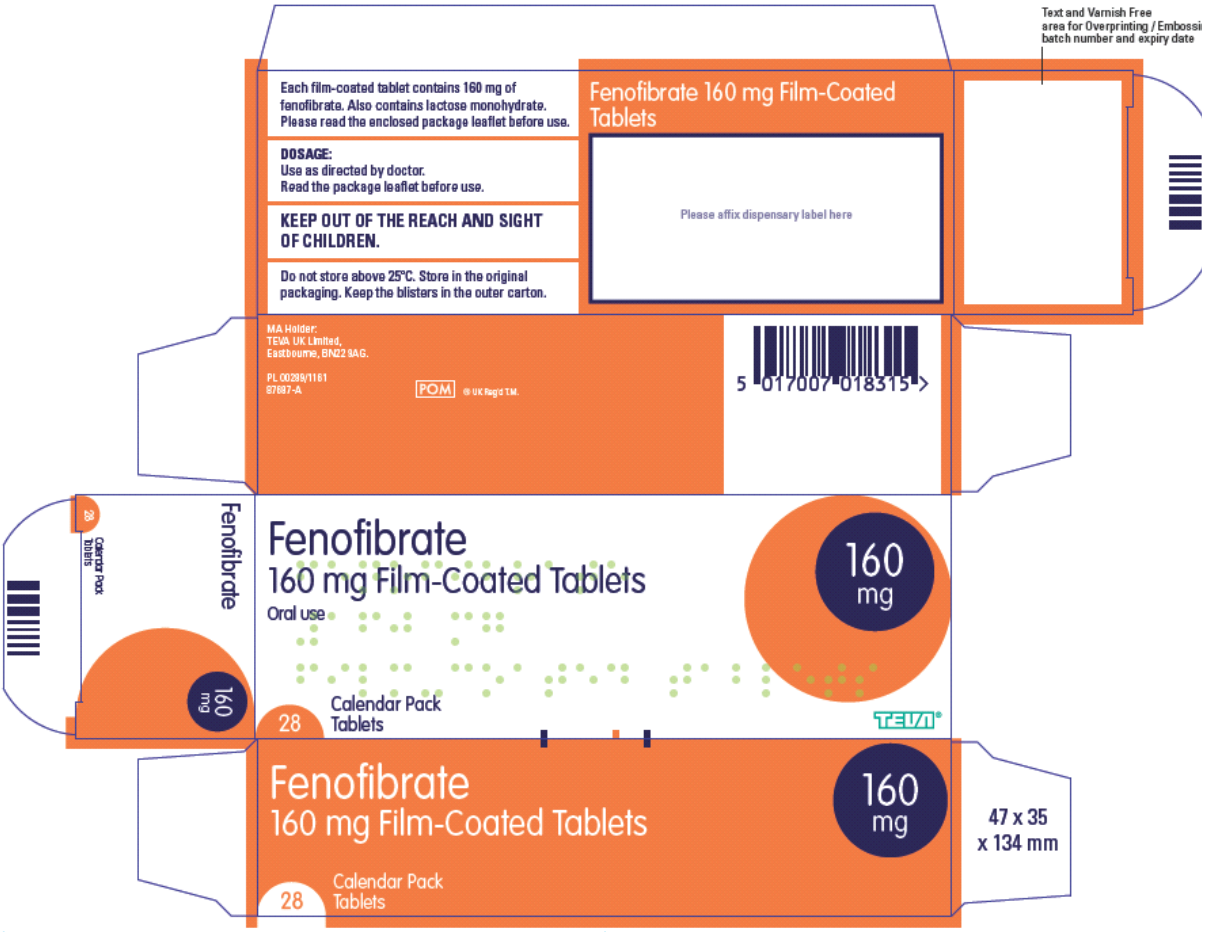
PL 00289/1161

TEVA UK LIMITED

87688-A
160 x 323

Module 4

Labelling



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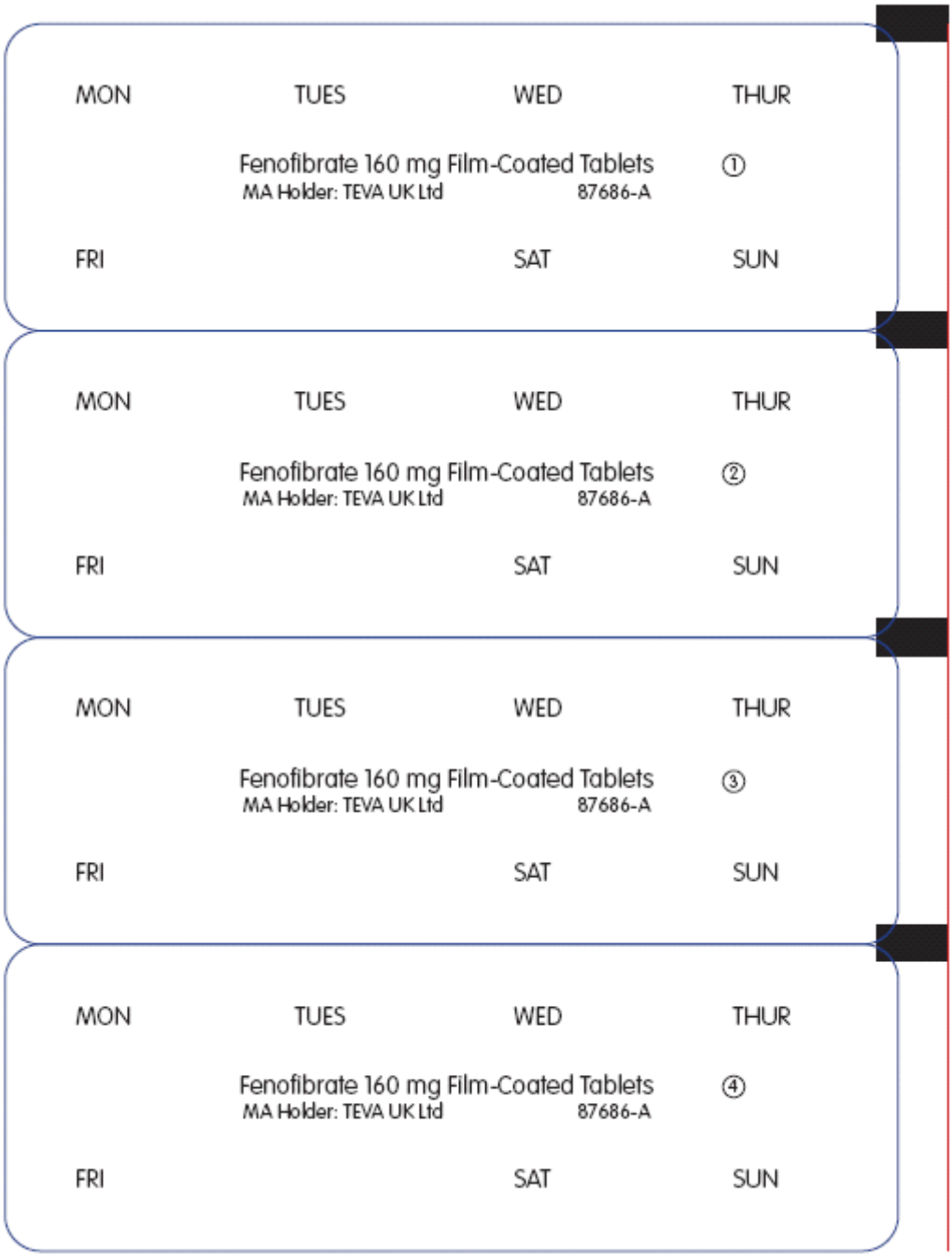
Fenofibrate
#160 mg
Film-Coated Tablets


MON TUES WED THUR
Fenofibrate 160 mg Film-Coated Tablets ①
MA Holder: TEVA UK Ltd 87686-A
FRI SAT SUN
MON TUES WED THUR
Fenofibrate 160 mg Film-Coated Tablets ②
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Fenofibrate 160 mg Film-Coated Tablets ④
MA Holder: TEVA UK Ltd 87686-A
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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 160 mg Film-coated Tablets, in the treatment of dyslipidaemia, is approvable.

This is a standard application submitted according to Art 10.1 of Directive 2001/83/EC, as amended, of the Decentralised Procedure (DCP) for generic applications. The originator product is the French product Lipanthyl® 200 mg Gelule authorised to Fournier on 20th March 1990. Cross-reference is made to the UK brand leader product, PL 00512/0389, Supralip® 160 mg film-coated tablets, currently licensed in the UK to Solvay Healthcare Ltd following change of ownership in July 2007. Supralip 160 Tablets were first authorised to Fournier Pharmaceuticals Ltd in September 2000 as a line extension of Lipantil Micro 200 Capsules, first authorised in the UK in November 1993. The medicinal product used for the bioequivalence study was Lipanthyl 160 mg Tablets (Laboratoires Fournier SA-France).

With the UK as the Reference Member State in this Decentralised Procedure, Teva UK Limited is applying for the Marketing Authorisation for Fenofibrate 160 mg Film-coated Tablets in BG, CY, CZ, DE, EL, ES, PL, RO, SI and 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

Name of the product in the Reference Member State	Fenofibrate 160 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Fenofibrate
Pharmacotherapeutic classification (ATC code)	C10A B05
Pharmaceutical form and strength(s)	Film-Coated Tablet and 160mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1566/01/DC
Reference Member State	United Kingdom
Member States Concerned	BG, CY, CZ, DE, EL, ES, PL, RO, SI, SK
Marketing Authorisation Number(s)	PL 00289/1161
Name and address of the authorisation holder	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG

SCIENTIFIC OVERVIEW AND DISCUSSION

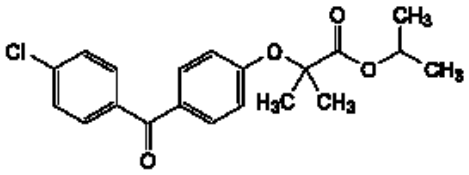
II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: fenofibrate

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

Structure:



Molecular Formula: $\mathbf{C_{20}H_{21}CLO_4}$

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, povidone K30, crospovidone, lactose monohydrate, sodium laurilsulfate, croscarmellose sodium, povidone K25, microcrystalline cellulose (avicel PH101), sodium stearyl fumarate, sodium starch glycolate (Type A) and Opadry AMB OY-B-28920 White.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry AMB OY-B-28920 White which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.
There are no excipients of human or animal origin except Lactose monohydrate sourced from DMV International. The supplier has provided confirmation of compliance with the current TSE Guideline.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

The aim of the pharmaceutical development was to obtain a tablet with identical qualitative/quantitative composition with respect to the active ingredient, and same bioavailability to the brand leader tablets.

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 2 years has been set for the unopened product, with the storage instructions ‘Do not store above 25 ° C’, ‘Keep container in the outer carton’ and ‘Store in the original package’.

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 this product.

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 Authorisation is granted for this application.

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

Administrative details

An open-label, single dose, randomised, two-period, two-sequence, two-treatment, crossover comparative bioavailability study between the test generic product, Fenofibrate 160 mg Film-coated Tablets (B/No K-33298) and the reference product, Lipanthyl 160 mg tablets from Fournier SA in France (B/No: 77157), was conducted in healthy subjects under fed conditions. Thirty-six subjects were dosed in Period I but only thirty-five 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, 12, 24, 48, 72 and 96 hours post-dose.

The French reference product (Lipanthyl) is considered to be equivalent to the UK reference product, Supralip.

Pre-defined bioequivalence acceptance criteria

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

Protocol

Inclusion and exclusion criteria are stated.
Subjects were admitted to the clinical facility at least 10.5 hrs prior to drug administration until 24hr post-administration (with the exception of one subject who was marginally late at the start of period 2). Subjects were served a high-fat, high-calorie breakfast at 30min prior to drug administration (they were fasted for 10hrs beforehand and 4hrs afterward). Subjects were entered into a randomisation scheme to receive the test or reference product.

The test and reference products were administered with 240mL of water

The protocol in terms of handling of subjects appears adequate.
The duration of sampling following dosing was adequate for AUCt > 80% of AUCinf.
The sampling frequency around Tmax was sufficient for accurate Cmax estimation.
The washout period of 14 days was adequate to avoid carryover (the UK SPC states that "practically all the drug is eliminated within 6 days"). There were "zero baseline plasma levels" at the start of period 2.

Method of data analysis

ANOVA was carried out on "ln-transformed" results for AUC and Cmax. Tmax was analysed by non-parametric means.

Results for main pharmacokinetic parameters (using geometric means except Tmax where arithmetic mean is shown, results are shown to 3 significant figures

Analyte: fenofibric acid

	Test	**Reference**
C_{max} (mg/L)	9.45	10.2
AUC_t (mg.h/L)	145	153
AUC_∞ (mg.h/L)	150	157
T_{max} (h)	3.66	3.39

Individual plasma concentration – time curves have been inspected and appear acceptable.

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):

	Test:reference % (mean, 90%CI)
C_{max}	93.00, 89.77 – 96.34
AUC_t	95.14, 90.58 – 99.92
AUC_∞	95.35, 90.77 – 100.17

The 90% confidence intervals for test/reference lie within the 0.80 – 1.25 acceptance criteria.

Management of withdrawals and other protocol deviations
One subject withdrew after period 1 for personal reasons. This was handled appropriately. 35 subjects completed the study.
Protocol deviations are described. These are mostly minor deviations in time from timetable of venepuncture and length of time of centrifugation of samples. One subject was found to have consumed a nicotine product within 6 months of the trial. All deviations were considered "minor". This is acceptable.

Safety
16 subjects had "abnormal urine results" that were unlikely to be drug-related. 4 subjects reported nausea, dizziness or headache that were possibly related to drug-administration and which were handled appropriately.

Pharmacodynamics
New data are not submitted. New data are not required for a generic medicinal product 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.

Module 1 – Administrative information
MAA forms
The MAA form is medically satisfactory.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPC is consistent with that for the originator product.

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

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.

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. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. 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

Date submitted	Application type	Scope	Outcome