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Micronised Fenofibrate

An Updated Review of its Clinical Efficacy in the Management of Dyslipidaemia

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Data Selection

Sources: Medical literature published in any language since 1980 on fenofibrate, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'fenofibrate' or 'micronised fenofibrate'. EMBASE search terms were 'fenofibrate' or 'micronised fenofibrate'. AdisBase search terms were 'fenofibrate' or 'micronised fenofibrate'. Searches were last updated 18 July 2002.

Selection: Studies in patients with dyslipidaemia who received micronised fenofibrate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Fenofibrate, dyslipidaemia, hypercholesterolaemia, hypertriglyceridaemia, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Micronised fenofibrate is a synthetic phenoxy-isobutyric acid derivative (fibric acid derivative) indicated for the treatment of dyslipidaemia. Recently, a new tablet formulation of micronised fenofibrate has become available with greater bioavailability than the older capsule formulation. The micronised fenofibrate 160mg tablet is bioequivalent to the 200mg capsule.

The lipid-modifying profile of micronised fenofibrate 160mg (tablet) or 200mg (capsule) once daily is characterised by a decrease in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels, a marked reduction in plasma triglyceride (TG) levels and an increase in high-density lipoprotein cholesterol (HDL-C) levels.

Micronised fenofibrate 200mg (capsule) once daily produced greater improvements in TG and, generally, in HDL-C levels than the hydroxymethylglutaryl coenzyme A reductase inhibitors simvastatin 10 or 20 mg/day, pravastatin 20 mg/day or atorvastatin 10 or 40 mg/day. Combination therapy with micronised fenofibrate 200mg (capsule) once daily plus fluvastatin 20 or 40 mg/day or atorvastatin 40 mg/day was associated with greater reductions from baseline than micronised fenofibrate alone in TC and LDL-C levels. Similar or greater changes in HDL-C and TG levels were seen in combination therapy, compared with monotherapy, recipients.

Micronised fenofibrate 200mg (capsule) once daily was associated with significantly greater improvements from baseline in TC, LDL-C, HDL-C and TG levels than placebo in patients with type 2 diabetes mellitus enrolled in the double-blind, randomised Diabetes Atherosclerosis Intervention Study (DAIS) [≥3 years follow-up]. Moreover, angiography showed micronised fenofibrate was associated with significantly less progression of coronary atherosclerosis than placebo.

Micronised fenofibrate has also shown efficacy in patients with metabolic syndrome, patients with HIV infection and protease inhibitor-induced hypertriglyceridaemia and patients with dyslipidaemia secondary to heart transplantation.

Micronised fenofibrate was generally well tolerated in clinical trials. The results of a large (n = 9884) 12-week study indicated that gastrointestinal disorders are the most frequent adverse events associated with micronised fenofibrate therapy. Elevations in serum transaminase and creatine phosphokinase levels have been reported rarely with micronised fenofibrate.

In conclusion, micronised fenofibrate improves lipid levels in patients with primary dyslipidaemia; the drug has particular efficacy with regards to reducing TG levels and raising HDL-C levels. Micronised fenofibrate is also effective in diabetic dyslipidaemia; as well as improving lipid levels, the drug reduced progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. The

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results of large ongoing studies (e.g. FIELD with ≈10 000 patients) will clarify whether the beneficial lipid-modifying effects of micronised fenofibrate result in a reduction in cardiovascular morbidity and mortality.

Pharmacodynamic Properties

Fenofibrate reduces plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and very-low-density lipoprotein (VLDL) cholesterol levels, and increases high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) AI and ApoAII levels in patients with dyslipidaemia. The lipid-modifying effects of fenofibrate are mediated via the activation of the peroxisome proliferator-activated receptors (PPARs). Fenofibrate activates PPARα which regulates a number of genes involved in lipid metabolism (e.g. those encoding for ApoCIII, ApoAI, ApoAII and lipoprotein lipase). Fenofibrate also promotes the β-oxidation of fatty acids in liver cells, and reduces the production of small, dense LDL particles in favour of larger, more buoyant LDL particles with a higher affinity for cellular LDL receptors. In addition, PPARα activators, including fenofibrate, up-regulate the synthesis of cholesterol transporters.

Increased levels of fibrinogen or plasminogen activator inhibitor (PAI-1) are associated with an increased risk of atherosclerosis and coronary heart disease (CHD). Fenofibrate reduces plasma fibrinogen levels in both normolipidaemic individuals and those with dyslipidaemia, and was significantly more effective than simvastatin, atorvastatin or pravastatin. In one study, atorvastatin treatment resulted in a significant increase in fibrinogen, while fenofibrate had no significant effect. Thirty days of treatment with fenofibrate or ciprofibrate produced similar reductions in fibrinogen in patients with type IIb dyslipidaemia; however, only fenofibrate significantly reduced PAI-1 levels in this study.

The inflammatory marker C-reactive protein (CRP) has been implicated in the pathogenesis of atherosclerosis and CHD. Fenofibrate has an inhibitory effect on CRP in hyperlipidaemic individuals. In one study, micronised fenofibrate 200 mg/day (capsule) was significantly more effective than atorvastatin 10 mg/day in reducing plasma levels of CRP. The production of interleukin-6, another inflammatory marker, was also significantly reduced in hyperlipidaemic patients treated with fenofibrate.

Both atorvastatin 10 mg/day and micronised fenofibrate 200 mg/day (capsule) were associated with a significant increase in peak blood flow over baseline in hyperlipidaemic men; however, flow-mediated dilation was not significantly affected by either drug.

Hyperuricaemia is common in patients with dyslipidaemia and has been implicated as a possible risk factor for CHD. Fenofibrate has demonstrated beneficial effects on uric acid levels in patients with dyslipidaemia.

Pharmacokinetic Properties

In the tablet formulation, micronised fenofibrate is coated directly onto an inert excipient core and *in vitro* dissolution is increased by 46% over the non-microcoated micronised capsule form of the drug. Bioavailability is also increased; fenofibrate 160mg microcoated tablets are bioequivalent to micronised fenofibrate 200mg capsules. The interindividual variation in maximum plasma concentration (C_{max}) and the variation in the area under the plasma concentration-time curve associated with food intake were reduced with the microcoated tablet compared with the capsule formulation.

The C_{max} of fenofibric acid occurs within 6 to 8 hours after fenofibrate administration and the absorption of fenofibrate is increased when administered with food. With the microcoated tablets, the extent of absorption is increased by ap-

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proximately 35% under fed compared with fasting conditions. The fat content of a meal eaten at the time of fenofibrate administration does not have a marked effect on pharmacokinetics.

Steady-state plasma concentrations of fenofibric acid are achieved after 5 days and the drug does not accumulate over time with repeated administration. At steady-state, the mean C_{max} of fenofibric acid was 23 mg/L, and was reported approximately 5.4 hours after administration of micronised fenofibrate 200mg (capsule) to six healthy volunteers. Serum protein binding (mainly to albumin) exceeds 99% and is concentration-independent over the therapeutic dose range.

The half-life of fenofibric acid is 20 hours, allowing for once-daily administration. Fenofibrate is excreted mainly in the urine (≈60%), but faecal excretion also occurs to a variable extent depending on the rate of absorption. Under steady-state conditions the total body clearance of micronised fenofibrate was 0.01 L/h/kg.

The clearance of fenofibrate is greatly reduced in patients with renal dysfunction and the dosage should be reduced in this group. No pharmacokinetic studies of fenofibrate have been carried out in patients with hepatic impairment.

Fenofibrate has low potential for drug-drug interactions. *In vivo* data suggest that fenofibrate and fenofibric acid do not undergo significant oxidative metabolism by cytochrome P450 (CYP450) and do not inhibit CYP450 isoforms CYP3A4, CYP2D6, CYP2E1 or CYP1A2, but weakly inhibit CYP2C19 and CYP2A6. They are mild to moderate inhibitors of CYP2C9 at therapeutic levels. Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time. Fenofibrate should be taken at least 1 hour before or 4 to 6 hours after bile acid binding resins, so as not to impede the absorption of fenofibrate.

Interaction between fenofibrate and cyclosporin after long-term use has been reported. Whereas whole-blood levels of cyclosporin were significantly reduced in heart transplant patients, serum creatinine levels were significantly increased. Caution is therefore advised when administering fenofibrate with cyclosporin or other potentially nephrotoxic agents.

Clinical Efficacy

In clinical trials, patients received the capsule formulation of micronised fenofibrate unless stated otherwise. In patients with type IIa, IIb or IV dyslipidaemia who received micronised fenofibrate 160mg (tablet) or 200mg once daily, reductions from baseline in TC levels ranged from about 12 to 30%. LDL-C levels were decreased in patients with type IIa or IIb dyslipidaemia by about 13 to 35%, but underwent minimal change in patients with type IV dyslipidaemia (type IV dyslipidaemia is characterised by elevated TG levels, with normal or elevated TC levels). Greater reductions in TG levels tended to be seen in patients with type IIb or IV dyslipidaemia (–32 to –53%) than in patients with type IIa dyslipidaemia (–15 to –43%). Increases in HDL-C levels of up to 27% in patients with type IIa dyslipidaemia, of up to 34% in those with type IIb dyslipidaemia and of up to 22% in those with type IV dyslipidaemia were achieved.

Greater reductions in TG levels were seen in patients with dyslipidaemia who received micronised fenofibrate 200mg once daily (–26 to –53.2%) than in recipients of atorvastatin 10 or 40 mg/day, simvastatin 10 or 20 mg/day or pravastatin 20 mg/day (–32.2 to +24.7%). HDL-C levels also tended to increase to a greater extent in micronised fenofibrate than in hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor recipients (+1.3 to +33.6% *vs* –0.8 to +16.5%).

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Improvements in TC (–12.1 to –27.3%) and LDL-C (–7.7 to –33.5%) levels were seen in micronised fenofibrate recipients, although reductions were usually greater in HMG-CoA reductase inhibitor recipients (reductions of –15.0 to –35.3% for TC and –17.0 to –38.6% for LDL-C).

In a retrospective pharmacoeconomic analysis of direct costs, the cost per successfully treated patient (based on 1995 costs) was considerably lower with micronised fenofibrate 200mg once daily than with simvastatin 20 mg/day (DM768 *vs* DM2080) in patients with type IIb dyslipidaemia (12 weeks' therapy). In patients with type IIa dyslipidaemia, micronised fenofibrate was only marginally more cost effective (DM450 *vs* DM517 per responder).

Limited data are available comparing micronised fenofibrate with other fibrates. Greater improvements in lipid levels tended to be seen after administration of micronised fenofibrate than after administration of gemfibrozil or bezafibrate.

Combination therapy with micronised fenofibrate 200mg once daily plus fluvastatin 20 or 40 mg/day or atorvastatin 40 mg/day was associated with greater reductions in TC, LDL-C and TG levels from baseline than micronised fenofibrate alone. Similar or greater changes in HDL-C levels were seen in combination therapy, compared with monotherapy, recipients.

Micronised fenofibrate 200mg once daily was associated with significantly greater improvements from baseline than placebo in TC, LDL-C, HDL-C and TG levels in patients with type 2 diabetes mellitus (n = 418) enrolled in the double-blind, randomised Diabetes Atherosclerosis Intervention Study (DAIS) [≥3 years follow-up]. Moreover, angiography showed micronised fenofibrate was associated with significantly less progression of coronary atherosclerosis than placebo [changes in the average minimum lumen diameter of –0.06 *vs* –0.10mm (indicating 40% less progression; $p = 0.029$ *vs* placebo) and in the average percentage diameter stenosis of +2.11 *vs* +3.65% (indicating 42% less progression; $p = 0.02$ *vs* placebo)]. A smaller decrease in mean segment diameter was seen with micronised fenofibrate compared with placebo [change in mean segment diameter of –0.06 *vs* –0.08mm (indicating 25% less progression; $p = 0.171$ *vs* placebo)].

Twelve weeks' therapy with micronised fenofibrate 200mg once daily was associated with significant improvements from baseline ($p < 0.05$) in mean TC, LDL-C, HDL-C, TG, fibrinogen and fasting serum insulin levels, factor VII activity, the insulin response during an oral glucose tolerance test, and blood pressure in a noncomparative study that enrolled 37 men with metabolic syndrome.

Treatment with micronised fenofibrate 200 to 268 mg/day was associated with reductions from baseline in TG levels in patients with HIV infection and protease inhibitor-induced hypertriglyceridaemia in two small noncomparative studies.

Significant reductions from baseline ($p < 0.05$) in mean TC, LDL-C and TG levels were seen in 43 heart transplant recipients with dyslipidaemia who received micronised fenofibrate 200mg once daily for up to a year. A significant increase from baseline in serum creatinine levels was also seen, necessitating discontinuation of therapy in 14 patients.

Tolerability

Micronised fenofibrate is generally well tolerated. In a post-marketing surveillance programme in 9884 patients with type IIa, IIb or IV dyslipidaemia who received micronised fenofibrate 200mg once daily for 12 weeks, 380 patients (3.8%) reported adverse events. The most common adverse events affected the gastrointestinal system (1.9% of patients), skin and appendages (0.6%), the ner-

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vous system (0.4%), the cardiovascular system (0.3%) and the body as a whole (0.3%). Forty-three of 9884 patients (0.4%) experienced serious adverse events. Eight patients developed abnormal liver function tests and two patients experienced elevated creatine phosphokinase levels.

In two noncomparative trials (n = 177 and 198) examining the tablet formulation of micronised fenofibrate 160mg, adverse events were experienced by 24 and 40% of patients. However, none of the eight serious adverse events in these studies were considered drug-related. In both studies, few patients (n ≤ 3) developed creatine phosphokinase levels that were 4 to 5 or >5 times the upper limit of normal (ULN), or AST or ALT levels that were >3 times ULN.

There were no significant differences between micronised fenofibrate 200mg (capsule) once daily (n = 207) and placebo (n = 211) recipients in the frequency of serious adverse events in the DAIS study (cancer, gall bladder symptoms and/or cholecystectomy, hepatic events, abdominal pain, diarrhoea, dizziness, musculoskeletal system events or events affecting the joints occurred in <3.5% of patients in each treatment group).

Data on the comparative tolerability of micronised fenofibrate and other lipid-modifying drugs are limited. In trials comparing micronised fenofibrate 200 mg/day (capsule) with simvastatin 20 mg/day, atorvastatin 10 or 40 mg/day or pravastatin 20 mg/day, both drugs were generally well tolerated. In a 24-week, double-blind study comparing micronised fenofibrate 200mg once daily (n = 116) with gemfibrozil 1200mg once daily (n = 118), 3.4 and 4.2% of patients in the corresponding treatment groups withdrew from the study because of adverse events.

In a 16-week, double-blind study, patients received micronised fenofibrate 200 mg/day (capsule) [n = 33], micronised fenofibrate 200 mg/day plus fluvastatin 20 mg/day (n = 35) or micronised fenofibrate 200 mg/day plus fluvastatin 40 mg/day (n = 34). Musculoskeletal adverse events (e.g. myalgia) occurred in 24, 17 and 15% of patients in the corresponding treatment groups, gastrointestinal adverse events occurred in 26, 6 and 24%, respectively, and respiratory adverse events occurred in 15, 11 and 24%, respectively. No significant between-group differences in the percentage changes in laboratory values (i.e. creatinine, AST, ALP, alkaline phosphatase, creatine phosphokinase or myoglobin levels) were seen.

Dosage and Administration

Micronised fenofibrate is indicated, as an adjunct to diet, for the treatment of patients with type IIa, IIb, IV or V dyslipidaemia; in Europe, the drug is also indicated for use in type III dyslipidaemia.

For adults, the recommended initial daily dosage is one 160mg tablet, taken during a main meal. For adults with hypertriglyceridaemia, US labelling recommends initiating treatment at a dosage of 54 to 160 mg/day and adjusting the dosage according to patient response. The 160 mg/day dosage is not recommended in patients with renal impairment or in children. A lower dosage is recommended in elderly patients and patients with renal impairment in the US (54mg tablets), and in children and patients with renal impairment in Europe.

Fenofibrate is contraindicated in patients with severe renal disease or pre-existing gall bladder disease; the drug is also contraindicated in patients with hepatic dysfunction in the US and in patients with severe hepatic dysfunction in Europe. Fenofibrate should generally not be used in pregnant women (US labelling states that fenofibrate should only be administered to pregnant women if the potential

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risk is justified by the potential benefit) or in breast-feeding women. Patients receiving micronised fenofibrate should undergo regular monitoring of their liver function.

In patients receiving concomitant therapy with a coumarin anticoagulant, the dosage of the anticoagulant should be reduced and adjusted as necessary according to the prothrombin time or international normalised ratio (these parameters should be monitored until they have stabilised). Combination therapy with micronised fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the potential benefit outweighs the potential risk. Micronised fenofibrate should be administered ≥1 hour before or ≥4 to 6 hours after bile acid sequestrants. The potential benefits and risks of administering micronised fenofibrate with immunosuppressants such as cyclosporin and other nephrotoxic agents should be carefully considered.

1. Introduction

The dyslipidaemias comprise a heterogeneous group of disorders arising from abnormal plasma lipid and lipoprotein profiles. Lipoproteins are responsible for the transfer of cholesteryl esters and triglycerides (TGs) from the site of synthesis and absorption to the site of utilisation. They are classified according to their protein to lipid ratio and resultant density. The four major types of lipoproteins include:

- chylomicrons, comprising mainly TGs
- very-low-density lipoproteins (VLDL), comprising mainly TGs
- low-density lipoproteins (LDL), which are the major cholesterol-containing lipoproteins
- high-density lipoproteins (HDL), which are integral to reverse cholesterol transport (i.e. the transfer of cholesterol from peripheral tissues to the liver for biliary elimination).

Raised total cholesterol (TC), LDL-cholesterol (LDL-C) and TG levels and low HDL-cholesterol (HDL-C) levels are important risk factors for coronary heart disease (CHD).[1] Evidence accumulated from major epidemiological and intervention studies clearly indicates that altering the plasma lipoprotein profile has a major beneficial effect on morbidity and mortality associated with CHD.[2-4] Thus, improving the lipid profile is important in terms of both minimising the risk of developing CHD (primary prevention) and preventing the recurrence of vascular events in patients with established CHD and/or other atherosclerotic conditions (secondary prevention).

Fenofibrate is a phenoxy-isobutyric acid derivative (fibric acid derivative) with lipid-modifying properties in patients with dyslipidaemia. A standard formulation of the drug was originally launched in 1975.[5] The bioavailability of the standard formulation was subsequently improved through a comicronisation process, leading to the development of micronised fenofibrate capsules, available in Europe since 1992. More recently, the dissolution performance of micronised fenofibrate was further enhanced by the development of a tablet formulation (bioavailability was increased by a further 25%) [figure 1].[5] It is intended that the new tablet formulation will replace fenofibrate capsules (fenofibrate 160mg tablets are considered to be of equivalent efficacy to micronised fenofibrate 200mg capsules).

The pharmacodynamic properties and clinical efficacy of micronised fenofibrate in dyslipidaemia have been reviewed previously in *Drugs* by Adkins and Faulds.[6] This review updates the use of micronised fenofibrate (both capsule and tablet formulations) in patients with dyslipidaemia. Notably, micronised fenofibrate was recently approved in the US to increase HDL-C levels in patients with primary hypercholesterolaemia or mixed dyslipidaemia (types IIa and IIb dyslipidaemia).[7]

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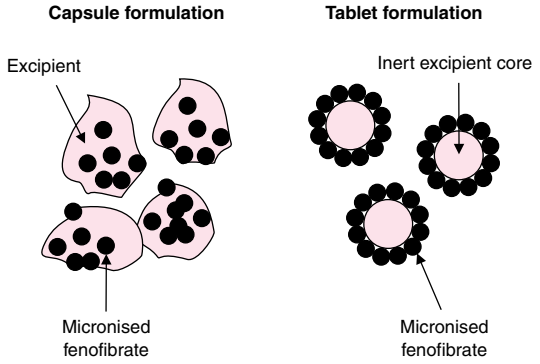

Fig. 1. Micronised fenofibrate formulations

2. Pharmacodynamic Properties

The pharmacodynamic properties of micronised fenofibrate are summarised in table I; the pharmacodynamic profile of the drug has been reviewed previously in *Drugs*[6] and elsewhere.[8-10]

Fenofibrate, a synthetic phenoxy-isobutyric acid derivative, is a prodrug that is rapidly hydrolysed by esterase *in vivo* to form the active moiety fenofibric acid. This metabolite is responsible for the primary pharmacodynamic effects of the drug: reductions in plasma TC, LDL-C, TG and VLDL-cholesterol (VLDL-C) levels, and increases in HDL-C and apolipoprotein (Apo) AI and ApoAII levels (section 4).

2.1 Mechanisms of Action

2.1.1 Effects on Lipids and Apolipoproteins

Recently, researchers have found that the lipid-modifying effects of fenofibrate are mediated via the activation of the peroxisome proliferator-activated receptors (PPARs). The PPARs are ligand-activated transcription factors that control gene expression by interacting with response elements located upstream from target genes.[57] Fenofibrate activates PPARα which regulates a number of genes involved in lipid metabolism including those encoding for ApoCIII, ApoAI, ApoAII and lipoprotein lipase (LPL).[58] Fatty acids and their derivatives (prostanoids) are the endogenous ligands for PPARα receptors. Fenofibrate-activated PPARα reduces the nuclear content of the positive transcription factor hepatic nuclear factor-4 and also displaces any hepatic nuclear factor-4 bound to the Apo-CIII promoter site.[8,12,59] This results in reduced plasma levels of ApoCIII which in turn leads to increased LPL activity. The enhanced catabolism of VLDL produces surface remnants that are transferred to HDL and returned to the liver through the circulation. Thus, the enhanced VLDL lipolysis together with increases in PPARα-mediated synthesis of ApoAI and ApoAII, augments the production of HDL and the rate of HDL-mediated reverse cholesterol transport.[21]

Fenofibrate promotes the β-oxidation of fatty acids in liver cells by inducing the synthesis of acyl coenzyme A synthetase and other genes involved in mitochondrial and peroxisomal β-oxidation.[9,11,13] Thus, the availability of free fatty acids for TG synthesis is reduced.[13]

Epidemiological studies have provided evidence of a (possibly independent) role for small, dense LDL particles in atherogenesis.[60-62] Fenofibrate reduces the proportion of small, dense LDL particles in favour of larger, more buoyant LDL particles with a higher affinity for cellular LDL receptors.[14-17] Catabolism of LDL via this pathway is less atherogenic than via the receptor-independent pathway.

2.1.2 Effects on Lipid Transporters

Although not investigated with fenofibrate, PPARα activators induce cholesterol removal from human macrophages through stimulation of ATP-binding cassette, sub-family A, member 1 (ABCA1).[36] This transporter is involved in the control of ApoAI-mediated cholesterol efflux from macrophages. A role for fenofibrate in the PPARα-mediated activation of the murine scavenger receptor class B type 1 (SR-B1) and its human homologue CD-36 and LIMPII analogous 1 (CLA-1) has also been proposed.[37] These cell-surface receptors have a high affinity for HDL and mediate the selective uptake of cholesterol esters from HDL in liver and steroidogenic tissue;[63] *in vitro* fenofibrate increases SR-B1 expression 2.3-fold.[37] Fibrates increase biliary phospholipid output in

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Table I. Overview of the pharmacodynamic properties of fenofibrate

Effects on lipids and lipoproteins	
↑ Lipolysis of triglyceride-rich particles	Mediated via activation of LPL (a key enzyme involved in lipoprotein metabolism and energy production)[11] and ↓ hepatic production of ApoCIII (an LPL inhibitor)[12]
↑ Plasma clearance of triglyceride-rich particles	Mediated via ↓ hepatic production of ApoCIII[12]
↑ β-oxidation of fatty acids	Fenofibrate promotes fatty acid oxidation by inducing acyl coA synthetase[9] and other genes involved in mitochondrial and peroxisomal β-oxidation[10,13]
↓Triglyceride synthesis	Attributable to ↓ availability of acyl coA esters, and inhibition of *de novo* fatty acid synthesis via a fibrate-dependent decrease in acetyl-coA carboxylase and fatty acid synthase activity[10,13]
Modulation of LDL subfraction distribution	Fenofibrate normalises the atherogenic LDL profile by ↓ levels of dense LDL subfractions resulting in ↑ levels of larger, less dense LDL particles with a high binding affinity for cellular LDL receptors.[14,15] This results in catabolism of LDL particles via the nonatherogenic LDL-receptor pathway as opposed to the receptor-independent atherogenic pathway[16,17]
↑ HDL cholesterol	Partially mediated via increased transcription of ApoAI and ApoAII genes, the major Apo constituents of HDL (see below)[10,13,18-20]
↓ CETP-mediated lipid transfer from HDL to VLDL	CETP-mediated transfer of lipid between ApoAI- and ApoB-containing lipoproteins, i.e. HDL and VLDL, may be ↓ as a result of normalisation of VLDL plasma levels.[14,21] This may be responsible for the ↑ in HDL cholesterol reported after fenofibrate therapy
↓ Lp(a)[a] levels	MF ↓ Lp(a) levels from baseline (range –7 to –23%) in patients with type II dyslipidaemia[24,25]
Effects on apolipoproteins	
↑ ApoAI[b] levels	Fenofibrate ↑ human ApoAI gene expression at the transcriptional level in transgenic mice (this may be mediated by PPAR).[19] MF ↑ ApoAI levels from baseline (range +5 to +16%) in patients with type II dyslipidaemia[26-32] (nonsignificant ↓ of –4 to –5% in one study[24])
↑ ApoAII[b] levels	Fenofibrate ↑ ApoAII levels in humans as a result of PPAR-mediated induction of ApoAII gene transcription.[20] MF ↑ ApoAII from baseline in dyslipidaemic (+29%)[27] and normolipidaemic individuals (+20%)[33]
↓ ApoB[c] levels	MF ↓ ApoB levels from baseline in patients with primary dyslipidaemia (range –6 to –30%),[24,26,27,29-32,35] in patients with diabetic dyslipidaemia (–18%)[15] and in normolipidaemic individuals (–17%)[33]
Effects on cholesterol transporters	
ABCA1	PPARα activators induce cholesterol removal from human macrophages through stimulation of ABCA1[36] (not yet investigated for fenofibrate)
SR-B1 (homologous with the human CLA-1 scavenger receptor)	SR-B1/CLA-1 have a high affinity for HDL and fenofibrate increases SR-B1 expression 2.3-fold[37]
↑ Biliary phospholipid output	In mice, fenofibrate increased the expression of *mdr2* mRNA 3-fold while biliary phospholipid output was increased by 26%[38]
Other Effects	
↓ Fibrinogen and PAI-1 levels[d]	MF ↓ plasma fibrinogen levels in normolipidaemic individuals (–3%)[33] and in dyslipidaemic patients (–7 to –23%).[24,26,27,29-31,35,42-45] The fibrinogen-lowering effect of fenofibrate was more pronounced in patients with type IIb compared with type IIa dyslipidaemia (–15 *vs* –7%)[30] and was significantly greater than that of simvastatin[24,30] or pravastatin[26] 20 mg/day or atorvastatin 10 mg/day.[31] PAI-1 ↓ by 19.7%[43]
↓CRP[e]	↓ CRP-induced expression of MCP-1 *in vitro*;[48] plasma levels of CRP ↓ in hyperlipidaemic patients by 28[49] or 51%[50]
↓IL-6 (inflammatory marker)	↓ in hyperlipidaemic patients treated with fenofibrate[49]
↑ Increase in blood flow (improved vasoreactivity)	20% ↑ in peak blood flow after fenofibrate compared with 27% ↑ after atorvastatin (p = NS)[50]
Uric acid[f] levels	Both MF and SF have demonstrated potentially beneficial uric acid-lowering effects in patients with dyslipidaemia[30,42,52-56]

a A cholesterol-rich lipoprotein considered to be an independent risk factor for CHD.[22,23]
b Major protein constituent of HDL and integral to the process of reverse cholesterol transport.[1]
c Major protein constituent of LDL and triglyceride-rich lipoproteins. Low levels are associated with beneficial antiatherogenic effects.[34]
d Risk factor for atherothrombosis.[39-41]
e Risk factor for atherosclerosis and CHD.[46,47]
f Hyperuricaemia is common in patients with dyslipidaemia and has been implicated as a possible risk factor for CHD.[51]

ABCA1 = ATP-binding cassette, sub-family A , member 1; **Apo** = apolipoprotein; **CETP** = cholesteryl ester transfer protein; **CHD** = coronary heart disease; **CLA-1** = CD-36 and LIMPII analogous 1; **coA** = coenzyme A; **CRP** = C-reactive protein; **HDL**= high-density lipoprotein; **IL** = interleukin; **LDL** = low-density lipoprotein; **Lp(a)** = lipoprotein(a); **LPL** = lipoprotein lipase; **MCP-1** = monocyte chemoattractant protein-1; **mdr** = multiple drug-resistance gene; **MF** = micronised fenofibrate 200mg (capsule) once daily; **NS** = not significant; **PAI-1** = plasminogen activator inhibitor-1; **PPAR** = peroxisome proliferator activated receptors; **SF** = standard fenofibrate; **SR-B1** = murine scavenger receptor class B type 1; **VLDL** = very-low-density lipoprotein; ↓ indicates a decrease; ↑ indicates an increase.

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mice and the hypothesis that this might be due to induction of multiple drug-resistance (mdr) genes has been tested.[38] Fenofibrate, at 0.5% in the diet of CF I mice, increased the expression of *mdr2* mRNA 3-fold ($p < 0.05$ *vs* control) while biliary phospholipid output was increased by 26%; the latter increase was not significantly different from the control group. Other fibrates did result in significantly increased biliary phospholipid output so it is possible that higher doses of fenofibrate would have had a greater effect.

2.1.3 Other Effects Relevant to Cardiovascular Disease

Increased levels of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) are associated with an increased risk of atherosclerosis,[41] and fibrinogen is an independent risk factor for CHD.[39,40] Numerous studies have demonstrated that fenofibrate reduces plasma fibrinogen levels in both normolipidaemic subjects[33] and those with dyslipidaemia.[24-27,29-31,35,42-45,49,64,65] The fibrinogen-lowering effect of fenofibrate was more pronounced in patients with type IIb dyslipidaemia compared with those with type IIa,[30] and was significantly greater than the effect of simvastatin ($p < 0.01$[24]; $p < 0.001$[30]), pravastatin ($p = 0.002$)[26] or atorvastatin ($p < 0.01$).[31] In one crossover study in 29 patients with mixed dyslipidaemia, atorvastatin treatment resulted in a significant increase in fibrinogen ($p = 0.0017$), while fenofibrate had no significant effect.[50] Thirty days of treatment with fenofibrate or ciprofibrate produced similar reductions in fibrinogen in patients with type IIb dyslipidaemia; however, only fenofibrate significantly reduced PAI-1 levels in this study ($p < 0.01$ *vs* baseline).[43]

Experimental studies have shown that fenofibrate has important anti-inflammatory effects on vascular cells, reducing the expression of adhesion molecules and proinflammatory cytokines.[49,66] Epidemiological studies have implicated the inflammatory marker C-reactive protein (CRP) in the pathogenesis of atherosclerosis and CHD,[46] while an *in vitro* study has shown that CRP can induce the expression of adhesion molecules,[47] in particular monocyte chemoattractant protein-1 (MCP-1), by endothelial cells.[48] Fenofibrate blocked the CRP-induced expression of MCP-1 in cultured human endothelial cells.[48] More importantly, an inhibitory effect on CRP has also been demonstrated in hyperlipidaemic individuals *in vivo*.[49,50] In one of these studies, micronised fenofibrate 200 mg/day (capsule) was significantly more effective than atorvastatin 10 mg/day in reducing plasma levels of CRP ($p = 0.028$).[50] The production of interleukin-6, another inflammatory marker, was also significantly reduced in hyperlipidaemic patients treated with fenofibrate ($p < 0.03$).[49] It should be noted that the levels of fenofibrate used in the *in vitro* studies reported above (≈100 μmol/L) are somewhat higher than the plasma fenofibrate levels reported during clinical studies (≈60 μmol/L).

Vasoreactivity is impaired in patients with coronary artery disease and in those with atherosclerotic risk factors.[67,68] The hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to improve endothelial function,[69,70] and the ability of fenofibrate to improve vasoreactivity has recently been evaluated in comparison with atorvastatin.[50] Both atorvastatin 10 mg/day and micronised fenofibrate 200 mg/day (capsule) were associated with a significant increase in peak blood flow over baseline in 29 men with untreated mixed dyslipidaemia ($p = 0.04$ and 0.03 for fenofibrate and atorvastatin, respectively); however, flow-mediated dilation (FMD) was not significantly affected by either drug.[50] In addition to its beneficial effects on arterial circulation, one study has suggested that fenofibrate may also improve capillary circulation (microcirculation) in patients with hyperlipidaemia.[71]

Hyperuricaemia is common in patients with dyslipidaemia and has been implicated as a possible risk factor for CHD.[51] Fenofibrate has demonstrated potentially beneficial uric acid-lowering effects in patients with dyslipidaemia[30,42,52-56,72] (reviewed by Adkins and Faulds[6]).

Increased plasma levels of homocysteine have been linked with an increased risk of atherosclero-

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sis.[73-75] Administration of fibrates, including fenofibrate, has been shown to increase homocysteine levels.[76-82] The clinical implications of this are uncertain, although in one study a significant reduction ($p = 0.006$) in the risk of major cardiovascular events was seen in patients receiving gemfibrozil, compared with placebo, despite a significantly greater increase from baseline ($p < 0.0001$) in homocysteine levels.[82] The increase in homocysteine levels seen with fenofibrate can be significantly attenuated with folate supplementation.[83]

3. Pharmacokinetic Properties

There are little published pharmacokinetic data on the new fenofibrate 160mg tablet. Most of the data presented here were obtained with the fenofibrate 67 or 200mg capsule formulation (table II) or the older, nonmicronised, formulation.

In the tablet formulation, micronised fenofibrate is coated directly onto an inert excipient core (figure 1). As a result the micronised fenofibrate particles are immediately exposed to the dissolution medium and *in vitro* dissolution after 10 minutes is increased by 46% over the non-microcoated micronised (capsule) form of the drug.[5] *In vivo* bioavailability is also increased and equivalent plasma levels of fenofibrate are obtained with lower doses of the tablet compared with the capsule formulation. Fenofibrate 160mg microcoated tablets are considered to be bioequivalent to micronised fenofibrate 200mg capsules.[5,7] The interindividual variation in maximum plasma concentration (C_{max}) and the variation in the area under the plasma concentration-time curve (AUC) associated with food intake were reduced with the microcoated tablet compared with the capsule formulation.[5]

The C_{max} of fenofibric acid occurs within 6 to 8 hours after fenofibrate administration (type of formulation and dosage not reported) and the absorption of fenofibrate is increased when administered with food. With the microcoated tablets the extent of absorption is increased by approximately 35% under fed as compared with fasting conditions.[7]

Table II. Mean pharmacokinetic parameters of fenofibric acid following single-dose oral administration of micronised fenofibrate 67mg (capsule formulation). The drug was administered after a standard meal to 24 healthy male volunteers[84]

Parameter	Value
C_{max} (mg/L)	3.8
t_{max} (h)	4.0
AUC_{∞} (mg • h/L)	62.1
$t_{½\beta}$ (h)	19.7

AUC_{∞} = area under the plasma concentration-time curve extrapolated to infinity; **C_{max}** = maximum plasma concentration; **t_{max}** = time to C_{max}; **$t_{½\beta}$** = plasma elimination half-life.

The fat content of a meal eaten at the time of fenofibrate administration does not have a marked effect on pharmacokinetics. After micronised fenofibrate 200mg capsules were administered with a high fat meal, the AUC, C_{max} and the elimination half-life were 176.7 mg • h/L, 11.0 mg/L and 15.4 hours, respectively. After fenofibrate was taken with a low fat meal, the corresponding values were 154.0 mg • h/L, 10.8 mg/L and 26.1 hours.[85-87]

Steady-state plasma concentrations of fenofibric acid are achieved after 5 days and the agent does not accumulate over time with repeated administration. At steady-state, the mean C_{max} of fenofibric acid was 23 mg/L, and was reported approximately 5.4 hours after administration of micronised fenofibrate 200mg (capsule) to six healthy volunteers.[33] Serum protein binding (mainly to albumin) exceeds 99% and is concentration-independent over the therapeutic dose range.[8]

The half-life of fenofibric acid is 20 hours, allowing for once-daily administration.[7] Fenofibrate is excreted mainly in the urine, primarily as fenofibric acid and fenofibric acid glucuronide. Faecal excretion also occurs to a variable extent depending on the rate of absorption. Approximately 60% of a dose of radiolabeled fenofibrate appears in the urine, and 25% is excreted in the faeces.[7] Under steady-state conditions the total body clearance of micronised fenofibrate was 0.01 L/h/kg.[33]

The oral clearance of fenofibrate in the elderly was 1.2 L/h compared with 1.1 L/h in young adults.[7]

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The clearance of fenofibrate is greatly reduced in patients with renal dysfunction [creatinine clearance <3 L/h (<50 ml/min)] and the dosage should be reduced in this group (section 6). In patients with creatinine clearance of 3 to 5.4 L/h (50 to 90 ml/min), the clearance and volume of distribution of fenofibrate are increased compared with healthy adults; however, no modification of dosage is recommended in this group. No pharmacokinetic studies of fenofibrate have been carried out in patients with hepatic impairment.[7]

3.1 Drug Interactions

Fenofibrate has low potential for drug-drug interactions. *In vivo* data suggest that fenofibrate and fenofibric acid do not undergo significant oxidative metabolism by cytochrome P450 (CYP450) and do not inhibit CYP450 isoforms CYP3A4, CYP2D6, CYP2E1 or CYP1A2, but weakly inhibit CYP2C19 and CYP2A6. They are mild to moderate inhibitors of CYP2C9 at therapeutic levels.[7] Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time. Two case reports have suggested that fenofibrate may potentiate the anticoagulant effects of warfarin,[88] and the authors recommend serial monitoring of patients receiving these agents in combination (section 6). Bile acid binding resins frequently reduce the absorption of drugs and if resins are being coadministered, fenofibrate should be taken at least 1 hour before, or 4 to 6 hours after, the resin so as not to impede the absorption of fenofibrate (section 6).[7]

Lipid-modifying drugs are commonly used in heart transplant patients to treat hypercholesterolaemia.[89,90] Cyclosporin is the most commonly used immunosuppressive drug in this group, and interaction between fenofibrate and cyclosporin after long-term use has been reported.[91] Whereas whole-blood levels of cyclosporin were significantly reduced in heart transplant patients (from 147 to 107 μg/L; $p = 0.03$), serum creatinine levels were significantly increased ($p = 0.003$) [section 4.4]. Cyclosporin binds to lipoproteins in plasma,[88] therefore, the coadministration of fenofibrate may interfere with cyclosporin metabolism, and the interaction of the two agents may increase the inherent nephrotoxicity of cyclosporin. Caution is therefore advised when administering fenofibrate with cyclosporin or other potentially nephrotoxic agents (section 6).[7]

4. Clinical Efficacy

The therapeutic efficacy of micronised fenofibrate 200mg (capsule) once daily has been evaluated in both comparative and noncomparative studies, and the therapeutic efficacy of micronised fenofibrate 160mg (tablet) has been evaluated in two noncomparative studies in patients with type IIa, IIb or IV primary dyslipidaemia (section 4.1); fenofibrate 160mg microcoated tablets are considered to be bioequivalent to micronised fenofibrate 200mg capsules.[5,7] The major lipid abnormality in type IIa and IIb dyslipidaemia is an elevation in TC levels (patients with type IIb dyslipidaemia also have elevated TG levels), and the major lipid abnormality in type IV dyslipidaemia is an elevation in TG levels (with normal or increased TC levels).[1] Studies have also been conducted in patients with type 2 diabetes mellitus and dyslipidaemia (section 4.2), in patients with protease inhibitor-induced hypertriglyceridaemia (section 4.3) and in patients with dyslipidaemia secondary to heart transplantation (section 4.4). The majority of micronised fenofibrate trials included a drug-free or placebo run-in period, in conjunction with dietary control for 1 to 6 months, prior to the initiation of active drug treatment. Dietary restrictions were generally maintained throughout the studies. Patients in these studies received the capsule formulation of micronised fenofibrate unless stated otherwise .

4.1 Primary Dyslipidaemia

Studies in patients with type IIa, IIb or IV dyslipidaemia treated with micronised fenofibrate 160mg (tablet) or 200mg (capsule) once daily have reported reductions in TC levels of 12 to 30%.[24-31,42,44,65,72,92-99] LDL-C levels were decreased in patients with type IIa or IIb dyslipidaemia, gener-

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ally by about 13 to 35%,[24-30,44,92-94,96,98-100] but underwent minimal change in patients with type IV dyslipidaemia.[92,94,100] There was a trend towards greater reductions in plasma TG levels in patients with type IIb or IV dyslipidaemia than in patients with type IIa disease (–32 to –53% *vs* –15 to –43%).[24,29,30,44,92-94,99,100] Increases in HDL-C levels with micronised fenofibrate 160 or 200mg once daily were more variable and ranged from 1 to 34% in patients with type IIa, IIb or IV dyslipidaemia.[24,29,30,44,92-94,99,100] The increase in HDL-C levels achieved with micronised fenofibrate therapy may depend on the HDL-C level at baseline (greater percentage increases in HDL-C levels have been seen with lower baseline HDL-C levels)[101,102] and may have contributed to the variation in the effect of fenofibrate on HDL-C seen between studies.

4.1.1 Noncomparative Studies

The results of noncomparative studies evaluating the efficacy of micronised fenofibrate are summarised in table III.

Treatment with micronised fenofibrate 160mg or 200mg once daily for 2 to 6 months consistently reduced LDL-C, TC and TG levels, and increased HDL-C levels.[25,29,42,44,65,72,92-94,97] Furthermore, significant reductions from baseline in the TC to HDL-C ratio (–21.3 to –33%; $p < 0.01$) were reported in micronised fenofibrate recipients with type IIa or IIb dyslipidaemia in three studies.[44,93] Beneficial long-term effects on TC, LDL-C, HDL-C and TG levels were also evident after 12 months of treatment with micronised fenofibrate 200mg once daily in three studies[95,100,103] and after a median of 4.6 years[96] of treatment in another study.

In the trials differentiating between dyslipidaemia subtypes (including two studies examining the use of the tablet formulation of micronised fenofibrate 160mg[44]), the greatest reductions in LDL-C levels occurred in patients with type IIa or IIb dyslipidaemia, and patients with type IIb or IV dyslipidaemia experienced the greatest reductions in TG levels.[29,44,92,94,100]

4.1.2 Comparative Studies

Comparisons with Placebo

Micronised fenofibrate had a greater lipid-modifying effect than placebo in two comparative studies in patients with type IIa or IIb hypercholesterolaemia (table IV).[27,98]

The largest study,[98] which enrolled a total of 340 patients with type IIa or IIb dyslipidaemia, reported significantly greater reductions ($p < 0.05$) in LDL-C (–31.6 to –38.8 *vs* +0.5%), TC (–24.5 to –31.9 *vs* +0.5%) and TG (–26.7 to –40.8 *vs* +3.5%) levels with micronised fenofibrate 200 to 400mg daily than with placebo after 3 months of treatment (table IV). The percentage of patients with LDL-C levels <3.36 mmol/L after the 3-month treatment period was also higher among micronised fenofibrate than placebo recipients (27.4 to 55.7 *vs* 0%).

In the smaller study conducted in 16 patients with type IIa dyslipidaemia attributable to familial defective apolipoprotein B-100, micronised fenofibrate 200mg once daily produced significantly greater reductions ($p < 0.05$) in TC, LDL-C and TG levels than those seen with placebo (table IV).[27] HDL-C levels were also increased with micronised fenofibrate, although this effect did not reach statistical significance versus placebo (baseline HDL-C levels were not presented).[27] However, as a consequence of the beneficial effect on both LDL-C and HDL-C levels, a significantly greater reduction in the LDL-C to HDL-C ratio was reported in micronised fenofibrate, compared with placebo, recipients (–25.0 *vs* +12.2%; $p < 0.05$).

The results of a small, randomised, crossover study[104] in 20 men with hypertriglyceridaemia and CHD (or ≥1 risk factor other than gender for CHD) revealed that fasting TG levels were 36% lower ($p < 0.01$) after 8 weeks' administration of micronised fenofibrate 200mg once daily than after 8 weeks' administration of placebo. Moreover, 4 hours after an oral fat-loading test, plasma levels of TG, TG-rich lipoprotein TG, TG-rich lipoprotein cholesterol, TG-rich lipoprotein ApoCIII and TG-rich lipoprotein ApoE were 32, 35, 29, 36 and

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Table III. Noncomparative trials assessing the efficacy of micronised fenofibrate[a] in patients with primary dyslipidaemia

Reference	Treatment duration	Dyslipidaemia type/lipid entry criteria (mmol/L) [no. of patients]	Change in plasma lipid levels[b] from the beginning to the end of drug treatment (%)			
			TC	LDL-C	HDL-C	TG
Tablet formulation						
Delaval and Salomon[44][c]						
study 1	12wk	IIa [88]	–14.9***	–22.9***	+10.6***	–27.5***
		IIb [83]	–14.5	–15.3	+12.9***	–46.3***
study 2	12wk	IIa [70]	–15.6	–19.1***	+11.0***	–28.1***
		IIb [112]	–11.5	–13.1	+14.5***	–46.6***
		IV [16]	+6.0		+5.3	–39.1*
Capsule formulation						
Julius & Schwartz[42]	12wk[d]	[933]	–21.6	–28.1	+17.7	–34.6
Kirchgässler et al.[94][e]	12wk	IIa [3304]	–21.1	–29.2	+21.5	–15.2
		IIb [2165]	–21.9	–26.4	+27.6	–33.6
		IV [3563]	–17.7	–0.3	+21.5	–42.7
Kornitzer et al.[65]	6mo	IIa, IIb, IV [1334]	–19.8***	–24.4***	+15.2***	–36.6***
Kornitzer et al.[103][f,g]	12mo	IIa, IIb, IV [735]		–26.4	+18.6	
Krempf et al.[72][f]	6mo[h]	TC >7.76 and/or LDL-C > 5.55 [112]	–29.0	–35.0	+3.0	–37.2
Lelieur et al.[100][f]	12mo	IIa [42]		–20 to –28[i]	+1.5 to +16[i]	
		IIb [33]		–20 to –28[i]	+1.5 to +16[i]	–38 to –51[i]
		IV [56]		–3 to +3[i]	+1.5 to +16[i]	–38 to –45[i]
März et al.[92]	12wk	IIa [1194]	–21	–30	+16	–15
		IIb [777]	–21	–26	+19	–32
		IV [966]	–17	–2	+12	–44
		Total cohort [3724][j]	–20	–26	+16	–27
Moisseyev et al.[93][f,k]	3mo	IIa [12], IIb [3]	–23**	–28**		–52**
Pavlova et al.[95][f]	12mo	TC >6.5 [27]	–25.0	–28	+4.0	–37.0
Pfützner et al.[25]	3mo	IIa, IIb [10]	–23.8**	–30.3**	+34.7	–31.7*
Rašlová et al.[29]	3mo	IIa [13]	–25.0**	–34.7**	+26.4**	–42.6**
		IIb [16]	–20.1**	–21.5**	+14.8*	–50.4**
Schmitz et al.[96][f,l]	median 4.6y	IIa, IIb, IV [80]	–22.1	–30.3	+16.7	–20.7
Sobolev et al.[97][f]	60d	IIb [8], III [9], IV [7]	–12.0		+10.0	–39.0

a Patients received the capsule formulation of micronised fenofibrate (usually 200mg once daily) in all but two studies[44] in which patients received the tablet formulation of the drug (160mg once daily).

b Values reported as means[25,29,42,65,72,94,96,103] or medians;[44,92] in some studies it was not stated if values were means or medians.[93,95,97,100]

c The results of two studies were reported in an abstract and poster.

d 860 patients received micronised fenofibrate 200 mg/day and 73 patients received 400 mg/day.

e This study was a drug monitoring programme; statistical analysis was not performed.

f Abstract.

g Extension of Kornitzer et al.[65] study with treatment period extended to 12mo.

h Patients received micronised fenofibrate 267mg once daily.

i Results reported as a range.

j 787 patients were not classified as having type IIa, IIb or IV dyslipidaemia because of a lack of laboratory data.

k All patients (n = 15) were postmenopausal, hypertensive women.

l Extension of drug monitoring programme[94] with treatment period extended to a median of 4.6y.

HDL-C = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TC** = total cholesterol; **TG** = triglycerides; * $p < 0.05$, ** $p \leq 0.001$, *** $p < 0.0001$ *vs* baseline.

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38% lower, respectively, with micronised fenofibrate than with placebo administration.

A double-blind, randomised, multicentre, placebo-controlled trial examined the use of micronised fenofibrate 67 to 201 mg/day in patients with dyslipidaemia and progressive renal impairment [corrected creatinine clearance of 1.20 to 4.44 L/h/1.73m^2 (20 to 74 ml/min/1.73m^2)].[105] After 6 months' treatment, a significantly greater reduction from baseline in mean TG levels was seen in micronised fenofibrate than in placebo recipients (–31 *vs* +1.3%; p = 0.003) [table IV].

Comparisons with HMG-CoA Reductase Inhibitors

The lipid-modifying effects of micronised fenofibrate 200mg once daily have been compared with those of the HMG-CoA reductase inhibitors simvastatin 20mg once daily, pravastatin 20mg once daily and cerivastatin 0.3 mg/day in five randomised, double-blind studies conducted in patients with type II dyslipidaemia (table V).[24,26,28,30,106] All five trials included treatment periods of 2 to 3 months' duration. One study was of a crossover design; however, the absence of a washout period between the first and second 3-month treatment period only permitted a comparison of the lipid-modifying effect of the two agents at the end of the first 3-month treatment period.[24] The results of the study[106] comparing micronised fenofibrate with cerivastatin will not be discussed, as cerivastatin has since been withdrawn from use.[107]

Assessment of the change in plasma lipid levels from the beginning to the end of treatment revealed

Table IV. Results of trials comparing the efficacy of micronised fenofibrate (MF) with placebo (PL) in patients with primary dyslipidaemia

Reference (study design) [treatment duration]	Treatment regimen[a] (mg/day)	Dyslipidaemia type/inclusion criteria (mmol/L) [no. of patients]	Change in plasma lipid levels[b] from the beginning to the end of drug treatment (%)			
			TC	LDL-C	HDL-C	TG
Genest et al.[104]c (co, db, r) [8wk]	MF 200	TG 2.3-6, HDL-C <0.91, LDL-C <5.0 [20]	–5.6	+1.2	+11.3	–27.2
	PL	TG 2.3-6, HDL-C <0.91, LDL-C <5.0 [20]	+1.6	–5.6	0.0	+13.6
Krempf et al.[98] (r, db, pll, mc) [3mo]	MF 200	IIa [65], IIb [4] (LDL-C >4.65, TG <3.99)	–24.5*	–31.6*	+8.0	–26.7*
	MF 267	IIa [55], IIb [14] (LDL-C >4.65, TG <3.99)	–26.9*	–32.5*	+8.2	–35.3*
	MF 340	IIa [57], IIb [9] (LDL-C >4.65, TG <3.99)	–31.9*	–38.8*	+5.8	–40.8*
	MF 400	IIa [58], IIb [9] (LDL-C >4.65, TG <3.99)	–29.2*	–36.0*	+4.1	–29.3*
	PL	IIa [58], IIb [11] (LDL-C >4.65, TG <3.99)	+0.5	+0.5	+1.3	+3.5
Levin et al.[105]d (db, r, mc, pll) [6mo]	MF 67-201	TG ≥2.3, LDL-C:HDL-C ≥5 [16]	–5.2		+13.0	–31**
	PL	TG ≥2.3, LDL-C:HDL-C ≥5 [12]	–3.7		–3.7	+1.3
März et al.[27]e (r, pll) [12wk]	MF 200	IIa [8][f]	–14.4*	–16.5*	+12.2	–35.9*
	PL	IIa [8][f]	+3.4	+11.5	–5.4	–12.2

a Micronised fenofibrate was administered once daily.

b Values reported as means in three studies;[98,104,105] in the other study it was not specified if values were means or medians.[27]

c This crossover study involved men (n = 20) with hypertriglyceridaemia; a 5-week washout period separated the two treatment periods.

d Patients in this study had progressive renal impairment [corrected creatinine clearance of 1.20 to 4.44 L/h/1.73m^2 (20 to 73 ml/min/1.73m^2)].

e Abstract.

f All patients had type IIa dyslipidaemia attributable to familial defective apolipoprotein B-100.

co = crossover; **db** = double-blind; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicentre; **pll** = parallel; **r** = randomised; **TC** = total cholesterol; **TG** = triglyceride; * p < 0.05, ** p < 0.01 *vs* PL.

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Table V. Summary of trials comparing once daily micronised fenofibrate (MF) with HMG-CoA reductase inhibitors in patients with dyslipidaemia

Reference (trial design) [treatment duration]	Treatment (mg/day)	Dyslipidaemia type/entry criteria (mmol/L)	No. of patients	Change[a] in plasma lipid levels from the beginning to the end of treatment (%)			
				TC	LDL-C	HDL-C	TG
Bairaktari et al.[31] (nb, pll) [16wk]	MF 200	TG 2.26-4.52, TC ≥6.22, LDL-C ≥4.14	46	–15.6	–17.6	+16.6†	–26.4††
	A 10		45	–24.8†	–35.3†	+5.0	–12.5
Chelly[28]b (mc, r, db, pll) [8wk]	MF 200	II[c] (TC > 6.5)	116	–17	–22	+7 to +8***	↓***†
	S 20		111	–23†††	–32†††	+7 to +8***	↓***
Crepaldi et al.[99]b (mc, r, pll) [6mo]	MF 200	IIa	60	–20.1	–26.6	+15.9	–31.8†††
		IIb	31	–13.0	–13.0	+30.0††	–45.0††††
	S 10	IIa	49	–21.8	–30.5	+13.8	+1.8
		IIb	37	–18.7	–24.7†††	+12.4	–16.1
Depres et al.[102] (r, nb, pll) [12wk]	MF 200	HDL-C <1.2 (women) or <1.1 (men), LDL-C >3.2, TG <4.5	79	–14.8	–16.2	+13.3†††	–29.9††
	A 10		86	–28.3††††	–38.6††††	+5.3	–15.4
Ducobu et al.[26]b (mc, r, db, pll) [3mo]	MF 200	II (TC ≥6.5, TG ≤4.6)	76	–18	–17	+14†	–39††††
	P 20		76	–15	–17	+6	–12
Farnier et al.[24]d (r, db, co) [3mo]	MF 200	IIa (TC ≥6.2, LDL-C ≥4.1, TG < 1.5)	15	–27.3[e]	–33.5[e]	+1.3	–36.1†††
		IIb (TC ≥ 6.2, 1.5 < TG < 5.2)	11	–22.6	–25.2	+24.5	–53.2†††
	S 20	IIa (TC ≥6.2, LDL-C ≥4.1, TG < 1.5)	16	–28.0[e]	–35.6[e]	+1.4	–1.0
		IIb (TC ≥ 6.2, 1.5 < TG < 5.2)	10	–21.1	–28.7	+15.0	+24.7
Kiortsis et al.[32]f (nb) [6wk]	MF 200	LDL-C ≥4.1, TG ≥3.6	12	–14.7*‡	–8.7*‡	+25.0*	–39.5**‡
	A 40		12	–35.3**‡	–37.0**‡	+14.3*‡	–27.6*‡
	MF 200 + A 40		12	–42.4**	–42.2**	+28.6*	–46.1**
Lemieux et al.[109] (r, pll) [16wk]	MF 200	IIa	36	–18*	–24*	+13*	–26*
	P 20[g]		43	–21*	–28*	+5*	–7*
Malik et al.[50] (sb, r, co) [10wk]	MF 200	TC >6.2, TG >1.5	29	–12.1**	–7.7	+12.7**††	–49.7**††
	A 10		29	–27.9***††††	–33.9***††††	–0.8	–32.2**
Steinmetz et al.[30] (mc, r, db, pll) [12wk]	MF 200	IIa (TC > 6.5) or IIb (TC > 6.5, 2.9 < TG ≤ 5.8)	66[h]	–19.5	–20.9	+18.5†	–41.4†††
		IIa (TC > 6.5)		–17.8	–21.2	+12.3	–32.0
		IIb (TC > 6.5, 2.9 < TG ≤ 5.8)		–22.3	–20.0	+33.6†††	–52.7†††

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	S 20	IIa (TC > 6.5) or IIb (TC > 6.5, 2.9 < TG ≤5.8)	64[h]	–24.6†	–34.9†††	+15.0	–16.5
		IIa (TC > 6.5)		–25.8†	–35.2†††	+16.5	–19.0
		IIb (TC > 6.5, 2.9 < TG ≤ 5.8)		–22.6	–34.4††	+11.4	–14.0

a Mean values quoted in studies except for Chelly et al.,[28] Crepaldi et al.,[99] and Ducobu et al.[26] (not specified).

b Abstract.

c Patients were described as having primary hypercholesterolaemia.

d Patients were randomised to treatment with MF for 3mo followed by S for 3mo or to S for 3mo followed by MF for 3mo. Because of the absence of a washout period between the first and second treatment period, the changes in serum lipoprotein levels from the beginning to the end of treatment are only reported for the first 3mo treatment period.

e Statistical significance *vs* baseline but degree of significance not stated.

f Patients in this study received MF monotherapy for 6wk then A monotherapy for 6wk then MF + A for 6wk.

g The pravastatin dosage was increased to 40 mg/day if patients had an unsatisfactory response after 8 weeks' treatment.

h Number of patients only available for type IIa and IIb patients combined.

A = atorvastatin; **co** = crossover; **db** = double-blind; **HDL-C** = high-density lipoprotein cholesterol; **HMG-CoA** = hydroxymethylglutaryl coenzyme A; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicentre; **nb** = nonblind; **P** = pravstatin; **pll** = parallel; **r** = randomised; **S** = simvastatin; **sb** = single-blind; **TC** = total cholesterol; **TG** = triglycerides; ↓ indicates a decrease; * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ *vs* baseline; † $p < 0.05$, †† $p \leq 0.01$, ††† $p \leq 0.001$, †††† $p \leq 0.0001$ *vs* monotherapy comparator; ‡ $p < 0.05$ *vs* combination therapy.

a greater decrease in TG levels with micronised fenofibrate than with simvastatin or pravastatin in patients with type II dyslipidaemia; this decrease reached statistical significance ($p < 0.05$) on all but one occasion (table V).[24,26,28,30] There was also a general trend towards a greater increase in HDL-C levels with micronised fenofibrate,[24,26,30] although a similar increase was reported with both micronised fenofibrate and simvastatin in one study (baseline levels of HDL-C were not stated).[28] The comparative effect of micronised fenofibrate and simvastatin or pravastatin on LDL-C and TC levels was more variable; micronised fenofibrate was significantly less effective ($p < 0.05$) than simvastatin at reducing LDL-C and TC levels in two studies[28,30] but was of similar efficacy to simvastatin and pravastatin in the other two studies.[24,26]

Efficacy data from two of these studies[24,30] (comparing micronised fenofibrate with simvastatin) were included in a retrospective cost-effectiveness analysis.[108] Only direct costs (including drug costs and the cost of an average number of physician visits and routine examinations) were considered. Response to treatment was defined as a 15% reduction in LDL-C levels in type IIa patients, and as a 15% reduction in LDL-C levels plus a 30% reduction in TG levels in type IIb patients. There was a small difference in the cost per successfully treated patient with type IIa dyslipidaemia between micronised fenofibrate and simvastatin (DM450 *vs* DM517; 1995 values); in this patient group, the increased acquisition cost of simvastatin was partially offset by the higher response rate with this drug (98 *vs* 78%). In contrast, micronised fenofibrate was associated with a higher response rate than simvastatin in patients with type IIb dyslipidaemia (57 *vs* 31%) resulting in substantial cost savings (DM768 *vs* DM2080 per responder). These results were robust to various sensitivity analyses. Further studies are required to determine whether these findings can be extended to patients receiving long-term (>1 year) therapy.

A single-blind, randomised, crossover study[50] and three nonblind studies[31,32,102] compared the efficacy of 6 to 16 weeks' treatment with micronised fenofibrate 200mg once daily with that of atorvastatin 10 or 40 mg/day. In three stud-

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ies,[31,50,102] fenofibrate recipients had significantly greater improvements ($p < 0.05$) from baseline in HDL-C and TG levels than atorvastatin recipients (table V). Compared with atorvastatin recipients, fenofibrate recipients had significantly smaller reductions from baseline in TC and LDL-C levels ($p < 0.05$). A similar pattern was seen in the fourth study (table V).[32] One of the studies included patients with dyslipidaemia who had low HDL-C levels; the greatest increases in HDL-C levels occurred in those with the lowest levels at baseline.[102]

Micronised fenofibrate 200mg once daily has also been compared with simvastatin 10mg once daily[99] and pravastatin 20 to 40 mg/day[109] in two randomised, parallel-group studies (trial blinding not stated) [table V].[99] In one study,[99] significantly greater reductions ($p < 0.001$) from baseline in TG levels were seen in micronised fenofibrate than in simvastatin recipients in patients with type IIa or IIb dyslipidaemia after 6 months' treatment. Among patients with type IIb dyslipidaemia, a significantly greater increase from baseline in HDL-C levels was seen in fenofibrate, compared with simvastatin recipients ($p < 0.01$); however, LDL-C levels were reduced by a significantly greater extent in simvastatin than in fenofibrate recipients ($p < 0.001$). The other study included only patients with type IIa dyslipidaemia.[109] Significant ($p < 0.05$) improvements from baseline in lipid levels were seen in both treatment groups; however, the reduction in TG levels and the increase in HDL-C levels tended to be greater in micronised fenofibrate, compared with pravastatin, recipients. Interestingly, the LDL peak particle size increased from baseline by a significant extent ($p < 0.05$) in micronised fenofibrate recipients, but not in pravastatin recipients.

Comparisons with Other Fibrates

Micronised fenofibrate has been compared with gemfibrozil in four studies,[45,110-112] three of which are available as abstracts.[45,110,111] The largest multicentre study[45] randomised patients with mixed dyslipidaemia (a TC to HDL-C ratio of ≥5.6 in women and ≥6.0 in men and a TG level of 2.2 to 5.6 mmol/L) to receive micronised fenofibrate 200mg (n = 116) or gemfibrozil 1200mg (n = 118) once daily for 24 weeks. Significantly greater reductions from baseline in TC, LDL-C, ApoB and fibrinogen levels, and in the TC to HDL-C ratio, were seen in micronised fenofibrate, compared with gemfibrozil, recipients ($p < 0.05$) [figure 2]. ApoAI levels increased from baseline by a significantly greater extent in micronised fenofibrate, compared with gemfibrozil, recipients ($p < 0.001$); there was no significant between-group difference in the change from baseline in TG or HDL-C levels (the baseline TG level was 3.5 mmol/L in both treatment groups and the baseline HDL-C level was 0.9 mmol/L in both treatment groups).

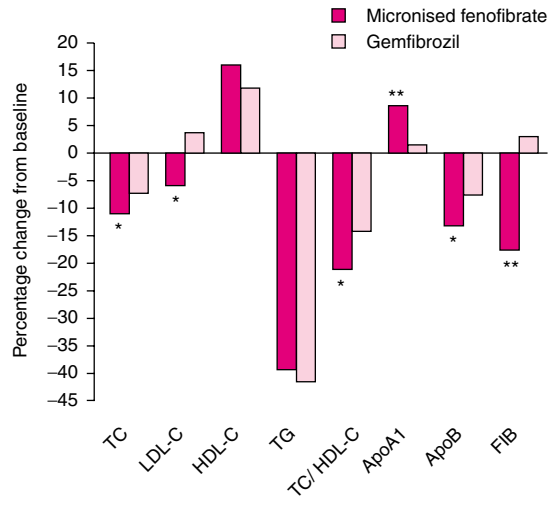

Fig. 2. Percentage changes from baseline in lipid levels, TC to HDL-C ratio and fibrinogen (FIB) levels in patients with mixed dyslipidaemia enrolled in a randomised, multicentre study, available as an abstract.[45] Patients were randomised to receive micronised fenofibrate 200mg once daily (n = 116) or gemfibrozil 1200mg once daily (n = 118) for 24 weeks. **ApoAI** = apolipoprotein AI; **ApoB** = apolipoprotein B; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TC** = total cholesterol; **TG** = triglycerides; * $p < 0.05$, ** $p < 0.001$ *vs* baseline.

The other three studies were of crossover design. Twenty-one patients with hypertriglyceridaemia received gemfibrozil 600mg twice daily for at least 3 months before switching to treatment with micronised fenofibrate 200 or 201 mg/day for

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3 months (recipients of micronised fenofibrate 201 mg/day received three 67mg tablets).[110] Following administration of micronised fenofibrate, TG levels (6.0 *vs* 13.7 mmol/L; p = 0.003) and the TC to HDL-C ratio (7.6 *vs* 12.3; p = 0.039) were significantly lower than after administration of gemfibrozil. In addition, HDL-C levels were significantly higher after micronised fenofibrate administration than after gemfibrozil administration (0.9 *vs* 0.8 mmol/L; p = 0.031).

The other two crossover studies enrolled patients with type IIa (n = 11[111] and 16[112]) or type IIb dyslipidaemia (n = 29[111] and 5[112]). In the larger study, 17 patients also had type 2 diabetes mellitus.[111] In this study,[111] patients received gemfibrozil 600mg twice daily for a mean duration of 23 months; patients switched to treatment with micronised fenofibrate 201mg once daily (lipid levels were assessed a mean of 11 weeks after the switch to micronised fenofibrate). In the smaller study,[112] patients received micronised fenofibrate 200mg and gemfibrozil 900mg once daily for 6 weeks each. Micronised fenofibrate, compared with gemfibrozil, recipients tended to have greater improvements in TC (–16[111] and –22%[112] *vs* –12[111] and –15%[112]), LDL-C (–18[111] and –27%[112] *vs* –13[111] and –16%[112]), TG (–49[111] and 54%[112] *vs* –40[111] and –46.5%[112]) and HDL-C (+19[111] and +9%[112] *vs* +15[111] and +9%[112]) levels. In one study,[111] the between-group difference in the reduction in TC, LDL-C and TG levels significantly favoured micronised fenofibrate in patients with type IIb dyslipidaemia ($p < 0.05$). Similarly, in the other study,[112] the between-group difference in the reduction in TC and LDL-C levels was significantly greater in micronised fenofibrate than in gemfibrozil recipients ($p < 0.02$).

A fifth study, of nonblind, crossover design, compared the use of micronised fenofibrate with that of bezafibrate in 23 patients with type III hyperlipoproteinaemia (all patients were homozygous for ApoE2).[113] Patients received bezafibrate 400 mg/day for 12 weeks before crossing over to treatment with micronised fenofibrate 200 mg/day for another 12 weeks (there was no washout period between the two active treatment periods). Serum levels of TC, VLDL-C, LDL-C, HDL-C and TG at baseline were 9.8, 6.1, 3.2, 0.8 and 7.1 mmol/L, respectively. After treatment with bezafibrate, levels of TC, VLDL-C and TG were significantly lower ($p < 0.01$) than at baseline (7.2, 3.6 and 5.1 mmol/L, respectively) and HDL-C levels were significantly higher than at baseline (1.0 mmol/L; p = 0.0019). Compared with baseline, significantly lower ($p < 0.05$) levels of TC, VLDL-C, LDL-C and TG were seen following micronised fenofibrate therapy (6.0, 2.8, 2.7 and 4.3 mmol/L, respectively). In addition, HDL-C levels were significantly higher than at baseline (1.1 mmol/L; $p < 0.0001$). Moreover, TC and VLDL-C levels were significantly lower ($p < 0.05$), and HDL-C levels were significantly higher (p = 0.0182), after administration of micronised fenofibrate than after administration of bezafibrate.

4.1.3 In Combination with HMG-CoA Reductase Inhibitors

Six or 16 weeks' combination therapy with micronised fenofibrate and an HMG-CoA reductase inhibitor resulted in greater improvements from baseline in TC, LDL-C and TG levels than those observed with micronised fenofibrate alone in a double-blind, randomised, multicentre study[114] and in a nonblind study[32] (table VI); combination therapy was also more effective than atorvastatin monotherapy in the nonblind study.[32] The double-blind study enrolled patients with type IIa or IIb dyslipidaemia; patients received micronised fenofibrate 200 mg/day alone or in combination with fluvastatin 20 or 40 mg/day.[114] The nonblind study enrolled patients with severe mixed dyslipidaemia; patients received micronised fenofibrate 200 mg/day monotherapy for 6 weeks followed by atorvastatin 40 mg/day monotherapy for 6 weeks followed by 6 weeks' treatment with micronised fenofibrate 200 mg/day plus atorvastatin 40 mg/day.[32]

Significant reductions from baseline in TC, LDL-C and TG levels ($p < 0.01$), and a significant increase from baseline in HDL-C levels ($p < 0.01$),

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Table VI. Results of trials assessing the efficacy of combination therapy with micronised fenofibrate (MF) and HMG-CoA reductase inhibitors in patients with primary dyslipidaemia

Reference (trial design) [treatment duration]	Lipid entry criteria (mmol/L)	Treatment (mg/day)	No. of patients	Mean change from baseline in plasma lipid levels (%)			
				TC	LDL-C	HDL-C	TG
Ellen & McPherson[115] [mean 2.06y]	LDL-C ≥3.4, TG ≥3.1 and/or HDL-C≤0.9	SF 300 or MF 200 + P 20 or S 10[a]	80	–27.3**	–31.2**	+14.8**	–49.0**
Farnier et al.[114] (db, r, pll, mc) [16wk]	LDL-C ≥4.9, TG ≤3.9	MF 200	32	–19††	–21††	+4†	–29†
		MF 200 + F 20	33	–27	–32	+14	–39
		MF 200 + F 40	31	–35	–41	+3	–40
Kiortsis et al.[32][b] (nb) [6wk]	LDL-C ≥4.1, TG ≥3.6	MF 200	12	–14.7*‡	–8.7*‡	+25.0*	–39.5**‡
		A 40	12	–35.3**‡	–37.0**‡	+14.3*‡	–27.6*‡
		MF 200 + A 40	12	–42.4**	–42.2**	+28.6*	–46.1**
Widimsky et al.[116][c] (r, nb) [78wk]	LDL-C ≥4.1, TG 2.5-4.5	F 40	NR[d]	–19.3	–29.7	+9.9[e]	–19.7[e]
		MF 200 + F 20	NR[d]	–21.5	–29.1	+26.0	–40.2

a Patients in this study received either SF or MF in combination with either P (n = 63) or S (n = 17).

b Patients in this study received MF monotherapy for 6wk then A monotherapy for 6wk then MF + A for 6wk.

c Abstract.

d A total of 104 patients were included in this study; the no. of pts in each treatment arm was not specified.

e The change in lipid level was significantly greater in F + MF recipients than in F monotherapy recipients although p-values were not reported.

A = atorvastatin; **db** = double-blind; **F** = fluvastatin; **HDL-C** = high-density lipoprotein cholesterol; **HMG-CoA** = hydroxymethylglutaryl coenzyme A; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **P** = pravastatin; **pll** = parallel; **r** = randomised; **S** = simvastatin; **SF** = standard fenofibrate; **TC** = total cholesterol; **TG** = triglycerides; * $p < 0.05$, ** $p < 0.01$ *vs* baseline; † $p < 0.05$, †† $p < 0.001$ (analysis of variance F test for the comparison of the three treatment groups); ‡ $p < 0.05$ *vs* combination therapy.

were seen in a noncomparative study that enrolled patients with mixed dyslipidaemia who had CHD or who were at high risk for CHD (table VI).[115] Patients received micronised fenofibrate 200mg once daily or nonmicronised fenofibrate 300mg once daily in combination with pravastatin 20mg once daily (n = 63) or simvastatin 10mg once daily (n = 17) for an average of 2.06 years. Before combination therapy, all patients received monotherapy comprising pravastatin, simvastatin, or micronised or nonmicronised fenofibrate (at previously mentioned dosages) for an unstated length of time.

Combination therapy tended to be more effective than fluvastatin monotherapy in a long-term, nonblind, randomised study (conducted over 78 weeks) that enrolled 104 patients with mixed dyslipidaemia and CHD (table VI).[116] TG levels decreased, and HDL-C levels increased, by a significantly greater extent in recipients of micronised fenofibrate 200 mg/day plus fluvastatin 20 mg/day than in recipients of fluvastatin 40 mg/day monotherapy (p-values not reported). Similar reductions in TC and LDL-C levels were seen in both treatment groups.

It should be noted that it is recommended that combination therapy with micronised fenofibrate and HMG-CoA reductase inhibitors be avoided unless the potential benefit (with regards to further reduction in lipid levels) outweighs the potential risk associated with this drug combination (section 6).[7]

4.2 Diabetic Dyslipidaemia

Dyslipidaemia is a common finding in type 2 diabetes mellitus; patients often have hypertriglyceridaemia and low HDL-C levels.[117-119] Treatment with micronised fenofibrate 200 mg/day has been associated with improvement in

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dyslipidaemia in patients with type 2 diabetes mellitus in a large (n = 418), double-blind, randomised, multicentre study [the Diabetes Atherosclerosis Intervention Study (DAIS)][120] and in several smaller studies (n = 11 to 120).[121-127]

In DAIS, significantly greater improvements from baseline in TC, LDL-C, HDL-C and TG levels were seen in micronised fenofibrate than in placebo recipients ($p < 0.001$) [table VII]. In addition, micronised fenofibrate slowed the angiographic progression of focal coronary atherosclerosis. Coronary angiography showed that micronised fenofibrate was associated with significantly less progression than placebo in average minimum lumen diameter [–0.06 *vs* –0.10mm (indicating 40% less progression; $p = 0.029$ *vs* placebo)] and average percentage diameter stenosis [+2.11 *vs* +3.65% (indicating 42% less progression; $p = 0.02$ *vs* placebo)]. A smaller decrease in mean segment diameter was seen with micronised fenofibrate compared with placebo [change in mean segment diameter of –0.06 *vs* –0.08mm (indicating 25% less progression; $p = 0.171$ *vs* placebo)]. During treatment, small increases from baseline in glycosylated haemoglobin levels were seen in both treatment groups. During DAIS, cardiac endpoints (e.g. myocardial infarction, coronary angioplasty, hospitalisation for angina pectoris, coronary artery bypass graft surgery) occurred in 38 micronised fenofibrate recipients and in 50 placebo recipients; however, the trial was not designed to examine between-group differences in cardiac endpoints.

Subgroup analysis in 46 patients from the DAIS study revealed that LDL peak particle diameter in-

Table VII. Effects of micronised fenofibrate (MF) on lipid levels in patients with type 2 diabetes mellitus: results of randomised comparative trials

Reference (trial design) [treatment duration]	Lipid entry criteria (mmol/L)	Treatment (mg/day)	No. of patients	Mean change from baseline in plasma lipid levels (%)			
				TC	LDL-C	HDL-C	TG
Compared with placebo (PL)							
DAIS Investigators[120] (db, mc, pll) [≥3y]	TC:HDL-C ratio ≥4 plus either LDL-C 3.5-4.5 and TG ≤5.2, or TG 1.7-5.2 and LDL-C ≤4.5	MF 200	207	–9.6**[a]	–5.9**[a]	+7.4**[a]	–28.5**[a]
		PL	211	+0.4[a]	+0.4[a]	+1.5[a]	+1.1[a]
Feher et al.[121]b (db, pll) [12wk]	TC ≥6	MF 200	16	–17**††††	–22*††††	+20**††	–44**†
		PL	16	+6	+4	–3	+21†
Compared with HMG-CoA reductase inhibitors							
Athyros et al.[127] (nb) [24wk]	TC >5.7, LDL-C >3.4, TG 2.3-4.5, HDL-C <1.04[c]	MF 200	40	–16††††‡	–15††††‡	+16	–41††††‡
		A 20	40	–31††††‡	–40††††‡	+9††††‡	–30††††‡
		MF 200 + A 20	40	–37††††	–50††††	+22††††	–50††††
Frost et al. [125] (co) [6wk]	LDL-C >3.5, TG >2.3	MF 200[d]	11	–16.0†††	–11.0	+11.0	–39.0†††
		A 10[d]	11	–24.0†††	–29.0††	+10.0†	–4.0
Sarano et al.[123]b (pll) [4wk]	LDL-C >4.1, TG 2.4-4.5	MF 200	16	–21.9††††	–25.5††††	+15.9††	–41.6††††
		F 40	16	–22.2††††	–28.1††††	+8.8	–23.0

a Values estimated from a graph.

b Abstract.

c Patients also had an apolipoprotein B level of >150 mg/dl.

d In this co study, a 6-wk washout period separated the two treatment periods.

A = atorvastatin; **co** = crossover; **DAIS** = Diabetes Atherosclerosis Intervention Study; **db** = double-blind; **F** = fluvastatin; **HDL-C** = high-density lipoprotein cholesterol; **HMG-CoA** = hydroxymethylglutaryl coenzyme A; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicentre; **nb** = nonblind; **pll** = parallel; **TC** = total cholesterol; **TG** = triglycerides; * $p < 0.01$, ** $p < 0.001$ *vs* PL; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.005$, †††† $p < 0.001$ *vs* baseline; ‡ $p < 0.05$ *vs* combination therapy.

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creased from baseline by a significant extent in micronised fenofibrate recipients (from 25.3 to 26.7 nmol/L; $p < 0.02$), but not in placebo recipients (from 25.1 to 25.9 nmol/L).[128]

Similarly, in another double-blind, randomised, placebo-controlled study in 32 patients with type 2 diabetes mellitus, micronised fenofibrate was associated with significantly greater improvements in LDL-C, HDL-C, TC and TG levels than placebo ($p < 0.01$) [table VII]. Moreover, as a consequence of its effect on LDL-C and HDL-C, the TC to HDL-C ratio was reduced from baseline by a significantly greater extent ($p < 0.001$) in micronised fenofibrate than in placebo recipients (–27 *vs* +10%).[121] A beneficial effect on the LDL subfraction distribution was also reported with micronised fenofibrate in this study (section 2.1.1).[15] The lipid-modifying effects of micronised fenofibrate in this study were not associated with alterations in glucose tolerance.

Three randomised studies[123,125,127] included patients with type 2 diabetes mellitus and dyslipidaemia (n = 11 to 120) who received monotherapy with micronised fenofibrate 200 mg/day, HMG-CoA reductase inhibitor monotherapy (atorvastatin 10 or 20 mg/day or fluvastatin 40 mg/day) or micronised fenofibrate 200 mg/day plus an HMG-CoA reductase inhibitor (atorvastatin 20 mg/day or fluvastatin 40 mg/day) [table VII]. In one arm of the largest study,[127] patients were randomised to receive micronised fenofibrate 200 mg/day plus atorvastatin 20 mg/day. The reductions from baseline in TC, LDL-C and TG levels were significantly greater ($p < 0.05$) in these patients than in monotherapy recipients (table VII). In addition, the increase from baseline in HDL-C levels was significantly greater ($p < 0.05$) in combination therapy recipients than in atorvastatin monotherapy recipients (table VII). In a second study,[123] 32 patients received micronised fenofibrate or fluvastatin monotherapy for 4 weeks (table VII); patients with an LDL-C level >2.6 mmol/L after this treatment period (n = 30) subsequently received micronised fenofibrate 200 mg/day plus fluvastatin 40 mg/day for 12 weeks. After combination therapy, TC, LDL-C, HDL-C and TG levels were further improved with changes from baseline of –31, –41, +25 and –45%, respectively ($p < 0.001$ *vs* baseline).

Micronised fenofibrate 200mg once daily was associated with significant improvements ($p < 0.05$) from baseline in serum TG and HDL-C levels in three small noncomparative studies (n = 35,[124] n = 50[126] and n = 21[122]) in patients with type 2 diabetes mellitus and dyslipidaemia; two studies are available as abstracts.[122,126] In one of them,[126] significant reductions from baseline were also seen in TC and LDL-C levels ($p < 0.05$); however, in the fully published study, in which patients had only mildly elevated cholesterol levels at baseline, only small reductions from baseline occurred in TC and LDL-C levels.[124]

4.2.1 In Metabolic Syndrome

Treatment with micronised fenofibrate 200mg once daily improved lipid levels and nonlipid parameters in a 12-week noncomparative study[64] in 37 men with metabolic syndrome (a syndrome characterised by dyslipidaemia, abdominal obesity, hypertension, increased thrombogenicity, hyperuricaemia and insulin resistance). After 12 weeks' treatment, patients had significant reductions ($p < 0.01$) from baseline in mean levels of TC, LDL-C and TG and a significant increase ($p < 0.01$) from baseline in the mean HDL-C level (figure 3). In addition, significant reductions from baseline in mean fibrinogen levels (from 2.27 to 1.84 g/L; $p < 0.01$) and uric acid levels (from 426.2 to 338.1 μmol/L; $p < 0.01$) and mean factor VII activity (from 111.9 to 91.5%; $p < 0.02$) were seen. Moreover, significant reductions from baseline in fasting serum insulin levels ($p < 0.01$) and the insulin response during an oral glucose tolerance test ($p < 0.05$) [by 26.8% and 18.7%, respectively], and in mean systolic (from 144.5 to 129.8mm Hg; $p < 0.001$) and diastolic (from 90.2 to 80.4mm Hg; $p < 0.001$) blood pressure, were observed.

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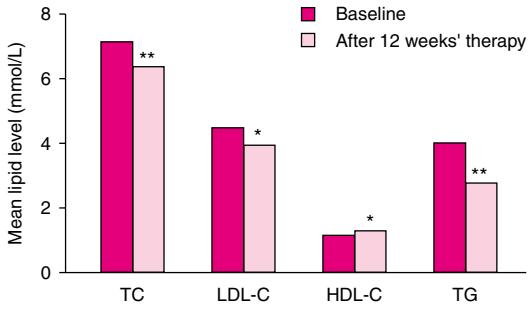

Fig. 3. Mean lipid levels at baseline and after 12 weeks' treatment in men (n = 37) with metabolic syndrome. Patients received micronised fenofibrate 200mg once daily for 12 weeks.[64] **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TC** = total cholesterol; **TG** = triglycerides; * $p < 0.01$, ** $p < 0.001$ *vs* baseline.

4.3 Protease Inhibitor-Induced Hypertriglyceridaemia

Patients with HIV infection who are receiving protease inhibitor therapy may develop metabolic abnormalities such as hypercholesterolaemia and hypertriglyceridaemia.[129] Micronised fenofibrate was associated with significant improvements from baseline in TG levels in patients with protease inhibitor-induced hypertriglyceridaemia in two briefly reported noncomparative studies[130,131] and in case reports.[132]

Nine patients with HIV infection and hypertriglyceridaemia (TG level of 11.17 mmol/L) associated with ritonavir or indinavir therapy received micronised fenofibrate 201 mg/day for 3 months.[130] Following treatment, the TG level decreased to 2.97 mmol/L ($p < 0.05$ *vs* baseline). In the other noncomparative study, eight patients with HIV infection and protease inhibitor-induced hypertriglyceridaemia received micronised fenofibrate 200mg once daily.[131] Preliminary results indicate that the median TG level was significantly lower ($p < 0.0001$) in the 6 months following the start of micronised fenofibrate therapy (9.16 mmol/L) than in the 4 months prior to treatment (18.66 mmol/L).

Treatment with micronised fenofibrate resulted in reductions in TG levels in two patients (a 50-year-old woman and a 36-year-old man) with HIV infection and protease inhibitor-induced hypertriglyceridaemia.[132] After 10 months' treatment (final fenofibrate dosage of 268 mg/day in both patients) the woman's TG level had decreased from 16.4 mmol/L at baseline to 3.8 mmol/L and the man had experienced a reduction in TG level from 22.4 to 3.6 mmol/L.

4.4 Dyslipidaemia in Heart Transplant Recipients

Abnormalities in lipid and lipoprotein levels are common in heart transplant recipients.[90] Significant reductions from baseline in mean TC levels (from 8.2 to 6.6 mmol/L; $p = 0.0001$), LDL-C levels (from 5.4 to 4.3 mmol/L; $p = 0.0001$) and TG levels (from 3.0 to 2.4 mmol/L; $p = 0.03$) were observed in 43 dyslipidaemic heart transplant recipients treated with micronised fenofibrate 200mg once daily for up to 1 year. However, treatment was associated with a significant increase in serum creatinine levels (from 171 to 201 mmol/L; $p = 0.003$), necessitating discontinuation of therapy in 14 patients.[91] The investigators suggested that an interaction between micronised fenofibrate and cyclosporin, which was also prescribed during the study, may have been responsible for the development of nephrotoxicity, although this requires confirmation (section 3.1).[133,134]

5. Tolerability

Micronised fenofibrate is generally well tolerated. A post-marketing surveillance programme involving 9884 patients with type IIa, IIb or IV dyslipidaemia who were treated with micronised fenofibrate 200mg once daily for 12 weeks provides the largest source of adverse event data for the drug to date (micronised fenofibrate was administered in the capsule formulation in studies discussed in this section unless stated otherwise).[94] A standardised questionnaire and direct patient questioning were used to assess the tolerability of the drug at 6-week intervals.

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During the study, 3.8% of patients (380 of 9884) reported adverse events. The most frequently reported adverse events were those affecting the gastrointestinal system followed by adverse events associated with the skin and appendages, nervous system, cardiovascular system and body as a whole (table VIII). Forty-three patients experienced serious adverse events (0.4% of the total population and 11.3% of the patients who experienced adverse events). Three of these adverse events were reported to be possibly related to the study drug (two cases of cholelithiasis and one case of hepatitis with jaundice). Among the evaluable patients, tolerability was rated as very good, good, moderate and unsatisfactory by 5872 (62.3%), 3335 (35.4%), 149 (1.6%) and 63 (0.7%) patients, respectively. Overall, 367 patients (3.7%) discontinued treatment; this was attributable to an adverse event (regardless of whether or not the adverse event was treatment related) in 165 patients (1.7%).

In another study (n = 1334; section 4.1.1), treatment with micronised fenofibrate 200mg once daily for 6 months resulted in four serious adverse events which were possibly related to drug therapy.[65] These included epistaxis in one patient receiving concomitant oral anticoagulant therapy, two episodes of acute pancreatitis (one a recurrence, the other an initial episode) and one case of hepatitis; these four serious adverse events resolved on discontinuation of micronised fenofibrate therapy.

Table VIII. Adverse events (AEs) in 9884 patients with dyslipidaemia who received micronised fenofibrate 200mg once daily for 12 weeks in a drug monitoring programme[94]

Organ system[a]	Frequency	
	% of patients	% of AEs
Gastrointestinal system	1.9	50.3
Skin and appendages	0.6	15.5
Nervous system	0.4	10.5
Cardiovascular system	0.3	8.7
Body as a whole	0.3	8.4
Musculoskeletal system	0.2	4.5
Urogenital system	0.2	4.5
Respiratory system	0.1	3.2
Metabolic and nutritional disorders	0.1	2.4
Endocrine system	0.1	1.8
Haematopoietic and lymphatic system	0.1	1.3
Special sense	0.0	0.8
Personality disorder	0.0	0.3

a AEs were classified using the COSTART code.[135]

The tolerability of the 160mg tablet formulation of micronised fenofibrate was assessed in two noncomparative 12-week trials (section 4.1.1).[44] At least one adverse event was experienced by 42 of the 177 patients (24%) in the first study and by 79 of the 198 patients (40%) in the second study. Of the 64 nonserious adverse events in the first study, 14 (22%) were considered to be possibly related to treatment; none of the seven serious adverse events were considered to be related to treatment. In the second study, 42 of the 139 (30%) adverse events were possibly drug related; the one serious adverse event was not thought to be drug related.

Data from the post-marketing surveillance study of micronised fenofibrate identified only a small number of patients with abnormal laboratory parameters [abnormal liver function tests in eight patients and raised creatine phosphokinase levels in two patients (one of these patients discontinued treatment because of muscle pain)]; however, the infrequent monitoring of laboratory parameters by some physicians may have contributed to the low incidence of biochemical abnormalities reported.[94] In the other study (n = 1334) evaluating treatment with micronised fenofibrate 200mg once daily for 6 months, increases in AST and ALT levels to >3 times the upper limit of normal (ULN) were reported in ≤2% of patients.[65] Five patients had creatinine levels >177 μmol/L, although two patients had elevated creatinine levels at study entry. In the studies examining the use of the 160mg tablet formulation of micronised fenofibrate,[44] creatine phosphokinase levels were 4 to 5 times the ULN in one patient in the first study and >5 times the ULN in two patients in the second study. ALT levels of >3 times the ULN occurred in one patient in the first study and in two patients in the second study, and AST levels of >3 times the ULN oc-

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curred in one patient in the first study and in three patients in the second study.

Several case reports have described increases from baseline in serum creatinine levels in patients with hyperlipidaemia receiving micronised fenofibrate.[136] A significant increase from baseline in plasma creatinine levels (from 147 to 170 mmol/L; p = 0.014) was also reported in a study in patients with hyperlipidaemia and mild to moderate renal failure [creatinine clearance of 1.8 to 6.6 L/h (30 to 110 ml/min)] who received fenofibrate 200 mg/day.[137] Interestingly, there were no significant changes in renal haemodynamics or glomerular filtration rate, suggesting that a deterioration in renal function is not responsible for the increase in plasma creatinine levels. Some researchers recommend monitoring serum creatinine levels at baseline and 1 to 2 months after starting treatment with micronised fenofibrate,[136] although this recommendation is not made in the prescribing information.[7]

Few data are available on the long-term (>1 year) tolerability of micronised fenofibrate. In a noncomparative study evaluating the efficacy and tolerability of micronised fenofibrate 200mg once daily over a 1-year period (section 4.1.1), 7 of 131 patients (5%) developed adverse events and withdrew from treatment; these included gastric pain (n = 4), elevation of creatine phosphokinase levels (n = 1), loss of libido (n = 1) and elevation of liver transaminase levels to >3 times the ULN (n = 1).[100] Adverse events not resulting in treatment withdrawal included biliary colic (in a patient with pre-existing cholelithiasis), chest pain and nervousness in one patient and gastrointestinal symptoms in seven patients. 146 patients enrolled in the post-marketing surveillance study[94] of micronised fenofibrate were followed-up for a mean of 4.6 years. Micronised fenofibrate was well tolerated with only three patients (2%) discontinuing therapy because of adverse events.[96]

There were no significant differences between micronised fenofibrate 200mg once daily (n = 207) and placebo (n = 211) recipients in the frequency of serious adverse events in the DAIS study (section 4.2).[120] Cancer occurred in 2.4% of micronised fenofibrate recipients and in 3.3% of placebo recipients, gallbladder symptoms and/or cholecystectomy occurred in 0.5 and 1.4%, hepatic events occurred in 1.5 and 0%, abdominal pain occurred in 0.5 and 1.4%, diarrhoea occurred in 0 and 0.5%, dizziness occurred in 0.5 and 0%, musculoskeletal system events occurred in 0 and 0.5%, and events affecting the joints occurred in 3.4 and 2.5%. Patients in this study had type 2 diabetes mellitus and were followed-up for ≥3 years.

5.1 Compared with Other Lipid-Modifying Drugs

Data on the comparative tolerability of micronised fenofibrate and other lipid-modifying drugs are limited.

Both micronised fenofibrate 200mg once daily and HMG-CoA reductase inhibitors (atorvastatin 10 or 40 mg/day, simvastatin 10 or 20 mg/day or pravastatin 20 mg/day) were similarly well tolerated in studies of 6 weeks to 6 months' duration (section 4.1.2).[24,26,28,30-32,50,99,102] In both micronised fenofibrate and HMG-CoA reductase inhibitor recipients, the most frequently reported adverse events were gastrointestinal in nature (e.g. abdominal pain, dyspepsia, nausea),[24,50,99,102] with elevated liver enzyme levels being the most commonly reported laboratory abnormality,[24,30,31,102] (although the changes in liver enzyme levels were generally reported as being mild).

Similarly, micronised fenofibrate 200mg once daily and gemfibrozil 900 or 1200 mg/day were well tolerated in two double-blind studies (section 4.1.2).[45,112] In the parallel-group study,[45] 4 of 116 micronised fenofibrate recipients (3.4%) and 5 of 118 gemfibrozil recipients (4.2%) withdrew from the study because of adverse events. Of 21 patients enrolled in the crossover study,[112] three patients withdrew while receiving micronised fenofibrate and two patients withdrew while receiving gemfibrozil because of adverse events. The adverse events responsible for withdrawal included elevation in liver enzyme levels, abdominal pain,

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diarrhoea, nausea, headache, rash and asthenia.[45,112]

5.2 In Combination with HMG-CoA Reductase Inhibitors

The incidence of adverse events was similar in recipients of micronised fenofibrate 200 mg/day (n = 33), micronised fenofibrate 200 mg/day plus fluvastatin 20 mg/day (n = 35) and micronised fenofibrate 200 mg/day plus fluvastatin 40 mg/day (n = 34) in a double-blind 16-week study (section 4.1.3).[114] Musculoskeletal adverse events (e.g. myalgia) occurred in 24, 17 and 15% of patients in the corresponding treatment groups, gastrointestinal adverse events occurred in 26, 6 and 24%, respectively, and respiratory adverse events occurred in 15, 11 and 24%, respectively. Percentage changes in clinical laboratory values are shown in figure 4; no significant between-group differences in the percentage change in laboratory values were observed. One recipient of micronised fenofibrate 200 mg/day plus fluvastatin 40 mg/day discontinued treatment because of an increase in AST and ALT levels to >3 times the ULN.

No clinically significant changes from baseline in ALT or muscle creatinine kinase levels were seen in patients receiving standard fenofibrate 300mg once daily or micronised fenofibrate 200mg once daily in combination with pravastatin 20mg once daily or simvastatin 10mg once daily in a noncomparative study (n = 80) [section 4.1.3].[115] In this study, 41 patients received monotherapy with standard or micronised fenofibrate before starting combination therapy. Significant increases from baseline (9.7 mmol/L) in mean serum creatinine levels were seen after both fenofibrate monotherapy (10.9 mmol/L) and combination therapy (10.4 mmol/L) [$p < 0.001$]. In addition, significant reductions from baseline (0.40 mmol/L) in mean serum uric acid levels were seen after both fenofibrate monotherapy (0.32 mmol/L) and combination therapy (0.31 mmol/L) [$p < 0.001$].

Limited tolerability data are available from other studies examining combination therapy with

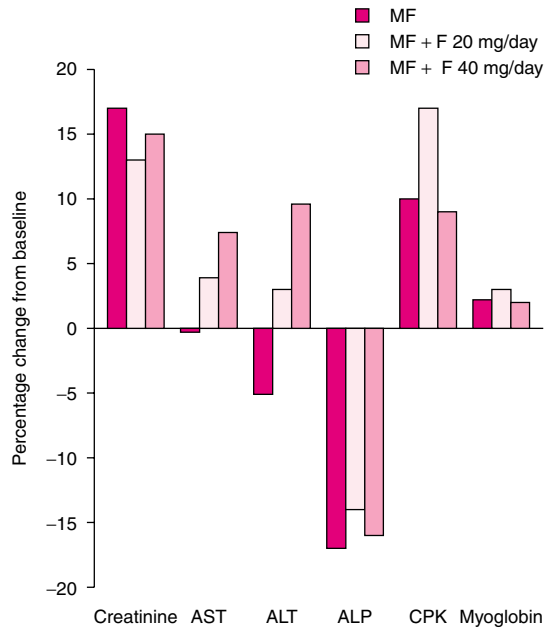

Fig. 4. Percentage changes from baseline in laboratory parameters in patients with severe primary hypercholesterolaemia enrolled in a double-blind, randomised, parallel-group, multicentre study. Patients were randomised to receive micronised fenofibrate (MF) 200mg once daily (n = 33), MF 200mg once daily plus fluvastatin (F) 20mg once daily (n = 35) or MF 200mg once daily plus F 40mg once daily (n = 34) for 16 weeks.[115] **ALP** = alkaline phosphatase; **CPK** = creatine phosphokinase.

fenofibrate plus an HMG-CoA reductase inhibitor;[32,106,116] It is recommended that such therapy be avoided unless the potential benefit outweighs the potential risk (section 6).[7] The use of fibric acid derivatives in combination with HMG-CoA reductase inhibitors has been associated with rhabdomyolysis, markedly elevated levels of creatine kinase and myoglobinuria in numerous case reports; with a high proportion of these patients developing acute renal failure.[7] Two cases of rhabdomyolysis have been reported in recipients of micronised fenofibrate monotherapy.[138] However, both patients had renal failure and received micronised fenofibrate at a dosage of 200 mg/day; the drug is in fact contraindicated in patients with severe renal impairment (section 6).[7]

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6. Dosage and Administration

Given that it is intended that the new 160mg tablet formulation of micronised fenofibrate will replace micronised fenofibrate 200mg capsules, this section will focus on dosage recommendations for the newer formulation for both the US and Europe. For an overview of dosage recommendations relating to the 200mg capsule formulation of micronised fenofibrate, see the review by Adkins and Faulds.[6]

In Europe, micronised fenofibrate tablets are indicated for the treatment of patients with type IIa, IIb, III, IV or V dyslipidaemia who have failed to respond to dietary control and other nonpharmacological interventions.[139] The recommended initial daily dosage of micronised fenofibrate for adults is one 160mg tablet, taken during a main meal.[139] A dosage of 160 mg/day is not considered appropriate in patients with renal impairment or in children.

In the US, micronised fenofibrate tablets are indicated for use as an adjunct to diet to reduce increased TC, LDL-C, TG and ApoB levels and increase HDL-C levels in patients with primary hypercholesterolaemia or mixed dyslipidaemia (types IIa and IIb dyslipidaemia); micronised fenofibrate is also indicated for use in patients with hypertriglyceridaemia (types IV and V dyslipidaemia).[7] The recommended initial daily dosage in patients with primary hypercholesterolaemia or mixed dyslipidaemia is 160 mg/day and in patients with hypertriglyceridaemia is 54 to 160 mg/day (54mg tablets of micronised fenofibrate, which are equivalent to 67mg capsules of micronised fenofibrate, are available in the US).[7] The dosage of micronised fenofibrate should be adjusted according to patient response; the maximum recommended daily dosage is 160mg. Micronised fenofibrate tablets may be started at a dosage of 54 mg/day in patients with impaired renal function and in the elderly.[7] Patients should commence a lipid-lowering diet prior to starting treatment with micronised fenofibrate and this diet should be continued during drug therapy.[7] Micronised fenofibrate should be discontinued in patients who have not responded to treatment after receiving 160 mg/day of the drug for 2 months.[7]

Fenofibrate is contraindicated in patients with pre-existing gall bladder disease or severe renal impairment.[7,139] In the US, the drug is also contraindicated in patients with hepatic dysfunction,[7] whereas in Europe it is contraindicated in patients with severe hepatic dysfunction.[139] In addition, fenofibrate should generally not be used in pregnant or breast-feeding women. US prescribing information recommends that micronised fenofibrate should only be administered to pregnant women if the potential risk to the fetus is justified by the potential benefit. Patients receiving micronised fenofibrate should undergo regular monitoring of their liver function and treatment should be discontinued if enzyme levels are persistently >3 times the ULN.[7] Myopathy may occasionally occur in recipients of micronised fenofibrate and should be considered in patients presenting with diffuse myalgias, muscle tenderness or weakness and/or markedly elevated creatine phosphokinase levels.[7] Micronised fenofibrate should be discontinued in patients who develop markedly elevated creatine phosphokinase levels or in whom myopathy is diagnosed.

Fenofibrate potentiates the effect of coumarin anticoagulants (section 3.1). In patients receiving concomitant therapy with a coumarin anticoagulant and micronised fenofibrate, the dosage of the coumarin anticoagulant should be reduced and subsequently adjusted as necessary according to the prothrombin time or international normalised ratio.[7] Frequent monitoring of the prothrombin time or international normalised ratio is recommended until these parameters have stabilised. Combination therapy with micronised fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the potential benefit (with regards to further improvement in lipid levels) outweighs the potential risk associated with this drug combination (section 5.2). Micronised fenofibrate should be administered ≥1 hour before or ≥4 to 6 hours after bile acid sequestrants (section 3.1).[7] Given that the primary route of elimination of

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micronised fenofibrate is via renal excretion, the potential benefits and risks of administering micronised fenofibrate with immunosuppressants such as cyclosporin and other nephrotoxic agents should be carefully considered (section 3.1).[7]

7. Place of Micronised Fenofibrate in the Management of Dyslipidaemia

CHD is the leading cause of morbidity and mortality in industrialised countries[140] and pre-existing atherosclerosis is associated with approximately 50% of myocardial infarctions and 70% of deaths from CHD.[141]

The benefits associated with improving the plasma lipoprotein profile in patients with dyslipidaemia are well established.[2-4] Interventions aimed at correcting dyslipidaemia have, therefore, become an integral part of CHD primary and secondary prevention strategies.

Among patients with premature CHD, most have abnormal levels of lipoproteins such as low plasma levels of HDL-C and/or high levels of LDL-C or TGs. Available data clearly demonstrate a causal relationship between elevated LDL-C levels and CHD (reviewed by Naito et al.[142]) and that treatment that lowers LDL-C levels reduces the risk of CHD.[143] Conversely, high levels of HDL-C play a protective role in atherogenesis and have emerged as an important protective factor against CHD.[140] Moreover, a low HDL-C level is a strong independent risk factor for CHD.[143,144] Thus, the ratio of atherogenic LDL-C or TC to nonatherogenic HDL-C is an important predictor of risk. TGs are present in plasma as VLDL or chylomicron remnants. The finding that hypertriglyceridaemia is an independent risk factor for CHD has been confirmed in several recent studies,[145,146] including the Prospective Cardiovascular Münster (PROCAM) study.[147,148]

In addition to abnormal lipid levels, lipoprotein(a) excess has also been identified as a predictor of myocardial infarction or death from CHD in specific cohorts of patients, chiefly men with hypercholesterolaemia.[149,150] Similarly, elevated plasma fibrinogen levels have emerged as an important independent risk factor for atherothrombosis.[142,151,152] Ischaemic heart disease, stroke and peripheral arterial disease are associated with increased plasma levels of fibrinogen.[142] Additional emerging risk factors for CHD include raised homocysteine levels and proinflammatory factors (e.g. CRP).[1] It is thought that homocysteine damages vessel walls, leading to intimal fibrosis, and that markers such as CRP may help to predict a patient's risk of experiencing an atherosclerotic event.[1]

Lipid-modifying drugs are currently indicated for patients with CHD or dyslipidaemia that is inadequately controlled by dietary therapy (calorie restriction and reduced fat intake) or other lifestyle modifications (e.g. cessation of smoking and increased exercise) alone.[143] The fibric acid derivatives or fibrates, which include fenofibrate, gemfibrozil, bezafibrate, ciprofibrate and clofibrate, are one such group of lipid-modifying drugs; others include the HMG-CoA reductase inhibitors or 'statins' such as lovastatin, fluvastatin, simvastatin, atorvastatin and pravastatin, the bile acid sequestrants (e.g. cholestyramine) and nicotinic acid. The primary target of lipid-modifying therapy is the reduction of elevated LDL-C levels.[143] Current guidelines generally recommend the first-line use of HMG-CoA reductase inhibitors to achieve this goal.[1,143]

The lipid-modifying profile of the fibrates is characterised by a moderate reduction in TC and LDL-C levels together with a marked reduction in plasma TG levels and an increase in HDL-C levels.[153-155] As a group, the fibrates have demonstrated beneficial lipid-modifying effects in many types of dyslipidaemia but are particularly well suited to the treatment of patients with hypertriglyceridaemia with or without hypercholesterolaemia (type IIb or IV dyslipidaemia).[156] This is particularly true for patients with type 2 diabetes mellitus, for whom cardiovascular disease is a major cause of morbidity and mortality.

Interestingly, fibrate therapy may also have a role to play in patients whose primary lipid abnormality comprises low HDL-C levels. In the Veter-

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ans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT),[157] a 22% reduction ($p = 0.006$ *vs* placebo) in the risk of nonfatal myocardial infarction or death from CHD occurred in men with CHD and low HDL-C levels (≤1 mmol/L) and LDL-C levels (≤3.6 mmol/L) who received gemfibrozil. Moreover, fibrate therapy was associated with an 11% reduction in the risk of nonfatal myocardial infarction or death from CHD for each 0.13 mmol/L increase in HDL-C level.[158] Study results have shown that compared with the well selected group of patients in VA-HIT, fibrates were not successful in reducing mortality or cardiovascular event rates in a patient population that was less well selected [i.e. patients with CHD, moderately elevated serum TC levels (4.66 to 6.48 mmol/L) and low HDL-C levels (≤1.17 mmol/L)[159]] or in unselected patient populations (i.e patients with CHD who were receiving lipid-lowering therapy[160]).

The National Cholesterol Education Program's Adult Treatment Panel III guidelines state that treatment of isolated low HDL-C levels should mostly be reserved for patients with CHD or CHD risk equivalents.[143] Recent expert group recommendations[161] are more specific. They state that an HDL-C level of ≥1 mmol/L should be the goal in patients with cardiovascular disease and in those who do not have clinical cardiovascular disease but are at high risk. Fibrate therapy should be considered in patients with low HDL-C levels whose LDL-C levels are considered low risk (i.e. LDL-C levels that do not meet the threshold for LDL-C-lowering drug therapy).

Compared with standard fenofibrate, micronised fenofibrate has a more convenient once-daily administration schedule and a lower daily dosage. The enhanced bioavailability of the capsule formulation of micronised fenofibrate, compared with standard fenofibrate, has been further improved in the new 160mg tablet formulation. To date, the results of only two noncomparative 12-week studies assessing the use of the 160mg tablet formulation of micronised fenofibrate are available (section 4.1.1).[44] In these studies, micronised fenofibrate was associated with significant improvements from baseline in HDL-C and TG levels in patients with type IIa or IIb dyslipidaemia. In addition, in patients with type IIa dyslipidaemia, micronised fenofibrate was associated with significant improvements from baseline in TC and LDL-C levels in one study, and in LDL-C levels in the other. Treatment was also associated with a significant improvement from baseline in TG levels in patients with type IV dyslipidaemia. These findings are consistent with those obtained with previous fenofibrate formulations.

The approved indications for the tablet formulation of micronised fenofibrate reflect its broad lipid-modifying ability; in the UK, the drug is indicated for the treatment of patients with type IIa, IIb, III, IV or V dyslipidaemia,[139] and in the US, it is indicated to reduce increased TC, LDL-C, TG and ApoB levels and increase HDL-C levels in patients with primary hypercholesterolaemia or mixed dyslipidaemia (types IIa and IIb dyslipidaemia) and for use in patients with hypertriglyceridaemia (types IV and V dyslipidaemia) [section 6].[7]

Micronised fenofibrate 200mg once daily (capsule formulation) produced greater changes in TG and, generally, HDL-C levels than simvastatin 10 or 20 mg/day, pravastatin 20 mg/day or atorvastatin 10 or 40 mg/day but had a similar or lesser effect on LDL-C and TC levels than these agents (section 4.1.2). Beneficial effects on cardiovascular morbidity and mortality have been demonstrated in large multicentre trials examining the use of HMG-CoA reductase inhibitors in the primary[162,163] and secondary[164-166] prevention of cardiovascular events. Results of similar large-scale clinical trials conducted with micronised fenofibrate are not yet available, but such trials are currently underway [e.g the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[167,168] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[169]].

Study results[32,114] indicate that greater improvements in lipid levels are achieved with combination therapy comprising micronised fenofi-

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brate plus an HMG CoA reductase inhibitor than with micronised fenofibrate monotherapy (section 4.1.3). Combination therapy was generally well tolerated in these studies (section 5.2). However, US prescribing information[7] states that combination therapy with micronised fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the potential benefit (with regards to further reduction in lipid levels) outweighs the potential risk associated with this drug combination (section 6). This is largely because of reports of rhabdomyolysis associated with the use of fibric acid derivatives in combination with HMG-CoA reductase inhibitors (section 5.2).[170] However, it should be noted that several studies with long durations of follow-up (>2 years) have found combination treatment with HMG-CoA reductase inhibitors and fibrates to be generally well tolerated.[171-173] Indeed, recent guidelines[1] include combination therapy with HMG-CoA reductase inhibitors and fibrates as an option in patients with dyslipidaemia, with the caveats that the HMG-CoA reductase inhibitor dosage should be kept low and that the use of such combination therapy should be avoided in the elderly, in patients with acute or serious chronic illness, in patients undergoing a surgical procedure and in patients receiving multiple medications. In addition, the guidelines recommend that patients undergo regular liver function monitoring.

The risk of CHD is increased 2- to 4-fold in patients with type 2 diabetes mellitus.[174] Fibrate monotherapy is the lipid-lowering therapy of choice in patients with diabetic dyslipidaemia in whom hypertriglyceridaemia and low HDL-C levels are the primary lipid abnormality.[1] Currently, results are not available from studies specifically assessing the effects of lipid-modifying agents on cardiovascular-related morbidity and mortality in patients with type 2 diabetes mellitus. Thus, to date, the practice of treating dyslipidaemia in patients with type 2 diabetes mellitus has been based upon the results of studies that have included small numbers of patients with type 2 diabetes mellitus [e.g. the Scandinavian Simvastatin Survival Study (4S),[175] the Cholesterol and Recurrent Events (CARE) study,[176] the Helsinki Heart Study[177] and the VA-HIT].[157] However, the FIELD study, in which the primary outcome is mortality from CHD, is currently underway. This double-blind, multicentre study has randomised 9795 patients with type 2 diabetes mellitus to receive micronised fenofibrate or placebo.[167,168] A second study, the ACCORD trial,[169] is being conducted in 10 000 patients with type 2 diabetes mellitus. This trial will evaluate the additional cardiovascular benefit of fenofibrate in patients receiving an HMG-CoA reductase inhibitor (the primary endpoint is the first occurrence of a major cardiovascular event). The largest study of micronised fenofibrate conducted to date in patients with type 2 diabetes mellitus, the DAIS study,[120] showed that lipid-lowering therapy with micronised fenofibrate, compared with placebo, significantly reduced the angiographic progression of coronary artery disease in patients with type 2 diabetes mellitus, as well as being associated with significantly greater improvements from baseline in lipid levels (section 4.2). Importantly, micronised fenofibrate was not associated with a deterioration in glycaemic control.

Metabolic syndrome is increasingly being recognised as a potential secondary target of lipid-modifying therapy.[143] Interestingly, micronised fenofibrate was associated with improvements in features of the metabolic syndrome (i.e. dyslipidaemia, hypertension, hyperinsulinaemia) in a small (n = 37) noncomparative study conducted in patients with this disorder[64] (section 4.2.1); more data are needed examining the use of micronised fenofibrate in this indication.

Dyslipidaemia is a common occurrence in patients with HIV infection who are receiving protease inhibitor therapy. The results of noncomparative studies and case reports indicate that micronised fenofibrate lowers triglyceride levels in patients with HIV infection and protease inhibitor-induced hypertriglyceridaemia (section 4.3).[130-132] More data are needed from large, well designed

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studies assessing the use of micronised fenofibrate in this indication.

In conclusion, micronised fenofibrate improves lipid levels in patients with primary dyslipidaemia; the drug has particular efficacy with regards to reducing TG levels and raising HDL-C levels and is generally effective at lowering LDL-C levels. Micronised fenofibrate is also effective in diabetic dyslipidaemia; as well as improving lipid levels, the drug reduces angiographic progression of coronary artery disease in patients with type 2 diabetes mellitus. The results of large ongoing studies will clarify whether the beneficial lipid-modifying effects of micronised fenofibrate result in a reduction in cardiovascular morbidity and mortality.

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