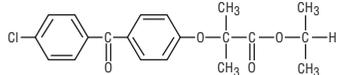


DESCRIPTION

Fenofibrate capsules (micronized) is a lipid regulating agent available as capsules for oral administration. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyloxy)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is C₂₀H₂₁O₄Cl and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79 to 82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Each 67 mg fenofibrate capsule (micronized) contains the following inactive ingredients: croscarmellose sodium, crospovidone, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, sodium lauryl sulfate, talc, D&C Red #28, FD&C Blue #1, FD&C Red #40, titanium dioxide and gelatin.

Each 134 mg fenofibrate capsule (micronized) contains the following inactive ingredients: croscarmellose sodium, crospovidone, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, sodium lauryl sulfate, talc, D&C Red #28, FD&C Blue #1, titanium dioxide and gelatin.

Each 200 mg fenofibrate capsule (micronized) contains the following inactive ingredients: croscarmellose sodium, crospovidone, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, sodium lauryl sulfate, talc, FD&C Red #40, D&C Red #28, FDA/E172 yellow iron oxide, titanium dioxide and gelatin.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo A) and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibrate, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo A1 and apo AII.

The effects of fenofibrate acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPAR α). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoproteins C-II (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Clinical experience has been obtained with two different formulations of fenofibrate: a "micronized" and "non-micronized" formulation, which have been demonstrated to be bioequivalent. Comparisons of blood levels following oral administration of both formulations in healthy volunteers demonstrate that a single capsule containing 67 mg of the "micronized" formulation is bioequivalent to 100 mg of the "non-micronized" formulation. Three capsules containing 67 mg fenofibrate are bioequivalent to a single 200 mg fenofibrate capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled fenofibrate appeared in urine, primarily as fenofibrate acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibrate acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With micronized fenofibrate, the absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibrate acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67 mg fenofibrate and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibrate acid; no unchanged fenofibrate is detected in plasma.

Fenofibrate acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibrate acid is reduced at the carbonyl moiety to a benzoyl metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibrate acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibrate acid and fenofibrate acid glucuronide. After administration of radiolabeled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibrate acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 to 87 years of age, the oral clearance of fenofibrate acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal Insufficiency

The pharmacokinetics of fenofibrate acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl] \leq 30 mL/min) showed 2.7 fold increase in exposure for fenofibrate acid and increased accumulation of fenofibrate acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30 to 80 mL/min) had similar exposure but an increase in the half-life for fenofibrate acid compared to that of healthy subjects. Based on these findings, the use of fenofibrate should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug Interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibrate acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C8, CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption. (See **WARNINGS** and **PRECAUTIONS**).

Concomitant administration of a single dose of fenofibrate (administered as 3 X 67 mg fenofibrate micronized capsules) with a single dose of pravastatin (40 mg) in 23 healthy subjects increased the mean C_{max} and mean AUC for pravastatin by 13%. The C_{max} and AUC of fenofibrate decreased by 2% and 1% respectively, after concomitant pravastatin. The mean C_{max} and AUC for 3 α -hydroxy-iso-pravastatin increased by 29% and 26%, respectively.

Concomitant administration of a single dose of fenofibrate (equivalent to 145 mg fenofibrate) and a single dose of fluvastatin (40 mg) resulted in a small increase (approximately 15 to 16%) in exposure to (+)3R,5S-fluvastatin, the active enantiomer of fluvastatin.

A single dose of either pravastatin or fluvastatin had no clinically important effect on the pharmacokinetics of fenofibrate acid.

Concomitant administration of fenofibrate (equivalent to fenofibrate 200 mg) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 6% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibrate acid were not significantly affected by atorvastatin.

Concomitant administration of fenofibrate (equivalent to fenofibrate 200 mg) once daily for 10 days with glimepiride (1 mg tablet) single dose simultaneously with the last dose of fenofibrate resulted in a 35% increase in mean AUC of glimepiride in healthy subjects. Glimepiride C_{max} was not significantly affected by fenofibrate coadministration. There was no statistically significant effect of multiple doses of fenofibrate on glucose nadir or AUC with the baseline glucose concentration as the covariate after glimepiride administration in healthy volunteers. However, glucose concentrations at 24 hours remained statistically significantly lower after pretreatment with fenofibrate than with glimepiride alone. Glimepiride had no significant effect on the pharmacokinetics of fenofibrate acid.

Concomitant administration of fenofibrate (54 mg) and metformin (850 mg) three times a day for 10 days resulted in no significant changes in the pharmacokinetics of fenofibrate acid and metformin when compared with the two drugs administered alone in healthy subjects.

Concomitant administration of fenofibrate (equivalent to fenofibrate 200 mg) once daily for 14 days with rosiglitazone tablet (rosiglitazone maleate) (8 mg) once daily for 5 days, Day 10 through Day 14, resulted in no significant changes in the pharmacokinetics of fenofibrate acid and rosiglitazone when compared with the two drugs administered alone in healthy subjects.

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types Ila and I Ib)

The effects of fenofibrate at a dose equivalent to 200 mg fenofibrate per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL, LDL-C 213.8 mg/dL, HDL-C 52.3 mg/dL, and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1: Mean Percent Change in Lipid Parameters at End of Treatment^a

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n = 646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n = 361)	-18.7% ^b	-20.6% ^b	+11.0% ^b	-28.9% ^b
Placebo (n = 285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type Ila)				
Mean baseline lipid values (n = 334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n = 193)	-22.4% ^b	-31.4% ^b	+9.8%	-23.5% ^b
Placebo (n = 141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type I Ib)				
Mean baseline lipid values (n = 242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n = 126)	-16.8% ^b	-20.1% ^b	+14.6% ^b	-35.9% ^b
Placebo (n = 116)	-3.0%	-6.6%	+2.3%	+0.9%

^a Duration of study treatment was 3 to 6 months

^b p < 0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials¹ of 147 hypertriglyceridemia patients (Fredrickson Type IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 200 mg fenofibrate per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2: Effects of Fenofibrate Capsules (micronized) in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Placebo				Fenofibrate Capsules (micronized)			
	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Baseline TG levels 350 to 499 mg/dL								
Triglycerides	28	449	450	-0.5	27	432	223	-46.2 ^a
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1 ^a
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1 ^a
HDL Cholesterol	28	35	36	4	27	34	40	19.6 ^a
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7 ^a

Study 2	Placebo				Fenofibrate Capsules (micronized)			
	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Baseline TG levels 350 to 499 mg/dL								
Triglycerides	44	710	750	7.2	48	726	308	-54.5 ^a
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6 ^a
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8 ^a
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9 ^a
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0 ^a
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4 ^a

^a = p < 0.05 vs. Placebo

The effect of fenofibrate on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

Fenofibrate capsules (micronized) are indicated as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides and apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types Ila and I Ib). Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

Fenofibrate capsules (micronized) are also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia².

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet (See **WARNINGS** and **PRECAUTIONS**).

Fredrickson Classification of Hyperlipoproteinemias				
Type	Lipoprotein Elevated	Lipid Elevation		
		Major	Minor	
I (rare)	Chylomicrons	TG		↑→C
Ia	LDL	C		-
Ib	LDL, VLDL	C		TG
III (rare)	IDL	C, TG		-
IV	VLDL	TG		↑→C
V (rare)	chylomicrons, VLDL	TG		↑→

C = cholesterol

TG = triglycerides

LDL = low density lipoprotein

VLDL = very low density lipoprotein

IDL = intermediate density lipoprotein

The NCEP Treatment Guidelines			
Definite Atherosclerotic Disease ^a	Two or More Other Risk Factors ^b	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Goal
No	No	≥190 (> 4.9)	< 160 (< 4.1)
No	Yes	≥160 (> 4.1)	< 130 (< 3.4)
Yes	Yes or No	≥130 ^c (≥ 3.4)	< 100 (< 2.6)

(a) Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

(b) Other risk factors for coronary heart disease (CHD) include: age (males: \geq 45 years; females: \geq 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C < 35 mg/dL (< 0.91 mmol/L); and diabetes mellitus. Subtract 1 risk factor if HDL-C is \geq 60 mg/dL (\geq 1.6 mmol/L).

(c) In CHD patients with LDL-C levels 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

CONTRAINDICATIONS

Fenofibrate capsules (micronized) are contraindicated in patients who exhibit hypersensitivity to fenofibrate.

Fenofibrate capsules (micronized) are contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

Fenofibrate capsules (micronized) are contraindicated in patients with preexisting gallbladder disease (see **WARNINGS**).

WARNINGS

Liver Function

Fenofibrate at doses equivalent to 134 mg to 200 mg fenofibrate per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminase related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving doses equivalent to 134 mg to 200 mg fenofibrate per day and was 0% in those receiving doses equivalent to 34 mg or 67 mg of fenofibrate per day or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibrate, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to fenofibrate 200 mg) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3 α -hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also CLINICAL PHARMACOLOGY, Drug-drug interactions.)

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrate alone, including fenofibrate capsules (micronized) may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

Mortality

The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5 year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate.

Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.89-0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p=0.18) and 19% (HR 1.19 [0.90, 1.57], p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.

In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between fenofibrate, clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to fenofibrate.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholelectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P= 91-164). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle aged men excluded from the primary

