

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-304/S005

MEDICAL REVIEW(S)

NDA# 19-304/S-005 (SE1)

Tricor (micronized fenofibrate)

Abbott Laboratories

Proposed indication: 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 IIa and IIb)

Date received: July 1, 1999

User fee goal (10-month): May 1, 2000

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Medical Team Leader Comments on sNDA

Background

The longstanding controversy as to the role of elevated triglycerides as a risk factor for atherosclerotic disease is a function of the great heterogeneity in TG-rich lipoproteins (not all types being atherogenic), of the substantial inpatient variability in plasma TG concentrations, and of the inverse correlation between TG level and HDL-C level, itself a strong predictor in multivariate analyses of CHD risk. With refinements in our understanding of the structure and metabolism of lipoproteins, it has become apparent that the TG measurement alone is too crude an assay to be of value in assessing atherosclerotic risk. The finding of associations of certain size, density, and apolipoprotein characteristics of TG-rich lipoproteins with CHD risk has led to an increasing understanding of mechanisms of benefit of certain lipid altering interventions, including those not acting primarily to lower LDL-C levels. Likewise, this has permitted hypotheses as to the mechanisms underlying persistent CHD risk despite apparently optimal lipid altering treatment (e.g., unprevented events in the statin trials). While changes in some of these non-LDL-C parameters cannot yet be accepted as fully validated surrogates for clinical benefit, for a growing number of drugs, an increasing number studied in large-scale endpoint trials, apparently salutary laboratory effects have accompanied favorable clinical outcomes associated with drug use as compared to placebo. This is the case for fenofibrate and related drugs.

Fenofibrate is a member of the class of fibric acid derivatives, which act pharmacologically as peroxisome proliferator-activated receptor (PPAR) agonists. PPARs are transcription factors that, when activated, bind to specific response elements and alter the transcription rate of target genes. The actions of fibrates are mediated primarily via PPAR α , expressed mainly in liver. Through this mechanism, fibrates induce expression of lipoprotein lipase, an enzyme responsible for catabolism of triglyceride-rich lipoproteins. In addition, they inhibit the transcription of the apoC-III gene, thereby reducing the amount of this apoprotein inhibitor of LPL on the surface of TG-rich lipoproteins. Fibrates also induce expression of apoA-I, and apoA-II, integral apoproteins of HDL, thereby increasing levels of HDL-C. Finally, fibrates are known to induce the expression of genes involved in mitochondrial and peroxisomal beta-oxidation of fatty acids.

As a result of these changes in fatty acid metabolism and in the structure and enzymatic catabolism of TG-rich lipoproteins, fibrates effect a number of changes in the lipid profile. Hepatic synthesis of fatty acids and thus secretion of TG-rich VLDL particles is reduced. Lipolysis of TG from these particles is enhanced by increased LPL activity and decreased particle content of apoC-III, thereby augmenting clearance and lowering fasting TG levels. LDL-C levels may be decreased because of changes in the structure and composition of LDL particles (from small-dense to larger more buoyant forms) that enhance binding and clearance by the LDL-receptor. The complete mechanisms by which fibrates lower LDL-C have not been established. Finally, levels of HDL-C are increased. These are all felt to be salutary alterations in the lipid profile, based upon human anatomical and pathophysiological studies, animal models of atherosclerosis, epidemiological risk factor analyses, and subgroup response analyses from drug trial databases. Of note, the independent benefit of any single lipid alteration related to fibrate therapy on cardiovascular disease outcomes has not been adequately studied.

Although there is now a consensus on the potential benefits of fibrates, the history of these agents has not been without controversy. In contrast to the case with statins, the endpoint trial data using fibrates have been somewhat variable. In the late 1970's and 1980's, the WHO Cooperative Trial on Primary Prevention of Ischemic Heart Disease using clofibrate and the Helsinki Heart Study (HHS) of gemfibrozil each showed benefits associated with fibrate therapy with regard to CHD endpoints (i.e., nonfatal and fatal MI). Disturbing, however, were the findings of increased non-cardiovascular deaths in both trials, attributed to violence and accidents, cancer, and post-cholecystectomy complications. At the time, these adverse outcomes were attributed variably to intrinsic toxicities of the drugs, to the risk of cholesterol lowering per se, or to chance. The failure to reproduce such findings in the large-scale statin trials in the 1990's silenced concerns about the potential adverse effects of cholesterol lowering. Finally, the more recent fibrate trials have not replicated the earlier concerns about possible intrinsic toxicities of these drugs.

In the early 1990's, several fibrate trials, smaller in scale than the WHO Trial and HHS, were not plagued by excess non-cardiovascular morbidity and mortality. A series of angiographic trials using fenofibrate, bezafibrate, and gemfibrozil have all shown favorable effects on progression of atherosclerosis in CHD patients with a range of baseline lipid levels.

Finally, in the past year, two endpoint trials have been completed. The Bezafibrate Infarction Prevention Trial was a secondary prevention trial conducted in Israel in patients with TC levels 180-250, HDL-C < 45 mg/dL, and TG < 180 mg/dL. This trial, not yet published, failed on its primary endpoint of fatal or NFMI and sudden death, with no significant difference between treatment groups in the time to first occurrence of one of these events. By contrast, the VA-HIT (HDL Intervention Trial) enrolled patients with CHD, average LDL-C levels (< 140 mg/dL), below average HDL-C levels (< 40 mg/dL), and moderately elevated TG (< 300 mg/dL). This trial did demonstrate a reduction in the gemfibrozil group in the incidence of nonfatal MI or CHD death (primary endpoint). There was an approximate 22% reduction in this endpoint associated with gemfibrozil

therapy in the setting of a mean 7% increase in HDL-C (2 mg/dL) and a mean 31% reduction in TG. Gemfibrozil had no effect on mean LDL-C levels. To re-emphasize, in contrast to the HHS, non-cardiovascular death and cancers were not increased in the gemfibrozil group.

Currently, a number of other endpoint trials using fibrates are being conducted. Two of note are focusing on diabetics. These are the Diabetes Atherosclerosis Intervention Study (DAIS) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study ongoing in Australia, New Zealand, and Finland.

The fibrates currently marketed in the U.S. are clofibrate (Atromid-S, Wyeth-Ayerst), gemfibrozil (Lopid, Parke-Davis), and fenofibrate. Atromid is indicated for the treatment of Type III (primary dysbetalipoproteinemia), as well as for Types IV and V hyperlipoproteinemia, these latter characterized by isolated elevations in TG. Lopid is indicated for the treatment of Types IV and V and also, based upon a subgroup analysis from the HHS, for the treatment of Type IIb to reduce the risk of developing CHD in those without existing CHD. Finally, fenofibrate is indicated for Types IV and V (currently rationalized because of the risk of pancreatitis in some of these patients).

Data in support of proposed labeling changes

The current application proposes changes in the Indications and Usage section for Tricor to add the indication for the treatment of Types IIa and IIb hyperlipoproteinemia. In support of the proposed changes, the sponsor has submitted analyses of data from 4 placebo-controlled trials, some previously submitted to FDA. A total of 361 patients treated with fenofibrate and 285 treated with placebo are included in the pooled analyses. This analysis excluded patients treated with doses of fenofibrate higher than those recommended in labeling. Dr. Parks' review contains extensive analyses of the effects of fenofibrate on lipid levels across the individual trials as well as for the pool as a function of baseline lipid phenotype (i.e., Fredrickson IIa vs. IIb). Table 16 (page 13) of her review summarizes the lipid altering data in the patients with elevated (> 160 mg/dL) LDL-C according to baseline TG level. Those with TG levels < 150 mg/dL were defined as Type IIa. Those with TG ≥ 150 mg/dL were defined as IIb. The table is reproduced here in part and this forms table 1 of the revised proposed labeling (March 24, 2000 submission).

Treatment group	Total-C	LDL-C	HDL-C	TG
Pooled cohort				
All FEN (n=361)	-18.7	-20.6	+11.0	-28.9
Placebo (n=285)	-0.4	-2.2	+0.7	+7.7
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Fredrickson IIa)				
All FEN (n=193)	-22.4	-31.4	+9.8	-23.5
Placebo (n=141)	+0.2	-2.2	+2.6	+11.7
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Fredrickson IIb)				
All FEN (n=126)	-16.8	-20.1	+14.6	-35.9
Placebo (n=116)	-3.0	-6.6	+2.3	+0.9

The subgroup analyses by lipid phenotype from the individual trials were consistent, by and large, with the pooled analysis. Two major points bear mention. First, the LDL-lowering effect of fenofibrate is clinically significant as defined by the 15% minimum reduction from baseline criterion for approval of lipid altering drugs for this indication. Admittedly, substantially greater LDL-C lowering can be achieved using increasing doses of available drugs, notably statins. Nevertheless, the LDL-lowering efficacy of fenofibrate is established by these data. Second, the subgrouping by baseline TG highlights the consistent finding across studies of a greater LDL-C lowering effect in patients without elevated TG and of a greater TG lowering effect in patient with elevated TG. The discrepant effects on LDL-C levels are due to the fact that the improved catabolism of TG rich remnant lipoproteins in the latter patients leads to an increase in the LDL fraction as these particles are processed and structurally modified. Data from other studies suggests that the resultant LDL particles are more buoyant, less prone to oxidation, and therefore less potentially atherogenic.

Safety

Dr. Parks' safety review highlights the increased incidence of transaminase elevations in the fenofibrate-treated patients relative to placebo. This is not a new finding, nor is it unique to fenofibrate within this class of drugs. No patient developed serious liver disease in these trials (marked elevation in bilirubin) and in all cases the abnormalities resolved, either spontaneously on treatment or after discontinuation of drug. Dr. Parks has proposed revision to the WARNINGS, Liver Function section of the label, with which I concur.

Financial disclosure

In compliance with 21 CFR 54, the sponsor has included Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical investigators) in the application. The sponsor has certified that none of the investigators for the covered studies in this application were compromised by a financial arrangement with the sponsor such as to impact on the integrity of the trial data.

Labeling comments

In addition to the changes pertaining to the newly proposed indication, the sponsor has added Table 2, summarizing the effects of fenofibrate in patients with Types IV and V hyperlipoproteinemia, based on data from the original NDA. These data were added at the Division's request in order to convey information on expected response to treatment in these patients.

I concur overall with Dr. Parks labeling comments. Indeed, as a result of labeling discussions already undertaken with the sponsor, many of her suggestions have been incorporated. My comments pertain to the current proposed labeling (March 24, 2000), itself substantially modified from the original proposed labeling in the initial submission. Specific comments follow:

WARNINGS, Liver Function

1st paragraph, 1st sentence, replace with: Fenofibrate at doses equivalent to 134 mg to 200 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)].

2nd paragraph, 2nd sentence, replace with: The incidence of transaminase elevations related to TRICOR therapy appears to be dose-related.

WARNINGS, Concomitant HMG-CoA reductase inhibitors

3rd paragraph, replace with:

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.

PRECAUTIONS, Drug Interactions, oral Anticoagulants

Bolded statement, replace with:

Caution should be exercised when coumarin anticoagulants are given in conjunction with Tricor. The dosage of the anticoagulants 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 the prothrombin/INR time has stabilized.

Dosage and Administration

3rd paragraph, 2nd sentence, replace with:

Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals.

Summary and conclusions

The sponsor has provided sufficient evidence of efficacy and safety, derived from adequate and well-controlled trials, to support the use of Tricor at doses up to 200 mg (3 X 67 mg) daily for the treatment of Types IIa and IIb hyperlipoproteinemia. The changes to labeling include efficacy data in Clinical Pharmacology, the new indication for use of the drug, as well as minor changes to the WARNINGS section that relate to LFT changes and fibrate-statin interactions.

Recommendation

After final agreement on labeling, this supplement may be approved.

ISI 4-7-00
David G. Orloff, M.D.,
Deputy Director/Medical Team Ldr
DMEDP/ODE-II/CDER/FDA

Recombination code: AP

CC:

19-304/S-005
Fenofibrate Types IIa and IIb

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NDA 19-304

HFD-510: Division file

References:

Fruchart JC, Brewer HB, Leitersdorf E. Consensus for the Use of Fibrates in the Treatment of Dyslipoproteinemia and Coronary Heart Disease. Am J Cardiol 1998; 81: 912-917.

Brewer HB. Hypertriglyceridemia: Changes in the Plasma Lipoproteins Associated with an Increased Risk of Cardiovascular Disease. Am J Cardiol 1999; 83 (9B): 3F-12F.

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**MEDICAL OFFICER'S REVIEW OF SUPPLEMENTAL
NEW DRUG APPLICATION**

NDA #: 19-304/S-005

Sponsor: Abbott Laboratories

Drug: Fenofibrate (Tricor)

Proposed Indication: to use as adjunctive therapy to diet for the reduction of LDL-C, total cholesterol, triglycerides, and apo B lipoproteins in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).

Date Received: July 1, 1999

User Fee Goal Date: May 1, 2000

Medical Reviewer: Mary H. Parks, MD

Volumes for Clinical Review: volumes 7-241

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INTRODUCTION

Fenofibrate, a fibric acid derivative, has been approved in the United States for the treatment of hypertriglyceridemia due to increases in very low-density lipoprotein cholesterol (VLDL-C) alone or in conjunction with increased chylomicrons (Fredrickson Types IV and V) since 1993. The mechanisms of lipid-altering have not been fully elucidated in this drug class although the triglyceride-lowering effect of fibrates is attributed to increased removal of triglyceride-rich lipoproteins through stimulation of lipoprotein lipase activity and decreased expression of apolipoprotein CIII (inhibits lipoprotein lipase).

Fredrickson Types IIa and IIb refer to lipid disorders which present with elevations in LDL-C levels. Although there is no defined lipid parameter distinguishing between these types of patients, it is generally accepted that type IIa refers to those patients with only hypercholesterolemia whereas the type IIb patients have hypercholesterolemia in the presence of hypertriglyceridemia. Patients may also shift from having a lipid profile representative of type IIb to type IV with marked elevations in triglyceride levels but normal to modest elevations of cholesterol. Regardless of the complexities involved in the accurate classification of the dyslipidemia, these patients have elevations of atherogenic lipid particles and increased risk for cardiovascular morbidity and mortality warranting pharmacologic intervention.

The effect of fenofibrate on cholesterol reduction has been described in several clinical trials involving subjects with type IIa and IIb dyslipidemia. Similar to the triglyceride-lowering effect, the mechanism for cholesterol reduction is not completely known but may be a result of the drug's binding to the peroxisome proliferator-activated receptor-alpha (PPAR- α) with resultant changes in the composition and structure of the LDL-C particle to a larger, more buoyant particle that has increased binding affinity to the LDL-receptor.

This supplemental new drug application is submitted to support a lipid-lowering indication for Tricor (micronized fenofibrate) in a patient population whose disorder is primarily hypercholesterolemia with normal or moderate hypertriglyceridemia (types IIa and IIb). Studies provided for support of this application were conducted independently over a 13-year period in both the United States and France. The formulation of fenofibrate used in these trials were the standard formulation administered at 300 mg daily doses or the bioequivalent micronized capsule administered at 200 mg daily doses.

STUDIES SUBMITTED FOR SUPPORT OF APPLICATION

Four placebo-controlled trials were submitted to support an indication for lipid-lowering in patients with Types IIa and IIb dyslipidemia. These data were presented individually for each study and in combination as a pooled analysis. Selection criteria for the placebo-controlled trials included:

- studies having non-diabetic patients with Fredrickson Type IIa or IIb hypercholesterolemia
- randomized, double-blind, parallel design studies
- prospectively conducted studies with individual Case Report Forms (CRFs)

- studies using a daily dose of 300 mg (standard formulation) or 200 mg micronized fenofibrate
- a treatment duration of at least 12 weeks

Table 1. Summary of Clinical Studies Submitted to NDA 19-304/S005

Study Number and Study Design	Patients Randomized	Duration	Treatment Groups
Study 8104 DB, PBC, RPT	227	6 month double-blind 6 months open-label	1. fenofibrate 100 mg tid 2. placebo
Study 8502 DB, PBC, RPT	106	3 months	1. fenofibrate 200 mg qam and 100 mg qpm 2. placebo
Study 8802 DB, PBC, RPT	189	3 months	1. fenofibrate 200 mg micronized qd 2. fenofibrate 100 mg tid 3. placebo
Study 9116 DB, PBC, RPT	340	3 months	1. fenofibrate 200 mg micronized qd 2. fenofibrate 267 mg micronized qd 3. fenofibrate 340 mg micronized qd 4. fenofibrate 400 mg micronized qd 5. placebo

Source: NDA 19-304/S005 Clinical Data Summary

DB = double-blind; PBC = placebo-controlled; RPT = randomized, parallel treatment

The pooled analysis was considered pivotal for determining clinical efficacy; however, the individual studies and their results will also be reviewed to evaluate consistency of treatment effect across trials and different fenofibrate formulations. Treatment effect within the different dyslipidemias will also be assessed. When available, the efficacy results are summarized in the intent-to-treat population.

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PLACEBO-CONTROLLED STUDIES**Study 8104 (conducted between January 1983 and February 1984)****Treatment Arms: fenofibrate 100 mg tid vs. placebo****Treatment Duration: 24 weeks double-blind treatment period (followed by 24 wks open-label period)****Study Centers: 11 sites in the U.S.****Lipid Eligibility Criteria:**

- males or postmenopausal females between ages 21-65 with total-C \geq 250 mg/dL
- LDL-C \geq 175 mg/dL with TGs < 250 mg/dL (type IIa) or \geq 250 mg/dL (type IIb)

Study Population:

Two hundred forty (240) patients entered the placebo run-in period, 227 entered the double-blind period [fenofibrate (116) vs placebo (111)], and 203 continued in the open-label period. Baseline demographics and patient characteristics are presented in the following table:

Table 2. Baseline Demographics and Characteristics of Study 8104 Patients

	Fenofibrate 100 mg tid (n=116)	Placebo (n=111)
Mean age (yrs)	52	51.7
Gender		
male	82 (71%)	71 (64%)
female	34 (29%)	40 (36%)
Height (cm)	170.8 \pm 10.2	169.9 \pm 9.6
Weight (kg)	74.3 \pm 12.8	74.8 \pm 12.1
TC (mg/dL)		
mean \pm SD	304.1 \pm 50.7	311 \pm 56.3
range	214-468	208-534
LDL-C (mg/dL)		
mean \pm SD	214.6 \pm 58.5	225.5 \pm 61.9
range	80-405	90-456
TG (mg/dL)		
mean \pm SD	163 \pm 134.4	160 \pm 99
range	56-977	53-648
HDL-C (mg/dL)		
mean \pm SD	48 \pm 11.5	47 \pm 11.9
range	26-81	20-88
Race		
Caucasian	103 (89%)	98 (88%)
Black	6 (5%)	9 (8%)
Hispanic	6 (5%)	2 (2%)
Asian	0	2 (2%)
Other	0	0
Unknown	1 (<1%)	0
Dyslipidemia (%)		
Type IIa	92 (79.3)	89 (80.2)
Type IIb	24 (20.7)	22 (19.8)

Source: NDA 19-304/S-005 demog.xpt, lab.xpt

The baseline lipid profile differed between the two dyslipidemic types with Type IIa patients having higher LDL-C and HDL-C levels while the Type IIb patients had

significantly higher baseline TGs levels [Ila mean (153.8 mg/dL) , IIb mean (349.3 mg/dL)].

Results: Lipid changes at the end of the double-blind treatment period were available in 116 of the fenofibrate-treated patients and 110 of the placebo-treated patients (one placebo-treated patient discontinued the study and end of study lipid levels were not available). The mean percent reduction for total-C, LDL-C, HDL-C, and TGs are summarized in Table 3.

Table 3. Mean % Reduction in Lipid Parameters in Study 8104 for Cohort and by Dyslipidemia (Ila or IIb)

Lipid Parameter	Fenofibrate 100 mg tid (n=116)	Fenofibrate-treated		Placebo (n=110)
		Type Ila (n=92)	Type IIb (n=24)	
Total-C (SE)	-15.9 (0.99)	-17.5	-15.8	+1.4 (1.12)
LDL-C (SE)	-16.1 (1.67)	-20.3	-6.1	+0.9 (1.55)
HDL-C (SE)	+12.1 (1.73)	+11.1	+15.3	-1.4 (1.37)
TG (SE)	-35.1 (1.84)	-37.9	-44.6	+3.9 (3.25)

Treatment with fenofibrate 100 mg tid resulted in significant reductions ($p < 0.01$) from baseline in mean total-C and TG levels and significant increases in HDL-C ($p < 0.01$) for both Types Ila and IIb and the cohort of fenofibrate-treated patients. Fenofibrate treatment also resulted in a significant reduction in LDL-C levels for the combined analysis of Types Ila and IIb. Separate analyses revealed a significant treatment effect only in those patients with Type Ila dyslipidemia. Patients with Type IIb had nonsignificant reductions in LDL-C ($p > 0.10$) compared to baseline.

Study 8502 (conducted between February 1985 and December 1986)

Treatment Arm: fenofibrate 300 mg daily (200 mg qam and 100 mg qpm) vs. placebo

Treatment Duration: 3 months double-blind treatment period

Study Centers: 2 medical centers in France

Study Design: 3-month randomized, double-blind, parallel group study comparing fenofibrate 300 mg daily to placebo in dyslipidemic patients (types Ila, IIb, and IV)

Lipid Eligibility Criteria:

- males or nonpregnant females between ages 21-69 with total-C > 300 mg/dL and LDL-C > 190 mg/dL
- TGs ≤ 200 mg/dL (type Ila) or > 200 mg/dL (type IIb)
- TGs > 200 mg/dL (type IV)

Study Population:

One hundred and six (106) patients were randomized to fenofibrate (n=53) or placebo (n=53) treatment. The baseline characteristics were similar between the 2 treatment groups with exception for significantly higher mean baseline TG levels in the fenofibrate group compared to placebo. This was largely due to the variability of TG levels in the Type IV subjects with values ranging from 215 to 9415 mg/dL.

Table 4. Baseline Demographics and Characteristics of Study 8502 Patients

	Fenofibrate 200mg qam and 100 mg qpm (n=53)	Placebo (n=53)
Mean age (yrs)	46	44.2
Gender		
male	36	42
female	17	11
Mean height (cm) ± SD	166.5 ± 7.9	169.7 ± 7.2
Mean weight (kg) ± SD	70.1 ± 13.8	72.6 ± 11.7
TC (mg/dL)		
mean ± SD	328.5 ± 174.3	309.0 ± 72.7
range	168-1491	166-486
LDL-C (mg/dL)		
mean ± SD	183 ± 72.4	194.4 ± 76.8
range	29.5-351	49-405
TG (mg/dL)		
mean ± SD	464 ± 1348.6	270.7 ± 247.3
range	51-9415	48-1128
HDL-C (mg/dL)		
mean ± SD	48.3 ± 24.6	42.0 ± 21.7
range	13.2-118	18-168
Dyslipidemia (%)		
Type IIa	23 (43.4)	21 (39.6)
Type IIb	8 (15.1)	13 (24.5)
Type IV	22 (41.5)	19 (35.8)

Source: NDA 19-304/S-005 demog.xpt, lab.xpt

Results: Lipid changes at the end of the double-blind treatment period were available in 52 of the fenofibrate-treated patients and 49 of the placebo-treated patients. Baseline values were obtained from the last pre-randomization value and end-of-study lipid values were obtained from the last post-randomization value.

Table 5. Lipid Changes in Study 8502 for Combined Types IIa, IIb, and IV Patients by Treatment Group after 5-6 months Compared to Baseline

Lipid Parameter	Fenofibrate 200mg qam and 100 mg qpm (n=52)	Placebo (n=49)
Mean % reduction in Total-C (SE)	-13.4 (19.2)	+0.2 (14.4)
Mean % reduction in LDL-C (SE)	-4.9 (72.3)	-3.8 (27.8)
Mean % increase in HDL-C (SE)	+12.8 (36.1)	+5.3 (41.6)
Mean % reduction in TG (SE)	-25.3 (29.3)	+7.4 (39.4)

Source NDA 19-304/S-005 volume 24-25

Significant reductions were only noted in total-C and TG levels for fenofibrate-treated groups compared to placebo ($p < 0.001$). Evaluation of lipid changes by dyslipidemias (Table 6) revealed significant reductions in total-C, LDL-C, and TG levels in the Types IIa and IIb population but nonsignificant reductions for total-C and increased LDL-C levels (+28.5%) in the Type IV patients.

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Table 6. Mean % Reduction in Lipid Parameters by Dyslipidemia in Study 8502

Dyslipidemia	Total-C	LDL-C	HDL-C	TGs
Type IIa fenofibrate (n=22)	-19.6	-29.1	+8.3	-23.2
Type IIb fenofibrate (n=8)	-19.4	-29.9	+26.7	-33.7
Type IV fenofibrate (n=22)	-5.1	+28.5	+12.3	-24.4

Source: NDA 19-304/S-005 Study CFEN 8104 Efficacy Results on CD Disc 2

Study 8802 (conducted between December 1988 and September 1989)

Treatment Arms: Fenofibrate 100 mg tid vs. Fenofibrate 200 mg micronized qd vs placebo in a parallel treatment design

Treatment Duration: 3 months double-blind treatment period

Study Centers: 39 centers in France

Lipid Eligibility Criteria:

- males and nonlactating, nonpregnant females ages 18-75 yrs with total-C \geq 250 mg/dL and TGs \leq 400 mg/dL after 2 months placebo run-in period
- subjects were further classified as Type IIa (TGs < 150 mg/dL) or IIb (\geq 150 mg/dL)

Study Population:

Two hundred and ninety-five (295) patients were screened and 189 were randomized to fenofibrate 100 mg tid (n=64), fenofibrate 200 mg micronized qd (n=64), and placebo (n=61).

Table 7. Baseline Demographics and Characteristics of Study 8802 Patients

	Fenofibrate 100 mg tid (n=64)	Fenofibrate 200 mg micronized qd (n=64)	Placebo (n=61)
Mean age (yrs)	56.4	55.4	53.8
Gender			
male	26	34	28
female	36	30	32
Mean height (cm) \pm SD	163.1 \pm 8.6	165.6 \pm 8.5	165.1 \pm 9.3
Mean weight (kg) \pm SD	66.9 \pm 11.4	68.3 \pm 11.3	67.8 \pm 11.0
TC (mg/dL)			
mean \pm SD	295.6 \pm 32.6	291.4 \pm 40.7	301.0 \pm 40.9
range	251.9-414.7	250-446.1	250.4-426.7
LDL-C (mg/dL)			
mean \pm SD	209.6 \pm 35.6	208.8 \pm 41.8	212.7 \pm 40.5
range	147.8-344.6	134.4-367.4	149.2-334.6
TG (mg/dL)			
median \pm SD	123.5 \pm 58.0	134.1 \pm 61.1	117.7 \pm 68.3
range	50.4-271.7	44.2-365.5	51.3-301.8
HDL-C (mg/dL)			
mean \pm SD	59.1 \pm 15.0	55.2 \pm 14.8	59.4 \pm 15.4
range	36.0-108.5	32.2-112	28.7-92.6
Dyslipidemia (%)			
Type IIa	41 (64.1)	41 (64.1)	38 (62.3)
Type IIb	23 (35.9)	23 (35.9)	23 (37.7)

Source: NDA 19-304/S-005 demog.xpt, lab.xpt

Results: Efficacy analyses were evaluated in 128 of the randomized subjects [fenofibrate 100 mg tid (n=41); fenofibrate 200 mg micronized (n=46); placebo (n=41)]. Ideally, all subjects randomized who received one dose of study drug and had a postrandomization efficacy measurement should be included in the efficacy analyses. In this protocol subjects were excluded from analyses for the following reasons: major protocol deviation (37); lost to follow-up (9); side-effects leading to withdrawal (2); wrongly included in study (7); and drop-out for reasons not associated with treatment (6).

Table 8. Lipid Changes in Study 8802 by Treatment Group

Lipid Parameter	Fenofibrate 100 mg tid (n=41)	Fenofibrate 200 mg micronized qd (n=46)	Placebo (n=41)
Mean % reduction in Total-C	-23.91	-20.54	-1.81
Mean % reduction in LDL-C	-31.84	-26.91	-3.64
Mean % increase in HDL-C	+10.82	+10.69	+0.66
Mean % reduction in TG	-30.87	-29.5	+16.88

Source: NDA 19-304/S-005 lab.xpt

There were significant reductions in total-C, LDL-C, and TG levels in both fenofibrate treatment groups with greater reductions observed in the group randomized to treatment with the standard formulation. Increases in HDL-C were significant and similar between both treatment groups. The effect of the different formulations of fenofibrate were evaluated by dyslipidemia (Table 9).

Table 9. Mean % Reduction in Lipid Parameters by Dyslipidemia and Fenofibrate Formulation

Dyslipidemia	Total-C	LDL-C	HDL-C	TGs
Type IIa				
fenofibrate 100 mg (n= 26)	-25.5	-35.5	+10.3	-26.8
fenofibrate 200 mg (n= 28)	-22.6	-30.8	+6.7	-24.0
Type IIb				
fenofibrate 100 mg (n= 15)	-20.7	-24.6	+11.8	-38.9
fenofibrate 200 mg (n= 18)	-17.4	-21.0	+16.7	-37.9

Source: NDA 19-304/S-005 Study CFEN 8802 Efficacy Results on CD Disc 2

Treatment with either formulation of fenofibrate resulted in significant changes in lipid profiles compared to baseline in both Types IIa and IIb dyslipidemia. The reductions in total-C and LDL-C levels were greater in those subjects with baseline TG < 150 (Types IIa) compared to Type IIb patients. The standard formulation of fenofibrate produced higher reductions in total-C, LDL-C, and TG levels than the micronized formulation in both dyslipidemic populations.

Study 9116 (conducted between July 1992 and February 1994)

Treatment Arms: Fenofibrate micronized formulation in the following doses (200mg, 267 mg, 340 mg, and 400 mg) administered daily vs. placebo

Treatment Duration: 3 months double-blind treatment period

Study Centers: 4 centers in France.

Lipid Eligibility Criteria:

- LDL-C \geq 180 mg/dL and TGs $<$ 350 mg/dL
- male or female ages 18 to 75 (inclusive), women of childbearing potential were excluded

Study Population:

This study did not select subjects and assign treatment by dyslipidemic classification. After randomization, patients were classified as Type IIa if baseline TGs were $<$ 250 mg/dL and Type IIb if TGs were greater than or equal to this value.

Table 10. Baseline Demographics and Characteristics of Study 9116 Patients

	Fenofibrate 200 mg micronized qd (n=69)	Placebo (n=69)
Mean age (yrs)	54.1	54.4
Gender		
male	31	28
female	38	41
Mean height (cm) \pm SD	163.7 \pm 9.4	165.1 \pm 8.8
Mean weight (kg) \pm SD	67.1 \pm 13.8	66.7 \pm 11.3
TC (mg/dL)		
mean \pm SD	304.9 \pm 37.1	313.6 \pm 38.8
range	241.1-475.2	243.0-414.0
LDL-C (mg/dL)		
mean \pm SD	225.1 \pm 34.1	228.2 \pm 36.6
range	181.4-390.9	181.1-335.2
TG (mg/dL)		
median \pm SD	106.2 \pm 57.0	223.0 \pm 61.8
range	40.7-290.3	38.1-300.9
HDL-C (mg/dL)		
mean \pm SD	55.7 \pm 14.5	58.3 \pm 16.8
range	31.0-90.0	26.0-108.1
Dyslipidemia (%)		
Type IIa	61 (88.4)	57 (82.6)
Type IIb	7 (10.1)	11 (15.9)
unknown	1 (1.5)	1 (1.5)

Source: NDA 19-304/S-005 demog.xpt, lab.xpt and volume

Results: Efficacy results are summarized only for the fenofibrate 200 mg micronized and placebo treatment arms. Data are presented for all subjects randomized in the following table.

Table 11. Lipid Changes in the Fenofibrate 200 mg and Placebo Groups

Lipid Parameter	Fenofibrate 200mg micronized (n=69)	Placebo (n=69)
Mean % reduction in Total-C (SE)	-24.5 (11.9)	+0.5 (11.0)
Mean % reduction in LDL-C (SE)	-31.6 (15.6)	+0.5 (14.2)
Mean % increase in HDL-C (SE)	+8.0 (20.0)	+1.3 (14.9)
Mean % reduction in TG (SE)	-26.7 (37.2)	+3.5 (33.9)

Source: NDA 19-304/S-005 Study CFEN 9116 Efficacy Results on CD Disc 2

Treatment with fenofibrate 200 mg micronized for 3 months in patients with moderate hypercholesterolemia resulted in significant changes in total-C, LDL-C, HDL-C, and TGs

levels from baseline. Lipid changes for Types IIa and IIb were not individually reported for this trial.

Conclusions On Efficacy of Fenofibrate from the Individual Placebo-Controlled Trials

There were 233 patients treated with the standard formulation of fenofibrate and 133 treated with micronized fenofibrate in these 4 placebo-controlled trials over a period of 3 to 6 months. Both formulations resulted in significant reductions in total-C, LDL-C, and TGs and increases in HDL-C from. Overall, the range of these changes were: total-C (- _____); LDL-C _____; HDL-C _____; and TGs _____

The lipid-altering effects of fenofibrate were evaluated by type of dyslipidemia in the individual studies except in Study 9116. There was a trend towards diminished total-C and LDL-C lowering in those patients with higher baseline TG levels. Although the subgroup analyses of the lipid effects by dyslipidemic types in the individual studies resulted in small sample sizes in some studies, the consistent finding of the increased baseline TG level resulting in an attenuated cholesterol lowering effect in the fenofibrate group warranted further exploration. The pooled analysis of these 4 placebo-controlled studies provided us an opportunity to examine fenofibrate's affect on the lipid profile in a diverse population of dyslipidemic subjects.

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POOLED ANALYSIS

Study Plan and Objectives

Patients from the 4 placebo-controlled studies who were treated with either the standard formulation of fenofibrate administered as 300 mg daily or the micronized formulation administered as 200 mg daily were considered in the pooled analysis. The objective of the pooled analysis was to demonstrate the LDL-C lowering effect of equivalent doses of fenofibrate in a population of patients with mild to moderate elevations of LDL-C and baseline TGs less than 250 mg/dL. The following table summarizes the patients from each study contributing to the pooled analysis.

Table 12. Summary of Placebo-Controlled Trials Included in the Pooled Analysis

Study Number	Treatment Group	Number of Randomized Subjects	Number of Subjects in the Pooled Analysis
8104	Feno 100 mg tid	116	116
	Placebo	111	111
8502	Feno 200 mg qam, 100 mg qpm	53	53
	Placebo	53	53
8802*	Feno 100 mg tid	64	62
	Feno 200 mg (m) qd	64	64
	Placebo	61	60
9116	Feno 200 mg (m) qd	69	69
	Feno 267 mg (m) qd	69	0
	Feno 340 mg (m) qd	66	0
	Feno 400 mg (m) qd	67	0
	Placebo	69	69
Total		862	657

Source: NDA 19-304/S-005 demog.xpt, lab. xpt

*2 fenofibrate-treated subjects and 1 placebo-treated subject were excluded from the pooled analysis because there was no documentation that study medication was ever dispensed

The pooled analysis included data from only those subjects treated with placebo, the standard formulation of fenofibrate, or marketed micronized formulation of fenofibrate (i.e. data from 267, 340, and 400 mg micronized formulation were not included). There were a total of 293 patients treated with placebo and 364 treated with fenofibrate (231 standard, 133 micronized) for 3 to 6 months. The lipid profiles obtained for the different fenofibrate formulations were combined (all FEN) and compared to the values obtained for the placebo-treated group. Of the 657 patients considered in the pooled analysis, only 646 had LDL-C endpoint measures for inclusion in efficacy assessment [all FEN (n=361); placebo (n=285)].

Baseline Lipid Characteristics in Pooled Cohort

The lipid eligibility criteria and definitions of Fredrickson dyslipidemia Types IIa and IIb differed across all 4 trials. The lipid profile defining subjects with Types IIa and IIb were not defined for the pooled analysis cohort. Rather, the sponsor summarized the lipid profiles of the subjects in the pooled analysis according to the categories outlined in Table 13.

Table 13. Subgrouping of Pooled Cohort by Baseline Lipid Profile as Presented by Sponsor-

Lipid Subgroup	Fenofibrate (n=361)	Placebo (n=285)
LDL-C < 130 mg/dL	17 (4.7%)	12 (4.2%)
LDL-C ≥ 130 mg/dL, TG < 250 mg/dL	301 (83.4%)	231 (81.1%)
LDL-C ≥ 130 mg/dL, TG ≥ 250 and < 400 mg/dL	34 (9.4%)	34 (11.9%)
LDL-C ≥ 130 mg/dL, TG ≥ 400 mg/dL	9 (2.5%)	8 (2.8%)

Based on this classification scheme the majority of patients in the pooled analysis had LDL-C ≥ 130 mg/dL and TG < 250 mg/dL (fenofibrate, 83.4% vs. placebo 81.1%).

Because the mean LDL-C was significantly higher than 130 mg/dL for both treatment groups [fenofibrate (210.1 mg/dL) vs placebo (218.6 mg/dL)] the FDA requested the cumulative distribution of baseline lipid parameters in the pooled cohort. These data are present in the following table as mean, median, 25th, and 75th percentile values for total-C, LDL-C, HDL-C, triglycerides, and LDL-C/HDL-C ratio.

Table 14. Baseline Distribution of Lipid Parameters in Fenofibrate and Placebo Groups by Mean and Percentile Values

Lipid Parameter	All FEN (n=361)	Placebo (n=285)
Total-C (mg/dL)		
mean	304.4	310.0
25 th	271.0	277.1
50 th	292.0	300.0
75 th	322.1	337.6
LDL-C (mg/dL)		
mean	210.1	218.6
25 th	182.0	184.8
50 th	207.4	212.0
75 th	232.0	243.8
HDL-C (mg/dL)		
mean	52.8	51.7
25 th	42.0	41.0
50 th	51.0	50.0
75 th	61.2	61.0
Triglycerides (mg/dL)		
mean	199.5	180.2
25 th	94.0	108.0
50 th	133.6	144.0
75 th	197.3	207.1
LDL-C/HDL-C ratio		
mean	4.3	4.7
25 th	3.2	3.3
50 th	4.1	4.3
75 th	5.0	5.6

From table 14 it is evident that the pooled cohort consisted of moderate to severe hypercholesterolemic patients with normal to mildly elevated triglyceride levels.

Results of Pooled Analysis

The sponsor presented the lipid altering effects of the different treatment groups by the lipid profiles summarized in table 15.

Table 15.

Efficacy Results Summarized in the Following Lipid Subgroups as Presented by Sponsor
1. LDL-C \geq 130 mg/dL, TG < 250 mg/dL <ul style="list-style-type: none"> • TG < 150 mg/dL • TG \geq 150 and < 250 mg/dL
2. LDL-C \geq 130 mg/dL, TG \geq 250 and < 400 mg/dL
3. LDL-C \geq 130 mg/dL, TG \geq 400 mg/dL

Again, because the mean LDL-C and total-C levels were significantly higher than 130 mg/dL, the FDA's presentation of efficacy results will be summarized for each treatment group by the following strata:

- pooled cohort refers to all subjects with baseline and endpoint LDL-C values
- baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa patients)
- baseline LDL-C \geq 160 mg/dL and TG \geq 150 mg/dL (Type IIb patients)
- baseline LDL-C < 160 mg/dL and TG \geq 150 mg/dL (Type IV patients)

This classification more accurately reflects the baseline lipid profile of the pooled subjects but does not significantly alter the efficacy results as summarized by the sponsor.

The following table summarizes the mean percent changes in lipid parameters for the pooled cohort by treatment group and dyslipidemia. Results are adjusted for the differences in efficacy results and size of the 4 individual studies contributing to the pooled analysis.

Table 16. Mean Percent Change in Lipid Parameters at End of Study

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
All FEN (n=361)	-18.7	-20.6	+11.0	-28.9
Placebo (n=285)	-0.4	-2.2	+0.7	+7.7
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
All FEN (n=193)	-22.4	-31.4	+9.8	-23.5
Placebo (n=141)	+0.2	-2.2	+2.6	+11.7
Baseline LDL-C \geq 160 mg/dL and TG \geq 150 mg/dL (Type IIb)				
All FEN (n=126)	-16.8	-20.1	+14.6	-35.9
Placebo (n=116)	-3.0	-6.6	+2.3	+0.9
Baseline LDL-C \leq 160 mg/dL and TG \geq 150 mg/dL (Type IV)				
All FEN (n=30)	-13.0	+24.0	+14.8	-51.0
Placebo (n=19)	+1.8	-7.2	-10.4	+13.6

Treatment with fenofibrate in doses equivalent to 300 mg daily resulted in a significant reduction of total-C, LDL-C, and TGs and increase in HDL-C in this cohort of patients with moderately elevated cholesterols and normal to mildly elevated triglycerides. Fenofibrate therapy resulted in an average reduction of total-C of -18.7% and LDL-C of 20.6%.

As observed in the review of the individual studies, the effect of fenofibrate is affected by the baseline triglyceride level. As summarized in Table 16, the effect of fenofibrate on total-C and LDL-C lowering (-22.4 and -31.4%, respectively) was greater in those subjects with baseline elevation in cholesterols but who were normotriglyceridemic (Type IIa). In the subgroup with both elevated baseline cholesterols and triglycerides (Type IIb), the effect of fenofibrate on total-C and LDL-C was somewhat diminished (-16.8 and -20.1%). The difference in treatment response between the two types of dyslipidemia was statistically significant for total-C, LDL-C, TGs changes ($p < 0.001$) but not in HDL-C ($p = 0.06$).

On-Treatment Lipid Values

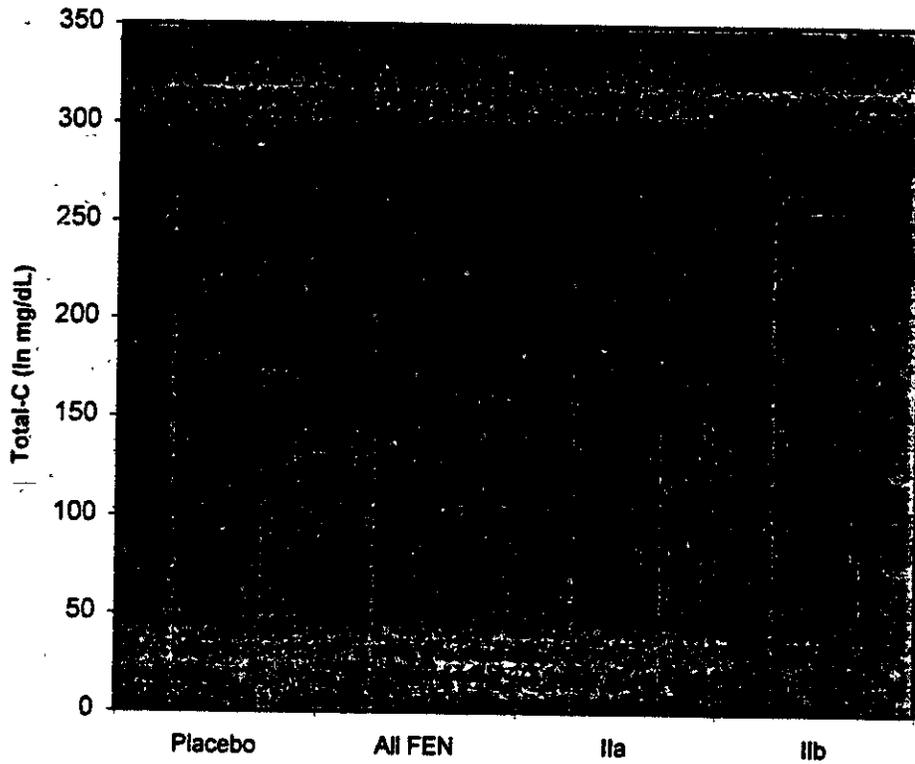
Treatment with fenofibrate resulted in mean LDL-C levels of 158 mg/dL in the pooled group. In patients with Type IIa and IIb dyslipidemia, fenofibrate therapy reduced LDL-C levels to mean values of 155 and 172 mg/dL, respectively. The mean on-treatment values for total-C and LDL-C for the placebo-treated group. All FEN patients, IIa, and IIb patients are depicted in Figures 1 and 2.

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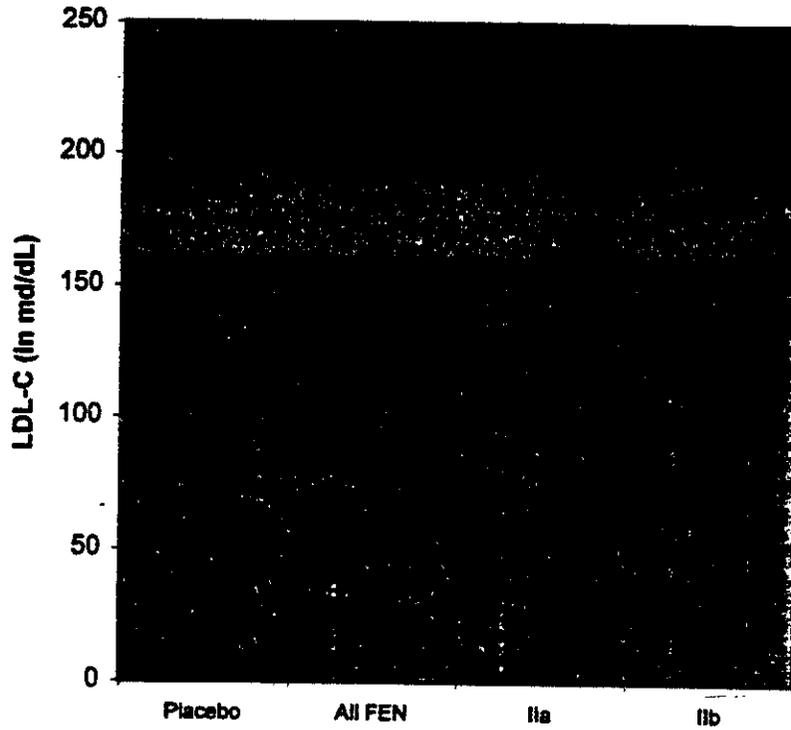
Figure 1. Mean Achieved Total-C Levels by Treatment Groups



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Figure 2. Mean Achieved LDL-C Levels by Treatment Group



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CONCLUSIONS

Fenofibrate at daily doses of 300 mg (standard formulation) or the bioequivalent 200 mg micronized formulation resulted in significant reductions of total-C, LDL-C, and triglycerides and significant increases in HDL-C levels in this pooled analysis of 4 placebo-controlled studies comprised of subjects with moderate to severe elevations of cholesterol and normal to mildly elevated triglyceride levels (Types IIa and IIb). The effect of fenofibrate on cholesterol reduction was greater in the subgroup of patients with hypercholesterolemia and normotriglyceridemia (type IIa) at baseline than those with elevations in both lipid parameters (type IIb). No clinical outcome data are available for fenofibrate treatment of dyslipidemias. Although treatment at the highest approved dose of fenofibrate resulted in statistically significant reductions in total-C and LDL-C in both types of patients, the achieved values after 3 to 6 months of therapy may not be clinically sufficient. Notably, the mean percent reduction in total-C and LDL-C achieved with the maximal dose of fenofibrate can be achieved or surpassed by the lower doses of some HMG-coA reductase inhibitors. Given the increased risk for cardiovascular events in these patients a more aggressive form of lipid-lowering may be required to achieve lower total-C and LDL-C goals.

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SAFETY REVIEW

Overview of Pooled Safety Data

The integrated summary of safety (ISS) submitted consisted of pooled data from 19 clinical studies (Table 17) using both the standard and micronized formulation of fenofibrate at different dosages and for different treatment duration. The studies were conducted at separate times over a 15-year period (1983-98). The rows indicated by an asterisk (*) represent studies with placebo controls.

Table 17. Clinical Studies Assessed in ISS

Daily Dose and Formulation	Duration of Treatment	Number of Subjects Exposed
300 mg standard*	6 months double-blind	116
	6 months open-label	203
250 mg standard*	3 months double-blind	16
300 mg standard*	2 months double-blind	22
300 mg standard*	3 months double-blind	53
300 mg standard*	2 months double-blind	75
300 mg standard*	2 months double-blind	14-16
200 mg micronized	1 year open-label	138
200 mg micronized*	3 months double-blind	64
300 mg standard*		64
200 mg micronized	3 months active-control, double-blind	20
200 mg micronized	3 months active-control, double-blind	60
50 mg standard*	8 weeks double-blind for all doses followed by 48 weeks open-label at 300 mg standard	28
100 mg standard*		30
200 mg standard*		30
300 mg standard*		34
300 mg standard		132
200-400 mg micronized	6 months active-control, double-blind	76
200 mg micronized*	3 months double-blind	69
267 mg micronized*		69
340 mg micronized*		66
400 mg micronized*		67
200 mg micronized	1 year open-label	2069
200 mg micronized	3 months active-control, double-blind	32
200 mg micronized*	6 months double-blind	16
200 mg micronized	6 months active-control, open-label	105
200 mg micronized	6 months active-control, double-blind	116
267 mg micronized	6 months open-label	112

A total of 2,882 subjects were exposed to at least one dose of fenofibrate with a minimum of 1,500 subjects exposed to at least 6 months and 500 subjects to 12 months of fenofibrate therapy.

A total of 12,331 adverse events were reported by 2,874 subjects in the pooled AE dataset. Three thousand four hundred and seventy-six (3,476) of these reports came

from 1,296 fenofibrate-treated subjects. The following table summarizes the AEs reported for the 19 pooled studies.

Table 18. Adverse Events Reported in the Pooled Studies for the ISS.

	Fenofibrate (n=1,296)	Placebo (n=210)	Active-Controls (n=153)*
Adverse events reported	3,476	573	260
Serious AEs			
yes	168	13	8
no	2,883	433	222
unknown	425	127	30
Deaths	4	0	1

*active controls consisted of subjects treated with simvastatin, pravastatin, lovastatin, or gemfibrozil

Deaths in the Fenofibrate-Treated Subjects

Four subjects died while on treatment with the 200 mg micronized formulation of fenofibrate; none were considered related to drug treatment.

Subject 1: 54-year old male died of bronchopneumonia after receiving fenofibrate for 163 days

Subject 2: 69-year old male who had a history of diabetes and cardiomyopathy; patient suffered cardiac arrest after receiving fenofibrate for 44 days

Subject 3: 65-year old female who had a history of scleroderma; patient died of respiratory failure after receiving fenofibrate for 214 days

Subject 4: 66-year old female died of sudden death after receiving fenofibrate for 43 days

The one death reported in the active-control group occurred in a 60-year old male subject treated with simvastatin 20 mg for approximately 163 days who suffered a mesenteric artery occlusion. Relation to study drug was not recorded.

Three other deaths were reported in the pooled cohort but took place during the baseline placebo run-in period and were not considered drug-related.

Adverse Events in Placebo-Controlled Trials

Adverse events occurring while on study were assessed in the 10 placebo-controlled trials to compare the incidence rates in AEs between fenofibrate and placebo-treated populations. From the AE.xpt dataset provided by the sponsor only studies which were placebo-controlled were selected. There were 1,118 AEs reported in 831 fenofibrate-treated subjects (22 were reported as serious) and 555 AEs reported in 460 placebo-treated subjects (12 serious). No deaths were reported in this dataset. The following table summarizes the AEs summarized in this dataset by body system that occurred at incidence rates of $\geq 1.0\%$ in either treatment group.

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Table 19. Adverse Events Occurring at Rates \geq 1.0% Reported by Body Systems in the Placebo-Controlled Trials

Body System Adverse Event	Fenofibrate (n=831)*	Placebo (n=460)
BODY AS A WHOLE		
abdominal pain	48 (5.8%)	23 (5.0%)
accidental injury	16 (1.9%)	9 (2.0%)
asthenia	30 (3.6%)	19 (4.1%)
back pain	31 (3.6%)	19 (4.1%)
chest pain	9 (1.1%)	5 (1.0%)
flu syndrome	28 (3.4%)	15 (3.3%)
headache	40 (4.8%)	22 (4.8%)
infection	6 (<1%)	9 (2.0%)
pain	8 (<1%)	8 (1.7%)
CARDIOVASCULAR SYSTEM		
hypertension	12 (1.4%)	0
DIGESTIVE SYSTEM		
constipation	23 (2.8%)	11 (2.4%)
diarrhea	25 (3.0%)	30 (6.5%)
dyspepsia	27 (3.2%)	10 (2.2%)
flatulence	18 (2.2%)	16 (3.5%)
increased appetite	14 (1.7%)	21 (4.6%)
LFTs abn/liver damage	103 (12.4%)	8 (1.7%)
nausea	17 (2.0%)	10 (2.2%)
nausea and vomiting	20 (2.4%)	3 (<1%)
rectal disorder	0	6 (1.3%)
gastroenteritis	11 (1.3%)	0
HEME AND LYMPHATIC SYSTEM		
anemia	15 (1.8%)	6 (1.3%)
METABOLIC AND NUTRITIONAL		
CK increased	32 (3.9%)	6 (1.3%)
creatinine increased	16 (1.9%)	2 (<1%)
SGOT increased	20 (2.4%)	2 (<1%)
SGPT increased	22 (2.6%)	6 (1.3%)
MUSCULOSKELETAL SYSTEM		
arthralgia	14 (1.7%)	9 (2.0%)
joint disorder	0	7 (1.5%)
leg cramps	0	5 (1.1%)
myalgia	18 (2.2%)	9 (2.0%)
NERVOUS SYSTEM		
dizziness	10 (1.2%)	8 (1.7%)
insomnia	9 (1.1%)	2 (<1%)
decreased libido	6 (<1%)	7 (1.5%)
paresthesia	0	6 (1.3%)
RESPIRATORY SYSTEM		
bronchitis	16 (1.9%)	5 (1.1%)
increased cough	7 (<1%)	7 (1.5%)
pharyngitis	33 (4.0%)	9 (2.0%)
respiratory disorder	33 (4.0%)	25 (5.4%)
rhinitis	27 (3.2%)	8 (1.7%)
sinusitis	20 (2.4%)	16 (3.5%)
SKIN AND APPENDAGES		
pruritus	15 (1.8%)	2 (<1%)
rash	18 (2.2%)	8 (1.7%)
UROGENITAL SYSTEM		
urinary tract infection	4 (<1%)	6 (1.3%)

*included both standard and micronized formulations

The most commonly reported AEs occurred under the gastrointestinal body system. Of significance was the higher incidence of abnormal LFTs and liver damage reported in the fenofibrate group versus placebo. The method of compiling AEs in this dataset allowed individual subjects to be counted more than once for any event. This explains the significant differences in some AE incidence rates. After adjusting for multiple reportings, the main differences were noted in reports of hypertension, liver abnormalities (including laboratory abnormalities and liver damage), creatine phosphokinase (CK) and creatinine increases. Only events associated with liver abnormalities, CK and creatinine increases were considered drug-related by the study investigators and will be discussed in detail in the following sections.

Liver Damage

The 6 reports of liver damage in the fenofibrate group occurred in 1 subject (Patient 8601.7404.101) who discontinued therapy after approximately 2 months of daily treatment with fenofibrate 300 mg. This patient was a 54-year old male who had a history of Type IV dyslipidemia whose concomitant medications included isosorbide, nitroglycerin, lasix, and potassium replacement. The patient was reported as a light to moderate alcohol consumer with no baseline reports of liver disease. At baseline, his SGOT and SGPT were below the upper limits of normal but were reported as > 3x ULN approximately 27 days into the study; bilirubin was normal. The liver was reported as enlarged and the patient complained of general malaise and right upper quadrant pain. The study medication was discontinued with subsequent decline in SGOT levels to within normal limits and SGPT slightly above normal (40 IU/mL). All signs and symptoms were reported as resolved with the exception of general malaise.

Liver Function Tests Abnormalities

The number of subjects reporting abnormal LFTs as an AE was 51 (6.1%) for the fenofibrate group and 5 (1.1%) in the placebo group with more than half of the 51 in the fenofibrate group reporting SGOT/SGPT elevations at > 3x ULN [28/51, (54.9%)]. Twelve of the fenofibrate-treated and 2 of the placebo-treated subjects discontinued therapy due to abnormal LFTs.

LFT values were summarized in a dataset (lab2.xpt) separate from the dataset for adverse events. The number of subjects with either SGPT or SGOT > 3x ULN in the 10 placebo-controlled trials is summarized in the following table by treatment group.

Table 20. Patients with SGOT or SGPT > 3x ULN in the Placebo-Controlled Trials

LFT Abnormalities	Fenofibrate (n=831)	Placebo (n=460)
Subjects with either SGPT or SGOT > 3xULN	44 (5.3%)	5 (1.1%)
Subjects with SGOT > 3xULN	14 (1.2%)	1 (<1%)
mean value (IU/ml)	120.4	NA
median value (IU/ml)	107	
range (IU/ml)		
Subjects with SGPT > 3xULN	44 (5.3%)	5 (1.1%)
mean value (IU/ml)	148.6	186.6
median value (IU/ml)	122	162
range (IU/ml)		

Source lab2.xpt file

ULN for SGOT = 22-41, SGPT 25-70

The incidence of having either an SGOT or SGPT increase of > 3x ULN was higher in the fenofibrate-treated subjects (5.3%) compared to placebo-treated subjects.

Laboratory abnormalities normalized or decreased with drug discontinuation in the majority of cases.

Increases in Creatine Phosphokinase (CK)

The number of subjects reporting elevations in CK levels was 14 (14/831, 1.4%) in the fenofibrate-treated group versus 5 (5/460, 1.1%) in the placebo group. The incidence of myalgias was similar between the two treatment groups. The mean CK level was 99.7 IU/mL (range _____ in the fenofibrate group compared to 85.8 IU/mL (range _____ in the placebo group. There were no cases of rhabdomyolysis reported in the ISS.

Creatinine Elevations

Thirteen subjects treated with fenofibrate reported having elevations in creatinine levels compared to 2 in the placebo group. The mean creatinine value was 1.2 mg/dL (range _____ in the fenofibrate group versus 1.1 mg/dL (range _____ in the placebo group. There was no significant clinical deterioration associated with creatinine elevations.

Conclusion

The integrated summary of safety submitted with this supplemental NDA provides extensive information on the exposure of subjects to fenofibrate from 3 months to over 12 months treatment duration. In placebo-controlled trials, the most commonly reported AE was liver function test abnormalities [fenofibrate (6.1%) vs. placebo (1.1%)]. The incidence of SGOT or SGPT > 3x ULN was 5.3% (fenofibrate) vs. 1.1% (placebo). The majority of these cases resolved upon study drug discontinuation or interruption. One patient was reported as having liver damage prompting closer inspection of the case report form. This subject had elevations of SGOT and SGPT as high as 183 and 360 IU/mL, respectively. After study drug discontinuation, laboratory abnormalities improved and the patient recovered without serious complications.

Other AEs and laboratory safety findings reported at higher rates than placebo included hypertension, CK and creatinine elevations. There were no serious clinical consequences associated with these reports and these findings are supported by the current label.

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REVIEW OF LABELING

There are significant changes to the sponsor's proposed labeling pertaining to clinical pharmacology, clinical efficacy, and safety issues. The review and comments of the label will be made directly on to the submitted proposed label using the following legend:

1. [REDACTED] within the proposed label are insertions made by the sponsor
2. ~~strikethroughs~~ represent deletions to the label made by the FDA reviewer
3. double-underlined sections represent insertions to the label made by the FDA reviewers
4. rationale for the reviewers' changes are provided in (*italicized comments within parentheses*)

Changes to the Proposed Label

Excerpts of the proposed label are inserted in this section with changes made by the medical officer as outlined above. Revisions by the clinical pharmacology reviewer will be summarized in the Biopharm Review.

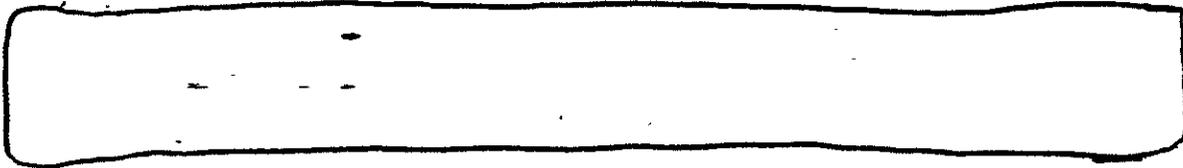
TRICOR™

(fenofibrate capsules), micronized

6 Page(s) Redacted

Draft

Labeling



FINANCIAL DISCLOSURE STATEMENT

In accordance with 21 CFR 54 the sponsor has submitted statements disclosing any information regarding financial interests and arrangements of clinical investigators, respective spouses, and dependent children of the investigators. There were no investigators who entered a financial arrangement with Groupe Fournier or Abbott Laboratories which could compromise the integrity of the trial results.

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ON ORIGINAL**

MEDICAL OFFICER'S COMMENTS ON SUPPLEMENTAL NDA

Summary of Efficacy and Safety of Fenofibrate

This supplemental NDA provides sufficient data to support the daily use of micronized fenofibrate 200 mg for the treatment of hypercholesterolemia in Fredrickson Type IIa and IIb dyslipidemia. In 4 placebo-controlled trials involving the 200 mg micronized formulation or the bioequivalent standard formulation, the effect on total-C and LDL-C lowering was consistent with mean changes of -18.7% for total-C and -20.6% for LDL-C. Interestingly, the cholesterol-lowering effect was affected by the baseline triglycerides with those patients having lower baseline triglycerides (Type IIa) achieving statistically significantly greater reductions in cholesterol compared to the IIb patients. This pattern was seen in the individual studies and supported in the pooled analysis.

The mean achieved levels of total-C and LDL-C were 246.4 mg/dL and 157.5 mg/dL, respectively; however, these may not be clinically adequate in a patient population with high risk for initial or recurrent cardiovascular events. Based on the National Cholesterol Education Program (NCEP) Guidelines, the recommended LDL-C goal is < 100 mg/dL for patients with established CAD and in the absence of CAD but with ≥ 2 risk factors, the targeted goal is < 130 mg/dL. Treatment with the maximal approved dose of fenofibrate in these trials achieved an LDL-C level of < 130 mg/dL in only about 25% of the 361 patients evaluated in the pooled analysis (Table 21).

Table 21. Distribution of Achieved LDL-C Values in Pooled Cohort Treated with Fenofibrate

All FEN (n=361)	
25 th percentile	124.6 mg/dL
50 th percentile	153.3 mg/dL
75 th percentile	182.8 mg/dL

These findings, in conjunction with the lack of clinical outcome data that have been generated in clinical trials with some of the HMG-coA reductase inhibitors, may limit the use of fenofibrate to those patients who do not require significant cholesterol-lowering (e.g. patients requiring <25-30% LDL-C reduction at low risk for a CHD event).

The review of the integrated summary of safety from a large pool (n=2,882) of patients exposed to fenofibrate from 3 months to > 1 year at daily doses as high as 400 mg confirms that fenofibrate does induce elevations in transaminases in approximately 5% of patients. These elevations may be significant (i.e. 8 -10 x ULN) but appear to resolve without sequelae with discontinuation of drug. The proposed labeling changes adequately reflect this adverse event and advise clinicians to perform periodic LFT monitoring with recommendations for discontinuation of therapy if enzyme levels persist above 3x ULN.

The finding of myalgias was similar for fenofibrate and placebo-treated (2.2% vs. 2.0%, respectively) subjects with no cases of rhabdomyolysis reported. The low incidence rate of this adverse event makes it exceedingly rare for any detection in controlled clinical trials but the continued reporting of rhabdomyolysis for fenofibrate (and other fibrates) alone and in combination with statins in spontaneous AEs reports warrant continued warnings for this side effect in labeling.

Recommendations

This supplemental NDA should be approved pending appropriate labeling changes.

/S/

3/19/00

Mary H. Parks, MD
Medical Officer
Division of Metabolic and Endocrine Drug Products
HFD-510

concur:

/S/

3/17/00

David G. Orloff, MD
Medical Team Leader
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recommendation code: AP

cc: NDA19-304

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ON ORIGINAL