CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-304/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	19-304	**Supplement:**	005
Brand Name:	Tricor™	**Generic Name:**	Fenofibrate, Micronized
Strength(s):	67 mg, 134 mg, and 200 mg Capsules		
Sponsor:	Abbott Laboratories 100 Abbott Park Road, D-491, AP6B-1SW, Abbott Park, IL 60064-6108		
Submission Date:	30-JUN-99	**Review Date:**	07-MAR-00
Submission Type:	SE1-005 – Supplemental New Drug Application – New Indication		
Reviewer:	Steven B. Johnson, B.Pharm, Pharm.D.		

Terms and Abbreviations

Agency	Food and Drug Administration
AUC	Area under the plasma-concentration-time curve
BE	Bioequivalence
C_{max}	Maximum drug concentration
CYP450	Cytochrome P450
DFE	Dosage-form equivalence
DMEDP	Division of Metabolic and Endocrine Drug Products
FF	Fenofibrate
FFA	Fenofibric Acid
HDL	High density lipoprotein
LDL	Low density lipoprotein
NDA	New Drug Application
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
PS	Pravachol
T_{max}	Time of maximum drug concentration

Synopsis

Abbott Laboratories has submitted supplement 005 to NDA 19-304 for micronized fenofibrate capsules. Micronized fenofibrate is a third generation fibric acid derivative that was approved by the Food and Drug Administration (FDA) in 1993. The original indication for fenofibrate (Tricor™) was as an adjunct to diet in the treatment of patients with hypertriglyceridemia at risk for pancreatitis. In this supplemental NDA, the sponsor seeks to amend the previously approved indication with the following additions: "... 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) with triglycerides less than 250 mg/dL." The manufacturer's recommended initial dose for adult patients with primary hypercholesterolemia or mixed hyperlipidemia is 200 mg daily with a meal. The maximum daily dose is 200 mg per day.

Two studies were presented in this application for Clinical Pharmacology and Biopharmaceutics review. These studies were included to facilitate metabolism and drug interaction labeling changes. The first study examined the effects of fenofibrate (FF) and fenofibric acid (FFA) on selected cytochrome P450-dependent enzyme activities using human liver microsomes. The second study assessed the pharmacokinetic interaction between fenofibrate and pravastatin in a three-period crossover study using normal healthy subjects. In addition, the sponsor has proposed numerous literature-based labeling changes.

Questions that have arisen during the course of this review are as follows:

1) Are three 67-mg Tricor capsules bioequivalent to a single 200-mg capsule?

2) What effects do fenofibrate and fenofibric acid have on selected cytochrome P450-dependent enzyme activities *in vitro*?

3) Does a drug interaction exist between fenofibrate and HMG-CoA reductase inhibitors?

4) Do either fenofibrate or fenofibric acid undergo oxidative metabolism to a significant extent?

Answers are provided in brief within this ***Synopsis*** and are discussed in more detail throughout the remainder of the review.

In vitro metabolism study results indicate that both FF and FFA demonstrate a concentration-dependent inhibition of CYP2C9-dependent methylhydroxylation of tolbutamide metabolism in human liver microsomes. Additionally, FF and FFA displayed inhibitory activity toward the CYP2C19-dependent 4-hydroxylation of S-mephenytoin and CYP2A6-dependent 7-hydroxylation of coumarin. Neither FF nor FFA was found to be inhibitory toward CYP3A, CYP2D6, CYP1A2, or CYP2E1 dependent metabolism in human microsomes.

Study two results showed that concomitant administration of FF and pravastatin (PS) had no effect on the C_{max} and AUC of FFA, and minimal effect on PS C_{max} and AUC. Both FFA and PS T_{max} values were statistically different ($p < 0.05$) between drug-alone and concomitant drug administration regimens. Furthermore, the C_{max} and $AUC_{0-\infty}$ values for the 3-α-hydroxy isomeric pravastatin metabolite were increased to a statistically significant extent after a single dose of FF and PS.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed supplement 005 of NDA 19-304 submitted 30-JUN-99. The overall Clinical Pharmacology and Drug Interactions Sections are acceptable to OCPB provided that the indicated labeling changes are made. Please convey ***Comments to Firm*** and ***Labeling Comments*** to the sponsor as appropriate. NDA 19-304 is approvable.

Table of Contents

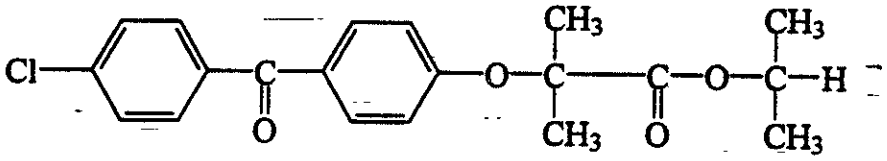
Protocol Index

Study Number	Study Title	Page
R&D/98/683	Effect of Abbott-52799 (fenofibrate) and fenofibric acid on cytochrome P450 selective enzyme activities in human liver microsomes.	11
M98-898	An assessment of the pharmacokinetic interaction between fenofibrate and pravastatin.	12

Background

Fenofibrate is a third generation fibric acid derivative that was approved by the FDA in 1993 for hypertriglyceridemia in patients at risk for pancreatitis. Fibric acid derivatives, including gemfibrozil, clofibrate, and fenofibrate, are generally effective in reducing triglyceride-rich lipoproteins and in increasing high-density lipoprotein cholesterol (HDL-C). Pharmacological effects are mediated by activation of peroxisome proliferator activated receptors that induce lipoprotein lipase, induce hepatic fatty acid uptake, reduce hepatic triglyceride production, reduce cholesteryl ester and triglyceride exchange, and increase HDL-production and stimulate reverse cholesterol transport. In addition, fenofibrate is thought to decrease total cholesterol and low-density lipoprotein cholesterol (LDL-C) in patients with hypercholeserolemia. The mechanism by which fenofibrate lowers LDL-C is through induction of small, dense, atherogenic forms to larger, less dense particles which appear to be more resistant to oxidation.

The chemical structure is shown below. Fenofibrate ($C_{20}H_{21}O_4Cl$) is a white solid with a molecular weight of 360.83, and insoluble in water. The melting point is 79-82 °C and is stable under ordinary conditions.



Bioequivalence

Has bioequivalence been established between three 67 mg capsules and one 200 mg capsule?

Dosage form equivalence between three 67 mg capsules and one 200 mg capsule was established and approved by the Agency on 05-MAY-99 for NDA 19-304, supplement 003. A bioequivalence study was conducted in 31 healthy male and female subjects under fed conditions (standardized breakfast – total fat calories = 30%) comparing the two dosage forms – review by Hae-Young Ahn, Ph.D. Results of this study support the proposed labeling as stated under Pharmacokinetics/Metabolism: "Three capsules containing TRICOR are bioequivalent to a single 200 mg TRICOR capsule."

Drug Interactions

In Vitro

What effects do fenofibrate and fenofibric acid have on selected cytochrome P450-dependent enzyme activities *in vitro*?

Inhibitory effects of fenofibrate and fenofibric acid on cytochrome P450-dependent enzyme activities were studied to evaluate the potential for CYP450 metabolism-based drug interactions. Inhibition study results (Table 1) show that there is a mild-to-moderate inhibition of isoform CYP2C9 and mild inhibition of CYP2C19 and CYP2A6.

CYP2C9 enzyme activity, in the presence of 20 µM fenofibrate and fenofibric acid, was 81.7% and 78.8% of control, respectively, and 42.0% and 32.6% of control at 200 µM. Further examination of both compounds, at concentrations of 1 to 400 µM (Plot 1), shows inhibition of CYP2C9 enzyme activity in a concentration-dependent manner. Findings indicate that the inhibitory concentration, which results in a 50% inhibition of enzyme activity (IC_{50}), were 127 µM for fenofibrate and 139 µM for fenofibric acid. Because the average therapeutic plasma concentration for both compounds is 20 to 30 µM, it would appear that metabolism-based drug interactions would not occur with other drugs via this pathway. However, there is a documented drug interaction between fibrate derivatives and warfarin, that potentiates the anticoagulant effect of warfarin. Because warfarin is a CYP2C9 substrate, has a narrow therapeutic range, and there is evidence to suggest a drug interaction between fibrates and warfarin, further *in vitro* studies are warranted.

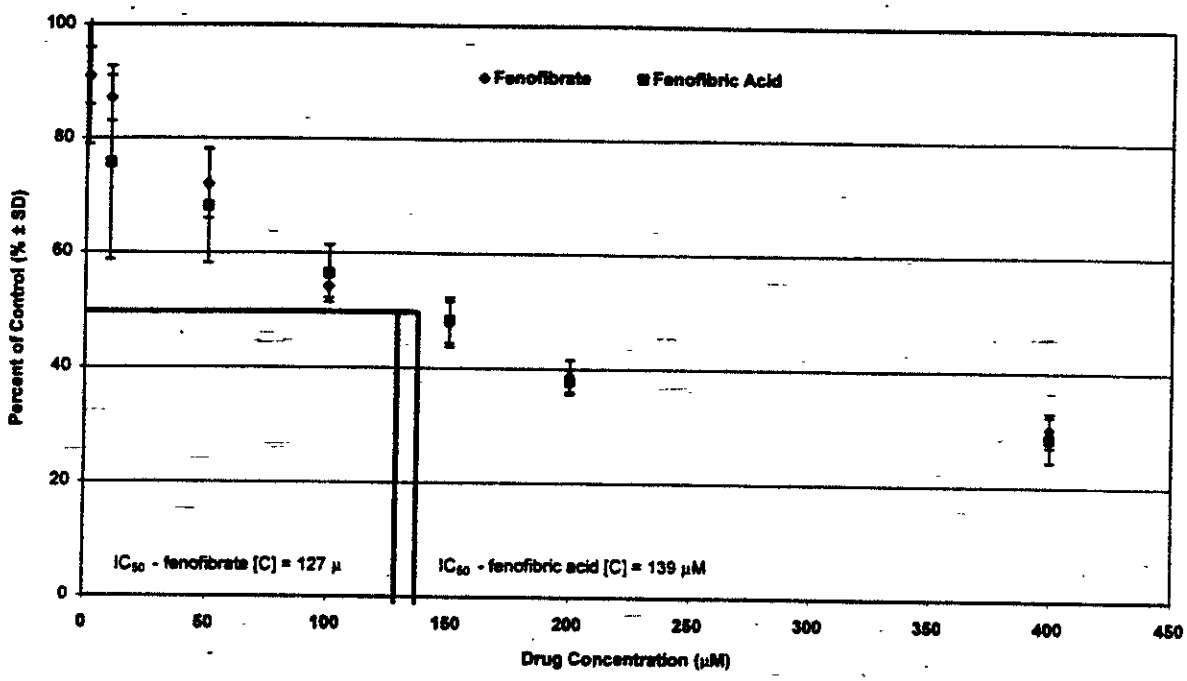
The mild inhibition of CYP2C19 and CYP2A6 enzymes are not likely to be clinically relevant, as the fenofibric acid concentrations necessary to cause inhibition are 8 to 10 times higher than is seen clinically. No inhibition was observed with CYP3A, CYP2D6, CYP1A2, or CYP2E1 dependent-metabolism in human microsomes.

Table 1: Effect of Tricor™ on CYP-Selective Enzyme Activities

CYP	Fenofibrate		Fenofibric Acid	
	20 µM	200 µM	20 µM	200 µm
	Percent of Control Activity			
1A2	99.9 ± 1	114.8 ± 18	101.6 ± 2	110.5 ± 23
2A6	[illegible]	[illegible]	90.1 ± 3	85.5 ± 1
2C9	[illegible]	[illegible]	78.8 ± 10	[illegible]
2C19	[illegible]	[illegible]	88.0 ± 2	[illegible]
2D6	101.0 ± 1	100.8 ± 3	102.8 ± 3	100.9 ± 3
2E1	95.7 ± 6	92.6 ± 3	98.5 ± 1	98.3 ± 10
3A4	97.3 ± 1	102.4 ± 2	96.0 ± 5	103.3 ± 3

Mean ± SD

Plot 1: Concentration-Dependent Effect of Fenofibrate and Fenofibric Acid on the CYP2C9-Dependent Methylhydroxylation of Tolbutamide in Human Liver Microsomes



Assay Validation

In Vivo

Does a drug interaction exist between fenofibrate and HMG-CoA reductase inhibitors?

Twenty-three healthy subjects were given three 67 mg fenofibrate capsules, three 67 mg fenofibrate capsules plus one 40 mg pravastatin tablet, or one 40 mg pravastatin tablet (regimens A, B, and C, respectively) in a three-period, single-dose, crossover study. Subjects were administered treatment doses 30 minutes following a standardized breakfast. Each treatment was separated by a 14-day washout period. Sixteen fenofibric acid blood samples were taken over 120 hours post dosing for each period. Twelve blood measurements were taken for both pravastatin and 3α-hydroxy iso-pravastatin over 24 hours post dosing.

Results indicate that there was a statistically significant reduction in fenofibric acid T_{max} (4.4 ± 1.4 hours versus 3.9 ± 1.0 hours) between regimens A and B, however, there were no changes in respective C_{max} or AUC values. Similarly, pravastatin T_{max} values were significantly increased between regimens C and B (1.4 ± 0.5 hours versus 1.8 ± 0.6 hours). Again, there were no significant changes in respective C_{max} or AUC values, though these parameters were increased by 11% and 13%, respectively. In contrast, the C_{max} and AUC values for the 3-α-hydroxy isomeric-pravastatin metabolite were significantly ($p < 0.05$) increased. AUC increased by approximately 30-percent and C_{max} increased by 28% after concomitant administration of fenofibrate and pravastatin, compared to pravastatin alone. Pharmacokinetic parameter estimates and corresponding 90% confidence intervals are presented in tables 3 and 4.

Table 3: Summary of BA Data – Fenofibrate versus Pravastatin

PK Parameter	Fenofibric Acid		Pravastatin		3-α-hydroxy iso-pravastatin	
	Treatment		Treatment		Treatment	
	A	B	C	B	C	B
T_{max} (h)	4.4 ± 1.4	3.9 ± 1.0*	1.4 ± 0.5	1.8 ± 0.6*	1.7 ± 0.5	1.9 ± 0.6
C_{max}[1]	9.49 ± 2.56	9.24 ± 2.06	35.20 ± 20.67	42.33 ± 28.00	36.66 ± 21.13	44.75 ± 22.12*
AUC_{0-t}[2]	147.5 ± 53.4	144.8 ± 46.3	68.6 ± 35.5	83.7 ± 53.3	75.0 ± 43.9	90.7 ± 43.4*
$AUC_{0-\infty}$[2]	149.1 ± 54.4	146.8 ± 47.5	71.2 ± 36.5	87.0 ± 53.6	77.0 ± 44.2	93.0 ± 43.9*
$t_{1/2}$ (h)[3,4]	17.8 ± 3.8	18.2 ± 3.9	1.6 ± 0.9	1.8 ± 1.0	1.2 ± 0.5	1.2 ± 0.5
Cl/F (L/h)	1.5 ± 0.5	1.5 ± 0.5	800.0 ± 611.6	774.1 ± 708.05	N/A	N/A

Mean ± SD
[1] fenofibric acid = µg/mL; pravastatin and metabolite = ng/mL
[2] fenofibric acid = µg-h/mL; pravastatin and metabolite = ng-h/mL
[3] Harmonic mean ± pseudo standard deviation
[4] Evaluations of $t_{½}$ were based on statistical tests for β
* Statistically different ($p < 0.05$)

Treatments:
A = 201 mg fenofibrate* capsules
B = 201 mg fenofibrate* plus 40 mg pravastatin
C = 40 mg pravastatin
* (201 mg = 3 x 67 mg capsules)

Treatment Comparison	Measure	Parameter	Point Estimate*	CI (low)	CI (high)
B vs. A	Fenofibric acid	C_{max}	97.5	87.8	108.6
		$AUC_{0-\infty}$	99.4	93.1	106.0
B vs. C	Pravastatin	C_{max}	113.0	85.4	149.6
		$AUC_{0-\infty}$	112.9	91.2	139.7
B vs. C	3-α-hydroxy iso-pravastatin	C_{max}	129.1	103.3	161.3
		$AUC_{0-\infty}$	126.4	101.9	156.8

* Antilogarithm of the difference of the least squares mean for logarithms

Reviewer Conclusions

A) Fenofibrate appears to inhibit CYP2C9 at mild to moderate effect levels.
- Caution must be used when IC_{50} is the sole measure for determining enzyme inhibition, because it is dependent upon the substrate concentration. Different levels of substrate concentration can yield changing results, perhaps leading to spurious assumptions. Therefore, definite conclusions regarding Tricor™'s potential to cause metabolism-based drug interactions with other drugs whose clearance is mediated primarily by CYP2C9 metabolism

cannot be made with definite assurance. Furthermore, warfarin, a widely used narrow therapeutic index agent, is metabolized via CYP2C9. Additional in vitro enzyme activity studies with S-warfarin (active isomer) should be considered.

B) A drug interaction does exist between fenofibric acid and the pravastatin metabolite.
- The relative potency of 3-α-hydroxy iso-pravastatin is approximately one-tenth to one-fortieth that of pravastatin. Therefore, it is unlikely that this drug-metabolite interaction is clinically significant. These results are consistent with those seen between gemfibrozil and pravastatin.
- However, because of the potential serious adverse drug reactions (ADRs) associated with these two classes of drugs, myopathy and rhabdomyolysis, and the fact that the mechanism of these ADRs have yet to be identified, labeling changes are not warranted.

Labeling Comments

(Where applicable, ~~strikeout~~ text should be removed from labeling. Double underlined text should be added to labeling. ☙ Indicates an explanation only and is not intended to be included in the labeling).

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 TRICOR are bioequivalent to a single 200 mg TRICOR capsule.

☙ These changes are acceptable. Bioequivalence between the micronized and non-micronized formulation was established in the original NDA, 19-304. Dosage-form equivalence between 67 mg and 200 mg capsules was established in supplement 003.

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

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

In vivo metabolism data indicate that neither fenofibrate or fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

☙ This claim is substantiated in the following citation: Weil A, Caldwell J, Strolin-Benedetti M. The metabolism and disposition of ^{14}C-fenofibrate in human volunteers. *Drug Metab Dispos.* 1987;18(1):115-120. Metabolites of this study include fenofibric acid, the benzhydrol, and their ester glucuronides.

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

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

- This clarification is acceptable.

Special Populations

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

- Wording is changed to reflect the FDA's more recent language used for the pediatrics subheading.

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.

- Acceptable

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

- The grammatical correction is acceptable.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2, weakly inhibited CYP2C19- and CYP2A6-dependent metabolism, and exhibited a mild-to-moderate inhibition of CYP2C9-dependent metabolism at therapeutic concentrations.

- Further *in vitro* drug interaction studies using S-warfarin should be completed.

Concomitant HMG-CoA reductase inhibitors: The combined use of TRICOR 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.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, 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 language used in this section is misleading and has an overtone that suggests that the combinations of Tricor™ and HMG-CoA reductase inhibitors are not associated with rhabdomyolisis – see Medwatch report # 1973813 (MFR Report #: B032673). In addition, the short-term studies, cited as the basis for these labeling additions, are not sufficient. In many of these studies, either low doses of HMG-CoA reductase inhibitor or fibrate derivative was used, or the concomitant agents were given in a manner which would decrease the bioavailability of one of the agents. Finally, results of the *in vivo* study submitted in this application shows increased parent pravastatin concentrations and statistically significant differences in C_{max} and AUC values for the pravastatin metabolite when administered with Tricor™. However, this was only a single dose study and "clinical significance" may be understated.

Drug Interactions
Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

- The position does not seem to be changed.

HMG-CoA reductase inhibitors: The combined use of TRICOR 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 (see WARNINGS).

- Changes are acceptable.

Comments to the Firm

In a teleconference held on 24-MAR-2000 the following topics were discussed: the use of the term "mild-to-moderate inhibition" in describing the *in vitro* CYP2C9 results and whether or not additional drug interaction studies were necessary. It has been concluded by the agency that the phrasing of the **Drug Interaction** section be revised as presented by the agency, and that further drug interaction studies are not necessary if the labeling changes are made.

Steven B. Johnson, B.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 07-MAR-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: _ /S/ 3/24/00

CC: NDA 19-304 (orig., 1 copy), HFD-510 (ParksM), HFD-850 (LeskoL), HFD-870 (HuangS, AhnH, JohnsonST), CDR

Code: AP

APPEARS THIS WAY
ON ORIGINAL

2.0 Study Synopsis

Abbott Laboratories	*(For National Authority Use Only):*
Investigational Products: Fenofibrate (Tricor™) and Pravastatin (Pravachol®)	
Active Ingredient: Fenofibric acid and pravastatin	**Phase of Development:** Phase I

Title of Study: An Assessment of the Pharmacokinetic Interaction between Fenofibrate and Pravastatin

Investigator(s): [redacted]

Study Site(s): [redacted]

Publication (reference): N/A

Studied Period: 44 days

Study Day -1 (day prior to first dose): August 10, 1998

Date of last dose administration: September 8, 1998

Date of last scheduled study procedure: September 13, 1998

Objective: To evaluate the potential pharmacokinetic interaction between fenofibrate and pravastatin.

Study Design: Single-dose, open-label, randomized, three-period, crossover, single-center study. The doses in the consecutive periods were separated by 14 days.

Subjects receiving Regimen A (fenofibrate alone) and Regimen B (fenofibrate and Pravachol concurrently) were confined to the research unit for approximately 7 days in each period. Subjects receiving Regimen C (Pravachol alone) were confined to the research unit for approximately 2 days in each period.

Number of Subjects: Planned: 24 Entered: 23 Completed: 23 Evaluated for Safety: 23 Evaluated for Pharmacokinetics: 23

Diagnosis and Main Criteria for Inclusion: Men and women in general good health between 18 and 50 years of age, inclusive. Women were postmenopausal, sterile, or if of child-bearing potential, were not nursing, and were practicing birth control.

Investigational Products: Fenofibrate (Tricor) and pravastatin (Pravachol)

Dose/strength/concentration: Three 67-mg fenofibrate capsules (Regimen A)
Three 67-mg fenofibrate capsules plus one 40-mg Pravachol tablet (Regimen B)
One 40-mg Pravachol tablet (Regimen C)

Mode of administration: oral

Lot numbers: Fenofibrate: Bulk Lot No. 38-003-3T-21; Finishing Lot No. 43-553-S2
Pravachol: D8J054A

Duration of treatment: Each subject was dosed once on Study Day 1 of each of the three study periods.

Criteria for Evaluation:

Pharmacokinetics: Maximum plasma-concentration (C_{max}), time to C_{max} (T_{max}), terminal phase elimination rate constant (β) and the corresponding half-life ($t_{1/2}$), and area under the plasma concentration-time curve (AUC) were determined for fenofibric acid, pravastatin and the 3α-hydroxy isomeric metabolite of pravastatin.

Safety: Adverse events assessment, vital signs measurements, laboratory tests assessment.

Statistical Methods: Analyses of variance (ANOVAs) with fixed effects for period, regimen, and regimen of the preceding period, and a random effect for subject were performed for T_{max}, β, C_{max} and the natural logarithms of AUC_{0-t} and $AUC_{0-\infty}$ of fenofibric acid. Since this analysis did not give evidence of an effect of the regimen of the preceding period, the final analysis was performed with this factor removed from the model. For C_{max} and $AUC_{0-\infty}$, within the framework of the final analysis, a 95% confidence interval was obtained for the bioavailability of Regimen B relative to that of Regimen A.

The same analyses were performed for T_{max}, β and the natural logarithms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of pravastatin and the 3α-hydroxy isomeric metabolite. Within the framework of the ANOVA of the natural logarithms of C_{max} and $AUC_{0-\infty}$ for pravastatin and the 3α-hydroxy isomeric metabolite, a 95% confidence interval was obtained for the bioavailability of Regimen B relative to that of Regimen C.

Summary:

Pharmacokinetic results:

Fenofibric acid - A summary (mean ± SD) of the pharmacokinetic parameters of fenofibric acid is presented in the following table.

Pharmacokinetic Parameter	Regimen£ A (N = 23)	Regimen£ B (N = 23)
T_{max} (h)	4.4 ± 1.4	3.9 ± 1.0*
C_{max} (µg/mL)	9.49 ± 2.56	9.24 ± 2.06
AUC_{0-t} (µg*h/mL)	147.5 ± 53.4	144.8 ± 46.3
$AUC_{0-\infty}$ (µg*h/mL)	149.1 ± 54.4	146.8 ± 47.5
$t_{1/2}$ (h)‡,$	17.8 ± 3.8	18.2 ± 3.9
CL/F (L/h)†	1.5 ± 0.5	1.5 ± 0.5

£ Regimen A: 3 x 67 mg fenofibrate capsule.
Regimen B: 3 x 67 mg fenofibrate capsule plus 1 x 40 mg Pravachol tablet.
‡ Harmonic Mean ± Pseudo Standard Deviation.
$ Evaluations of $t_{1/2}$ were based on statistical tests for β.
† Parameter was not tested statistically.
* Statistically significantly different ($p < 0.05$) from Regimen A.

The mean T_{max} of fenofibric acid was statistically significantly ($p < 0.05$) shorter with Regimen B compared with the T_{max} with Regimen A. The mean C_{max} and $AUC_{0-\infty}$ values of fenofibric acid did not differ significantly between the two regimens.

The 95% confidence intervals and the point estimates for relative bioavailability of fenofibric acid are shown in the following table.

Regimen Comparison£	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate	95% Confidence Interval
B vs. A	C_{max}	0.975‡	0.878 - 1.086
B vs. A	$AUC_{0-\infty}$	0.994$	0.931 - 1.060

£ Regimen A: 3 x 67 mg fenofibrate capsule.
Regimen B: 3 x 67 mg fenofibrate capsule plus 1 x 40 mg Pravachol tablet.
‡ Ratio (B vs. A) of the least squares means.
$ Antilogarithm of the difference (B minus A) of the least squares means for logarithms.

The point estimates indicate that the differences between the central values for C_{max} and $AUC_{0-\infty}$ between Regimen A and Regimen B were less than 5%. The confidence intervals consisted of a narrow range close to 1.0, showing that any interaction effect was quite small.

Pravastatin - A summary (mean ± SD) of the pharmacokinetic parameters of pravastatin is presented in the following table.

Pharmacokinetic Parameter	Regimen£	
	B (N = 23)	C (N = 23)
T_{max} (h)	1.8 ± 0.6*	1.4 ± 0.5
C_{max} (ng/mL)	42.33 ± 28.00	35.20 ± 20.67
AUC_{0-t} (ng*h/mL)	83.7 ± 53.3	68.6 ± 35.5
$AUC_{0-\infty}$ (ng*h/mL)	87.0 ± 53.6	71.2 ± 36.5
$t_{1/2}$ (h)‡,$	1.8 ± 1.0	1.6 ± 0.9
CL/F (L/h)†	774.1 ± 708.5	800.0 ± 611.6

£ Regimen B: 3 x 67 mg fenofibrate capsule plus 1 x 40 mg Pravachol tablet.
Regimen C: 1 x 40 mg Pravachol tablet.
‡ Harmonic Mean ± Pseudo Standard Deviation.
$ Evaluations of $t_{1/2}$ were based on statistical tests for β.
† Parameter was not tested statistically.
* Statistically significantly different ($p < 0.05$) from Regimen C.

Except for T_{max}, no tested pharmacokinetic parameters of pravastatin were statistically significantly different ($p>0.05$) between Regimens B and C.

The 95% confidence intervals and the point estimates for relative bioavailability of pravastatin are shown in the following table.

Regimen Comparison£	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate*	95% Confidence Interval
B vs. C	C_{max}	1.130	0.854 - 1.496
B vs. C	$AUC_{0-\infty}$	1.129	0.912 - 1.397

£ Regimen B: 3 x 67 mg fenofibrate capsule plus 1 x 40 mg Pravachol tablet
Regimen C: 1 x 40 mg Pravachol tablet
* Antilogarithm of the difference (B minus C) of the least squares means for logarithms.

The point estimates indicate that the central values for pravastatin C_{max} and $AUC_{0-\infty}$ were about 13% higher with Regimen B than those with Regimen C. The ranges of values covered by the confidence intervals were not expected to be associated with clinically important differences.

3α-hydroxy isomeric metabolite of pravastatin - A summary (mean ± SD) of the pharmacokinetic parameters of the 3α-hydroxy isomeric metabolite of pravastatin is presented in the following table.

Pharmacokinetic Parameter	Regimen£	
	B (N = 23)	C (N = 23)
T_{max} (h)	1.9 ± 0.6	1.7 ± 0.5
C_{max} (ng/mL)	44.75 ± 22.12*	36.33 ± 21.13
AUC_{0-t} (ng*h/mL)	90.7 ± 43.4*	75.0 ± 43.9
$AUC_{0-\infty}$ (ng*h/mL)	93.0 ± 43.9*	77.0 ± 44.2
$t_{1/2}$ (h)‡,$	1.2 ± 0.5	1.2 ± 0.5

£ Regimen B: 3 x 67 mg fenofibrate capsule plus 1 x 40 mg Pravachol tablet
Regimen C: 1 x 40 mg Pravachol tablet
‡ Harmonic Mean ± Pseudo Standard Deviation.
$ Evaluations of $t_{1/2}$ were based on statistical tests for β.
* Statistically significantly different ($p < 0.05$) from Regimen C.

The C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values of the 3α-hydroxy isomeric metabolite were statistically significantly ($p < 0.05$) higher after concurrent administration of fenofibrate and Pravachol (Regimen B) compared to those after administration of Pravachol alone (Regimen C). The mean T_{max} did not differ significantly between the two regimens.

The 95% confidence intervals and point estimates for relative bioavailability of the 3α-hydroxy isomeric metabolite of pravastatin are shown in the following table.

Regimen Comparison£	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate*	95% Confidence Interval
B vs. C	C_{max}	1.291	1.033 - 1.613
B vs. C	$AUC_{0-\infty}$	1.264	1.019 - 1.568

£ Regimen B: 3 x 67 mg fenofibrate capsule plus
1 x 40 mg Pravachol tablet
Regimen C: 1 x 40 mg Pravachol tablet
* Antilogarithm of the difference (B minus C) of the least squares means for logarithms.

The point estimates indicate that the central values for C_{max} and $AUC_{0-\infty}$ of the 3α-hydroxy isomeric metabolite were respectively 29% and 26% higher with Regimen B than those with Regimen C. However, the confidence intervals also show that the interaction effect would not be expected to be of clinical importance in view of the relatively small pharmacological potency of the metabolite. The confidence intervals did not extend to values of concern.

Safety results:

Nine treatment-emergent adverse events were reported during the study by six subjects. None of the adverse events was rated as severe. Eight adverse events were judged by the investigator to be possibly related and one to be probably not related to the study drug. The most frequently reported adverse event was headache: two subjects (8.7%) after administration of fenofibrate (Regimen A); four subjects (17.4%) after concurrent administration of fenofibrate and Pravachol (Regimen B); and two subjects (8.7%) after administration of Pravachol (Regimen C).

There were no clinically significant changes in clinical laboratory evaluations, vital signs or physical examination findings during the study.

Conclusions:

Concurrent administration of fenofibrate and Pravachol had little or no effect on the pharmacokinetics of either fenofibric acid or pravastatin. While the C_{max} and $AUC_{0-\infty}$ central values of the 3α-hydroxy isomeric metabolite were statistically significantly increased, the modest increase (less than 30%) in the formation of this metabolite of pravastatin is not expected to be clinically significant. Both fenofibrate and Pravachol were generally well tolerated by the subjects when given as single compounds and in combination.

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