

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-656

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

8/4/04

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW

NDA: 21-656	Submission Date(s): October 29, 2003; June 1, 2004; July 7, 2004
Brand Name	Tricor®
Generic Name	Fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Abbott
Submission Type	Original
Formulation; Strength(s)	Oral tablets; 48 and 145 mg
Indication	Type II, IV, and V hypercholesterolemia

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1 Executive Summary

On October 29, 2003, Abbott Laboratories submitted an original NDA for Tricor® — a new formulation and dosage strength, fenofibrate tablets, 48 mg and 145 mg. Tricor® — is indicated for the treatment of Types IIa, IIb, IV and V hyperlipidemia as described in the labeling for the currently marketed formulation for Tricor®.

The Clinical Pharmacology section contains one pivotal BE study (M02-558), one pivotal (KLF 178P 02 06 KH) and one pilot (K 178P 02 05 KH) food effect studies, drug interaction studies with pravastatin (M02-514) and atorvastatin (K 178 02 01 KH).

CPB Briefing was held on Aug. 2, 2004.

Attendees: Hank Malinowski, John Hunt, Mary Parks, Hae-Young Ahn, and Wei Qiu.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-656 submitted on October 29, 2003, June 1, 2004, and July 7, 2004, and finds it acceptable except the dissolution method and specification. The following dissolution method and specification are recommended. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

Dissolution Method and Specification:

Medium: 25 mM sodium lauryl sulfate (SLS)

Apparatus: USP Apparatus 2

Agitation: ---

Specification: Not less than --- (Q) in 30 minutes

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability of Tricor® — Fenofibrate Tablets Compared to Tricor® micronized capsule:

Relative bioavailability of Tricor® — fenofibrate tablets (one 145 mg or three 48 mg) was compared to Tricor® micronized fenofibrate capsule (200 mg) under low-fat fed condition. Tricor® fenofibrate tablets (one 145 mg or three 48 mg) were found to be bioequivalent to Tricor® micronized fenofibrate capsule (one 200 mg).

Ratios (Tricor® — fenofibrate tablet 1 x 145 mg / Tricor® micronized fenofibrate capsule 1 x 200 mg) of least-square means for AUC_{∞} and C_{max} of fenofibric acid were 86.2% and 100.8%, respectively. Ratios (Tricor® — fenofibrate tablet 3 x 48 mg / Tricor® micronized fenofibrate capsule 1 x 200 mg) of least-square means for AUC_{∞} and C_{max} of fenofibric acid were 86% and 97.9%, respectively. The 90% confidence intervals of AUC_{∞} and C_{max} ratios were within the range of 80% - 125%.

Food Effect on bioavailability of Tricor® — fenofibrate tablets

The absence of food effect on the bioavailability of Tricor® — fenofibrate tablet 145 mg was demonstrated. Ratios (High-fat fed / fasting) of least-square means for AUC_{∞} and C_{max} of fenofibric acid were 105.2% and 100.7%, respectively. Ratios (Low-fat fed / fasting) of least-square means for AUC_{∞} and C_{max} of fenofibric acid were 101.2% and 100.9%, respectively. The 90% confidence intervals of AUC_{∞} and C_{max} ratios were within the range of 80% - 125%.

Effect of Multiple Dose of Fenofibrate on Pravastatin

Co-administration of 160-mg fenofibrate tablet once daily for 10 days increased pravastatin steady state C_{max} and AUC values by 36% and 28%, respectively.

Drug Interaction with Atorvastatin

Co-administration of 160-mg fenofibrate tablet once daily for 10 days decreased steady-state atorvastatin AUC values 17% but did not affect the C_{max} values. Steady-state AUC or C_{max} values of fenofibric acid were not affected upon co-administration of 20-mg atorvastatin once daily for 10 days.

2 Question Based Review

2.1 General Attributes

Q. What is the formulation of the to-be-marketed drug product?

The quantitative compositions of the 48 mg and 145 mg tablets are shown in Table 1. The tablets were formulated to be exact weight multiples with respect to fenofibrate and major excipients. This formulation was developed with the NanoCrystal® technology, which uses a particle size _____ process for the preparation and formulation of nanoparticles of poorly water-soluble pharmaceuticals. This has resulted in a tablet containing nanoparticles of fenofibrate. The mean particle size of the drug substance in the tablet is maintained below _____ throughout the manufacturing process. This particle size is between _____ the drug substance particle size in the marketed Tricor® tablets.

Table 1. Quantitative Composition of Tricor® 48 mg and 145 mg tablets

Component	Amount (mg/48 mg tablet)	Amount (mg/145 mg tablet)
Fenofibrate	48.0	145.0
Hypromellose		
Docusate Sodium		
Sucrose		
Sodium Lauryl Sulfate		
Lactose Monohydrate		
Silicified Microcrystalline Cellulose		
Crospovidone		
Magnesium Stearate		
Total Weight	217.2	651.6

2.2 General Clinical Pharmacology

Not applicable.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Q. Does food affect the bioavailability of Tricor® 145 mg?

Food exhibited no effect on the bioavailability of Tricor® 145 mg.

The effect of food on the bioavailability of fenofibric acid from a 145 mg tablet was examined in study KLF 178P0206 KH. This was an open-label, single-dose, randomized, three-way, crossover study in healthy subjects. Forty-five volunteers were recruited and 44 subjects completed all treatments. Subjects received the following regimens in a randomized order:

Regimen A: a 145 mg tablet given under high-fat fed condition (HFF)

Regimen B: a 145 mg tablet given under low-fat fed condition (LFF)

Regimen C: a 145 mg tablet given under fasting condition

Pharmacokinetic parameters of fenofibric acid are summarized in Table 2. Study results showed that the AUC_t, AUC_∞, C_{max}, and T_{1/2} values obtained following the different regimens were comparable. However, the T_{max} values were prolonged from 2.33 hours under fasting condition to 3.56 hours and 4.27 hours under LFF and HFF conditions, respectively.

Table 2. Summary Statistics of PK Parameters of Fenofibric Acid (n=44)

PK Parameters		Regimen A HFF (n = 44)	Regimen B LFF (n = 44)	Regimen C Fasting (n = 44)
AUC _∞ (µg/mL.h)	Arithmetic mean ± SD CV %	129.9 ± 36.4 28	125.1 ± 35.8 29	123.8 ± 35.7 29
AUC _t (µg/mL.h)	Arithmetic mean ± SD CV %	127.9 ± 35.4 28	123.2 ± 35.0 28	121.6 ± 34.2 28
C _{max} (µg/mL)	Arithmetic mean ± SD CV %	7.96 ± 1.47 18	7.96 ± 1.43 18	7.94 ± 1.59 20
T _{max} (h)	Arithmetic mean ± SD CV %	4.27 ± 1.94 45	3.56 ± 1.18 33	2.33 ± 0.73 31
t _{1/2} (h)	Arithmetic mean ± SD CV % Harmonic mean	17.8 ± 4.1 23 16.8	18.7 ± 3.7 20 18.0	18.9 ± 4.7 25 17.9

Bioequivalence tests were conducted with AUC_∞, AUC_t and C_{max} values (Tables 3 and 4). The absence of food effect has been demonstrated as the 90% confidence intervals for the ratio of geometric means of AUC_∞, AUC_t, and C_{max} for HFF (Regimen A) or LFF (Regimen B) versus fasting (Regimen C) fell within the bioequivalence limit of 0.80 - 1.25.

Table 3. Comparison of HFF (Regimen A) versus Fasting (Regimen C) (n=44)

Parameter	Geometric Mean ^a HFF (Regimen A)	Geometric Mean ^a Fasting (Regimen C)	Point Estimate ^b	90% CI
AUC _∞	124.8	118.5	1.052	1.018 - 1.088
AUC _t	123.0	116.5	1.054	1.020 - 1.090
C _{max}	7.82	7.77	1.007	0.963 - 1.054

a Population geometric mean based on log-transformed data.

b Ratio A/C of geometric least square means.

Table 4. Comparison of LFF (Regimen B) versus Fasting (Regimen C) (n=44)

Parameter	Geometric Mean ^a LFF (Regimen B)	Geometric Mean ^a Fasting (Regimen C)	Point Estimate ^b	90% CI
AUC _∞	119.8	118.5	1.012	0.978 - 1.046
AUC _t	118.1	116.5	1.013	0.981 - 1.047
C _{max}	7.84	7.77	1.009	0.964 - 1.055

a Population geometric mean based on log-transformed data.

b Ratio B/C of geometric least square means.

Q. What is the effect of multiple doses of fenofibrate on the multiple-dose pharmacokinetics of pravastatin in healthy subjects?

Co-administration of 160 mg fenofibrate tablets for 10 days increased pravastatin C_{max} and AUC values by 36% and 28%, respectively.

The effect of multiple doses of fenofibrate on the multiple-dose pharmacokinetics of pravastatin was evaluated in study M02-514 in healthy subjects under low-fat fed conditions. Twenty-four subjects were recruited and 23 subjects completed all treatments. This was a multiple-dose, open-label study conducted according to a sequential design. All subjects took pravastatin (one 40 mg tablet QD) in the mornings of study Days 1 through 15. Fenofibrate (one 160 mg tablet QD) (Lipidil-Ter™) was co-administered with the pravastatin in the mornings of Study Days 6 through 15. The pharmacokinetic parameters of pravastatin and its metabolite 3 α -hydroxy-iso-pravastatin are summarized in Table 5.

Table 5. Mean \pm Standard Deviation (SD) Pharmacokinetic Parameters of Pravastatin and 3 α -hydroxy-iso-pravastatin

Pharmacokinetic Parameters (units)		Pravastatin Alone	Pravastatin with Single	Pravastatin with
		(Study Day 5)	Dose Fenofibrate	Multiple Dose
		(N = 24)	(Study Day 6)	Fenofibrate
			(N = 24)	(Study Day 15)
				(N = 23)
Pravastatin				
T _{max}	(h)	1.8 \pm 0.4	2.0 \pm 0.7	1.7 \pm 0.5
C _{max}	(ng/mL)	24.8 \pm 16.7	33.4 \pm 29.7	34.2 \pm 24.3*
AUC ₂₄	(ng•h/mL)	61.0 \pm 33.7	76.2 \pm 54.7*	79.8 \pm 50.7*
t _{1/2} ^g	(h)	2.31	2.07*	2.09
CL/F [†]	(L/h)	901 \pm 533	781 \pm 531	707 \pm 395
3α-Hydroxy-Iso-Pravastatin				
T _{max}	(h)	2.0 \pm 0.6	2.1 \pm 0.6	2.0 \pm 0.7
C _{max}	(ng/mL)	29.8 \pm 19.9	38.7 \pm 24.7	44.2 \pm 28.0*
AUC ₂₄	(ng•h/mL)	71.6 \pm 45.3	87.8 \pm 48.8	97.9 \pm 58.4*
t _{1/2} ^g	(h)	1.54	1.45	1.41

* Statistically significantly different from Study Day 5 (paired t-test, p < 0.050).

^g Harmonic mean; evaluations of t_{1/2} were based on statistical tests for λ_z .

[†] Parameter was not tested statistically.

Single and multiple doses of fenofibrate tended to increase C_{max} and AUC₂₄ values of both pravastatin and 3 α -hydroxy-iso-pravastatin while T_{max}, t_{1/2}, or CL/F were not affected. Statistical analysis was conducted for C_{max} and AUC₂₄ (Table 6). For pravastatin, single dose of fenofibrate increased C_{max} and AUC₂₄ 22% and 19%, respectively. Multiple doses of fenofibrate increased C_{max} and AUC₂₄ 36% and 28%, respectively. For 3 α -hydroxy-iso-pravastatin, single dose of fenofibrate increased C_{max} and AUC₂₄ 31% and 24%, respectively. Multiple doses of fenofibrate increased C_{max} and AUC₂₄ 55% and 39%, respectively. The metabolite 3 α -hydroxy-iso-pravastatin has 2.5 to 10% of the HMG-CoA reductase activity of the parent drug, pravastatin.

Analysis of pharmacokinetic parameters from individual subjects showed that the ratios of pravastatin AUC₂₄ and C_{max} values between Study Days 6 and 5 ranged from 0.77 to 2.20 and from 0.66 to 3.47, respectively. The ratios of pravastatin AUC₂₄ and C_{max} values between Study Days 15 and 5 ranged from 0.46 to 2.28 and from 0.31 to 4.21, respectively.

For 3 α -hydroxy-iso-pravastatin, the ratios of AUC and C_{max} values between Study Days 6 and 5 ranged from 0.28 to 4.22 and 0.30 to 6.04, respectively. The ratios of AUC₂₄ and C_{max} values between Study Days 15 and 5 ranged from 0.76 to 3.61 and 0.68 to 4.14, respectively.

Table 6. Point Estimates and 90% Confidence Intervals for the ratios of central values on Study Day 6 to those on Study Day 5, for Study Day 15 to those on Study Day 5 and for Study Day 15 to those on Study Day 6 for pravastatin and 3 α -hydroxy-iso-pravastatin C_{max} and AUC₂₄

Study Day Comparison	Pharmacokinetic Parameter	Central Values*		Relative Exposure	
		Test	Reference	Point Estimate [†]	90% Confidence Interval
Pravastatin					
6 vs. 5	C _{max}	24.69	20.26	1.219	1.011 – 1.470
	AUC ₂₄	62.20	52.22	1.191	1.060 – 1.338
15 vs. 5	C _{max}	27.60	20.29	1.360	1.108 – 1.670
	AUC ₂₄	66.69	52.22	1.277	1.092 – 1.493
15 vs. 6	C _{max}	27.60	24.90	1.108	0.889 – 1.382
	AUC ₂₄	66.69	62.88	1.061	0.903 – 1.245
3α-Hydroxy-Iso-Pravastatin					
6 vs. 5	C _{max}	31.02	23.74	1.307	1.040 – 1.641
	AUC ₂₄	72.38	58.27	1.242	1.027 – 1.502
15 vs. 5	C _{max}	36.96	23.91	1.546	1.290 – 1.853
	AUC ₂₄	82.43	59.37	1.389	1.195 – 1.613
15 vs. 6	C _{max}	36.96	33.32	1.109	0.927 – 1.328
	AUC ₂₄	82.43	78.63	1.048	0.889 – 1.236

* Geometric Mean.

† Antilogarithm of mean differences of logarithms.

Literature information with regards to the drug interactions between itraconazole or lopinavir/ritonavir with pravastatin suggested the inhibition of Pgp since itraconazole and lopinavir/ritonavir are Pgp inhibitors. Recently published pharmacogenetic data suggest that polymorphisms

pravastatin and 3 α -hydroxy-iso-pravastatin exposure observed in this study.

Q. What is the drug interaction between fenofibrate and atorvastatin in healthy male volunteers?

On average, a decrease in atorvastatin exposure of 17% in AUC values at steady state was observed upon co-administration of 160 mg fenofibrate tablet while no change in C_{max} values was seen. Neither AUC nor C_{max} of fenofibric acid was changed upon co-administration of 20 mg atorvastatin.

Potential pharmacokinetic drug interaction between fenofibrate and atorvastatin was evaluated in study K1780201KH in healthy male subjects. Twenty-four subjects were recruited and 22 subjects completed all treatments. This was a randomized, three-way crossover, multiple dose study. All subjects received 160 mg of fenofibrate (Lipanthyl®), 20 mg of atorvastatin (Tahor®), and the combination of both drugs in fed condition once daily on 10 consecutive days in a randomized manner. Dosing was performed in the evening after a dinner. The washout period between the treatment was 12 days.

Treatment A: Fenofibrate 160 mg tablet once daily in the evening on 10 consecutive days
 Treatment B: Atorvastatin 20 mg tablet, once daily in the evening on 10 consecutive days
 Treatment C: Fenofibrate 160 mg tablet and atorvastatin 20 mg tablet, once daily in the evening on 10 consecutive days.

In order to confirm the steady-state achievement, plasma levels before dosing on Days 8, 9, and 10 were determined for both fenofibric acid and atorvastatin. Irrespective of the treatment, mean pre-dose concentrations of fenofibric acid of about 4.5 µg/mL were determined on Days 8, 9, and 10 (Table 7). Following co-administration mean pre-dose concentration of atorvastatin were 0.53, 0.49, and 0.389 ng/mL on Days 8, 9 and 10, respectively (Table 8). Steady-state for both fenofibric acid and atorvastatin was achieved.

Table 7. Mean (SD) plasma fenofibric acid concentrations (µg/mL) obtained on Days 8, 9, and 10 after administration of 160 mg fenofibrate alone (Treatment A) and after co-administration of 160 mg fenofibrate plus 20 mg atorvastatin (Treatment C) in healthy male volunteers, in fed conditions

Plasma Fenofibric acid plasma concentrations (µg/mL)	Treatment A Fenofibrate alone (160 mg) N=22		Treatment C Fenofibrate (160 mg) + atorvastatin (20 mg) N=22	
	Mean	SD	Mean	SD
Day 8 before dosing	4.441	2.149	4.413	1.948
Day 9 before dosing	4.607	1.809	4.436	1.597
Day 10 before dosing	4.393	2.050	4.122	1.948

Table 8. Mean (SD) plasma atorvastatin concentrations (ng/mL) obtained on Days 8, 9, and 10 after administration of 20 mg atorvastatin alone (Treatment B) and after co-administration of 20 mg atorvastatin plus 160 mg fenofibrate (Treatment C) in healthy male volunteers, in fed conditions

Plasma Atorvastatin plasma concentrations (ng/mL)	Treatment B Atorvastatin alone (20 mg) N=22		Treatment C Atorvastatin (20 mg) + fenofibrate (160 mg) N=22	
	Mean	SD	Mean	SD
Day 8 before dosing	0.748	0.467	0.526	0.289
Day 9 before dosing	0.887	0.527	0.490	0.302
Day 10 before dosing	0.732	0.297	0.389	0.220

The pharmacokinetic parameters and statistical analysis results of fenofibric acid on Day 10 are presented in Tables 9 and 10, respectively. All evaluated pharmacokinetic parameters of fenofibric acid were not affected by co-administration of atorvastatin (20 mg once daily for 10 days)

Table 9. Pharmacokinetic Parameters of fenofibric acid obtained at steady-state on Day 10 after administration of 160 mg fenofibrate alone (treatment A) and after co-administration of 160 mg fenofibrate plus 20 mg atorvastatin (treatment C) in healthy male volunteers in fed conditions

Parameter	unit	Treatment A Fenofibrate alone (160 mg) N=22		Treatment C Fenofibrate (160 mg) + atorvastatin (20 mg) N=22	
		arithmetic mean	%CV	arithmetic mean	%CV
AUC _∞	h*µg/mL	175.54	33.96	172.15	36.96
AUC(0-4)	h*µg/mL	307.93	44.05	298.55	43.57
AUC(0-∞)	h*µg/mL	317.37	45.99	305.92	44.17
C _{max}	µg/mL	12.207	24.85	11.749	27.04
t _{max}	h	3.50	44.74	3.46	45.07
C _{min}	µg/mL	4.088	48.04	3.866	48.52
t _{1/2}	h	22.03	18.66	21.35	20.96
C _{trf}	µg/mL	7.31	33.96	7.17	36.96
PTF	%	118.91	27.50	117.45	24.70
CL _f	mL/min	14.82	31.16	15.32	32.85
V _d ^f	L	27.21	23.45	27.61	30.39

Table 10. Statistical Results

Parameter	Unit	Treatment A Fenofibrate alone	Treatment C Fenofibrate + Atorvastatin	Point estimate ratio C/A	90% Confidence Interval
		geom. mean	geom. mean		
AUC _∞	h*µg/mL	166.83*	162.35*	0.977*	0.92 : 1.04
C _{max}	µg/mL	11.88*	11.38*	0.96*	0.91 : 1.02
t _{10max}	h	3.0*	3.0*	±0*	-1 : +1
t _{1/2}	h	21.68*	20.96*	0.967*	0.92 : 1.01

*N = 22

The pharmacokinetic parameters and statistical analysis results of atorvastatin are presented in **Tables 11 and 12**, respectively. Co-administration with 160 mg fenofibrate tablets caused a decrease in atorvastatin exposure (AUC₀₋₂₄) of 17%.

Analysis of pharmacokinetic parameters from individual subjects showed that the ratios of atorvastatin AUC₀₋₂₄ and C_{max} values between co-administration with fenofibrate and administration alone ranged from 0.33 to 1.44 and 0.40 to 2.36, respectively.

Table 11. Pharmacokinetic parameters of atorvastatin obtained at steady-state on Day 10 after administration of 20 mg atorvastatin alone (treatment B) and after co-administration of 20 mg atorvastatin plus 160 mg fenofibrate (treatment C) in healthy male volunteers in fed conditions

Parameter	unit	Treatment B Atorvastatin alone (20 mg)		Treatment C Atorvastatin (20 mg) + fenofibrate (160 mg)	
		arithmetic mean	%CV	arithmetic mean	%CV
AUC _{ss}	h*ng/mL	41.51 (N=21)	53.54	34.40 (N=19)	40.91
AUC(0-24)	h*ng/mL	40.49 (N=22)	54.83	32.29 (N=22)	43.89
AUC(0-t _z)	h*ng/mL	49.53 (N=22)	55.28	34.62 (N=22)	48.22
AUC(0-∞)	h*ng/mL	64.92 (N=15)	42.35	46.60 (N=13)	39.21
C _{max}	ng/mL	4.657 (N=22)	65.95	4.248 (N=22)	39.52
t _{max}	h	1.66 (N=22)	74.70	2.07 (N=22)	53.44
C _{min}	ng/mL	0.662 (N=22)	47.21	0.361 (N=22)	61.31
t _{1/2}	h	14.19 (N=18)	20.83	12.10 (N=18)	31.17
C _{ave}	ng/mL	1.69 (N=22)	54.83	1.35 (N=22)	43.89
PTF	%	230.93 (N=22)	29.23	303.08 (N=22)	30.35
CL _r	mL/min	10093 (N=22)	40.87	11878 (N=22)	36.22
V _d /f	L	11786 (N=18)	52.66	11793 (N=18)	43.92

Table 12. Statistical Results

Parameter	Unit	Treatment B Atorvastatin alone	Treatment C Fenofibrate + Atorvastatin	Point estimate ratio C/B	90% Confidence Interval
		geom. mean	geom. mean		
AUC _{ss}	h*ng/mL	37.31 (N=21)	32.30 (N=19)	0.86* (N=19) #	0.76 : 0.95* #
AUC(0-24)	h*ng/mL	36.20*	29.98*	0.83*	0.74 : 0.93
C _{max}	ng/mL	3.96*	3.97*	1.00*	0.85 : 1.18
t _{max}	h	1.25*	1.75*	+0.5**	±0 : +1.25*
t _{1/2}	h	13.89 (N=18)	11.50 (N=18)	0.83 (N=15)	0.71 : 0.97

*N = 22 * nonparametric evaluation

AUC_{ss} Mixed model: Point estimate=0.83 with 90% CI [0.73 ; 0.95]

The sponsor indicated that when concentrations could not be quantified for a full 24-hour interval, the AUC_{ss} was derived by extrapolation based on C_z and lamda-z, where C_z represents the last quantifiable concentration and lamda-z represents the terminal rate constant. ANOVA tests of both AUC_{ss} and AUC₀₋₂₄ showed a decrease of 17% upon co-administration with fenofibrate. Nonparametric analysis showed a 14% decrease in atorvastatin AUC_{ss} by fenofibrate. The C_{min} values were decreased by 45%.

2.5 General Biopharmaceutics

Q. What is the bioavailability of Tricor® EZ Fenofibrate tablets compared to Tricor® micronized capsules?

Tricor® EZ fenofibrate tablets (one 145 mg or three 48 mg) were found to be bioequivalent to Tricor® micronized capsule 200 mg under low-fat fed conditions.

The bioavailability of fenofibric acid from two test fenofibrate tablets (Tricor® EZ tablets one 145 mg or three 48 mg) was compared to that from a reference 200 mg Tricor® micronized capsule in healthy subjects under low-fat fed condition in study M02-558. Seventy-two subjects were recruited and 68 subjects completed the study. This was an open-label, single-dose, randomized, three-period, crossover study.

Regimen A: one 145 mg tablet
 Regimen B: three 48 mg tablets
 Regimen C: one 200 mg capsule

The pharmacokinetic results are summarized in Table 13. The mean T_{max} values for Regimens A and B were earlier than that for the reference Regimen C. The C_{max} values from all three regimens were similar. The AUC_t and AUC_∞ values for test Regimens A and B were lower than the corresponding values for the reference Regimen C. The t_{1/2} values were shorter for test Regimens A and B than for the reference Regimen C.

Table 13. Mean +/- standard deviation pharmacokinetic parameters of fenofibric acid after administration of the three regimens

Pharmacokinetic Parameters (units)	Regimen		
	A: One 145 mg Tablet (Test) (N = 71)	B: Three 48 mg Tablets (Test) (N = 71)	C: One 200 mg Capsule (Reference) (N = 71)
T _{max} (h)	3.5 ± 1.2*	3.6 ± 1.3*	4.4 ± 1.7
C _{max} (µg/mL)	8.80 ± 1.67	8.54 ± 1.62	8.87 ± 2.29
AUC _t [‡] (µg•h/mL)	153.5 ± 40.7*	153.3 ± 41.8*	174.2 ± 43.6
AUC _∞ [‡] (µg•h/mL)	157.4 ± 44.2*	157.0 ± 45.1*	180.4 ± 49.4
t _{1/2} [§] (h)	20.7*	20.1*	22.0

* Statistically significantly different from reference regimen (Regimen C, ANOVA, p < 0.05).

‡ N = 70.

§ Harmonic mean; evaluations of t_{1/2} were based on statistical tests for λ_z.

Bioequivalence test was conducted with C_{max}, AUC_t and AUC_∞. For the two one-sided tests based on the analysis of log-transformed C_{max}, AUC_t and AUC_∞, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in Table 14. Both Regimens A (one 145 mg tablet) and B (three 48 mg tablets) were bioequivalent to the 200 mg micronized capsule since the 90% confidence intervals for log-transformed C_{max}, AUC_t and AUC_∞ were contained within the 0.80 to 1.25 range.

Table 14. Relative bioavailability and 90% confidence intervals for the bioequivalence assessment

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate [†]	90% Confidence Interval
A vs. C	C _{max}	8.646	8.582	1.008	0.968 - 1.049
	AUC _t	148.47	170.49	0.871	0.852 - 0.890
	AUC _∞	151.69	176.03	0.862	0.843 - 0.881
B vs. C	C _{max}	8.399	8.582	0.979	0.940 - 1.019
	AUC _t	148.29	170.49	0.870	0.851 - 0.889
	AUC _∞	151.34	176.03	0.860	0.841 - 0.879

* Antilogarithm of the least squares means for logarithms.

† Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

DSI inspection (Appendix 4.4) raised a concern about failure to assure the accuracy of data from diluted study samples at the analytical site. This reviewer conducted a bioequivalence test using the sponsor provided dataset excluding all data from subjects 118, 119, 123, 128, 130, 141, 142, 164, 165, 170; and 171 generated in runs 23, 24, 31, 52, 91, 94, and 100. No consequence to the assessment of bioequivalence was found.

Q. Was the dissolution method and specification adequately justified?

The sponsor proposed a dissolution method using USP Apparatus 2 in 25 mM sodium dodecyl sulfate (SDS) with the specification of not less than (Q) in minutes is not acceptable. The agency recommends a method using Apparatus 2 at in 25 mM SDS with the specification of not less than (Q) in 30 minutes.

To justify the dissolution method and specification, the sponsor conducted dissolution studies to evaluate the surfactant concentrations (25 and 50 mM), medium pH, and agitation rate.

The 50 mM SDS medium has been utilized for approved Tricor® tablets and capsules. The sponsor investigated a lower surfactant level of 25 mM. Since results showed that there was no difference between 25 mM and 50 mM, the 25 mM was chosen for Tricor® tablets.

The firm compared dissolution profiles in different media (including 25 mM SDS) in 0.1 N HCl, 0.05 M acetate buffer at pH 4.5 and 0.05 M phosphate buffer at . Because results showed that pH did not have a significant effect on the dissolution profiles, the medium of 25 mM SDS was chosen.

The sponsor further tested the agitation rate of . Dissolution testing was performed utilizing USP Apparatus 2 (in 1000 mL of 25 mM SDS medium (Tables 15 and 16). It was found that dissolution profiles at were comparable or slightly faster for some lots compared to . For example, the dissolution profiles of clinical batches used in study M02-558 (Elan #03010 (48 mg) and 03007 (145 mg)) were similar using agitation rate. Thus, is more appropriate.

With regard to the dissolution specification, not less than (Q) in 30 minutes is recommended since, on average, more than fenofibrate dissolved in 30 minutes.

Therefore, a dissolution method using USP Apparatus 2 and specification of not less than (Q) in 30 minutes is recommended.

1 Page(s) Withheld

 X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

2.6 Analytical Section

Q. Was the analytical method adequately validated?

The high-performance liquid chromatographic method with r _____ for fenofibric acid was adequately validated and shown to be specific, sensitive, precise and accurate.

The lower limit of quantitation (LLOQ) was _____ and the calibration range was _____ for fenofibric acid. The between-batch precision (% CV) and accuracy (% Nominal) of the QCs _____ of fenofibric acid ranged from _____ respectively.

3 Detailed Labeling Recommendations

Under CLINICAL PHARMACOLOGY Section Pharmacokinetics/Metabolism subsection:

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Under CLINICAL PHARMACOLOGY Section Drug-Drug Interactions subsection:

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. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

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

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

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR →) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3 α -hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively, in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR →) with atorvastatin (20 mg) once daily for 10 days resulted in an approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Under WARNING Section:

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.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3 α -hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also CLINICAL PHARMACOLOGY, Drug-drug interactions).

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

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

4 Appendix

4.1 proposed labeling

15 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Fenofibrate (ABT-799)		
Name of Active Ingredient: Fenofibric Acid		
Volume:		
Page:		
Title of Study: A Comparative Study of the Bioavailability of Fenofibric Acid from Two Fenofibrate Tablet Dosage Strengths (145 and 48 mg) Relative to that from a Reference 200 mg Fenofibrate Capsule		
Investigator: Patrick T. Horn, MD, PhD		
Study Site: Abbott Clinical Research Unit, Waukegan, IL		
Publications: Not applicable.		
Studied Period:		Phase of Development: 1
First Screening Procedure: 17 Feb 2003		
Date First Subject Dosed: 17 Mar 2003 (Cohort 1), 24 Mar 2003 (Cohort 2)		
Date Last Subject Completed Dosing: 21 Apr 2003		
Date of Last Study Procedure: 16 May 2003		
Objective: The objective of this study was to determine the bioavailability of fenofibric acid from two test fenofibrate tablets (145 and 48 mg dosage strengths) relative to that from a reference 200 mg fenofibrate capsule administered under nonfasting (low-fat meal) conditions.		
Methodology: This Phase 1, single-dose, open-label study was conducted according to a three-period, randomized crossover design. Subjects were randomly assigned in equal numbers to receive one of six sequences of Regimen A (one 145 mg fenofibrate tablet, test), Regimen B (three 48 mg fenofibrate tablets, test) and Regimen C (one 200 mg fenofibrate capsule, reference) under nonfasting conditions in the morning on Study Day 1 of each period. Washout intervals of 14 days separated the doses of the three study periods.		
Blood samples for fenofibric acid assay were collected by venipuncture into 5 mL evacuated collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 18, 24, 48, 72, 96 and 120 hours after dosing in each period. Sufficient blood was collected to provide approximately 2 mL plasma from each sample.		
Plasma concentrations of fenofibric acid were determined using a validated high-performance liquid chromatographic method with mass spectral detection at Abbott. The lower limit of quantitation (LLOQ) for fenofibric acid was established at _____ using a 0.150 mL plasma sample. Samples were analyzed between the dates of 25 April 2003 and 12 June 2003.		

Number of Subjects (Planned and Analyzed):

Planned: 72; Entered: 72; Completed: 68; Evaluated for Safety: 72; Evaluated for Pharmacokinetics: 71

For the 72 subjects who participated in the study, the mean age was 35.7 years (ranging from 18 to 55 years), the mean weight was 78.1 kg (ranging from 55 to 97 kg) and the mean height was 176.1 cm (ranging from 156 to 192 cm). For the 71 subjects included in the pharmacokinetic analyses, the mean age was 35.8 years (ranging from 18 to 55 years), the mean weight was 78.3 kg (ranging from 55 to 97 kg) and the mean height was 176.2 cm (ranging from 156 to 192 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, surgically sterile, or if of childbearing potential, were not pregnant or breast-feeding and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

	Regimen		
	A (Test)	B (Test)	C (Reference)
Dosage Form	Tablet	Tablet	Capsule
Strength (mg)	145	48	200
Manufacturers Lot Number	03007	03010	72940
Abbott Lot Number	02-494-AR	02-497-AR	016562E00
Potency (% of Label Claim)			
Manufacturer			
Batch Size			
Finishing Sublot Number	02-197-S2	02-198-S2	02-31-S2
Finishing	0681	0681	0671
Expiration/Retest Date			

Duration of Treatment: Three single doses were administered on 17 Mar 2003 (Cohort 1) or 24 Mar 2003 (Cohort 2), 31 Mar 2003 (Cohort 1) or 07 Apr 2003 (Cohort 2) and 14 Apr 2003 (Cohort 1) or 21 Apr 2003 (Cohort 2).

Criteria for Evaluation:

Pharmacokinetic: The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}), the terminal phase elimination rate constant (λ_z), terminal phase elimination half-life ($t_{1/2}$), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration (AUC_t) and the AUC from time 0 to infinite time (AUC_{∞}).

Safety: Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests.

Statistical Methods:

Pharmacokinetic: Analyses of variance (ANOVAs) were performed for T_{max} and the natural logarithms of C_{max} , AUC_t and AUC_{∞} . The model included effects for cohort, sequence, interaction of cohort and sequence, subject nested within cohort-sequence combination, period, regimen, interaction of cohort and period, and interaction of cohort and regimen. Within the framework of the ANOVA, each test regimen was compared to the reference with a significance level of 0.05 for each individual comparison.

The bioavailability of each test regimen relative to that of the reference regimen was assessed by the two one-sided tests procedure *via* 90% confidence intervals. Bioequivalence between a test regimen and the reference regimen was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC and C_{max} were within the 0.80 to 1.25 range.

Safety: The number and percentage of subjects reporting adverse events were tabulated by COSTART V term and body system with a breakdown by regimen. Laboratory test values that were Very High or Very Low according to predefined criteria were identified.

Summary/Conclusions:

Pharmacokinetic Results: Mean \pm standard deviation pharmacokinetic parameters of fenofibric acid after administration of the three regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimen		
	A: One 145 mg Tablet (Test) (N = 71)	B: Three 48 mg Tablets (Test) (N = 71)	C: One 200 mg Capsule (Reference) (N = 71)
T_{max} (h)	3.5 \pm 1.2*	3.6 \pm 1.3*	4.4 \pm 1.7
C_{max} ($\mu\text{g}/\text{mL}$)	8.80 \pm 1.67	8.54 \pm 1.62	8.87 \pm 2.29
AUC_t^{\ddagger} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	153.5 \pm 40.7*	153.3 \pm 41.8*	174.2 \pm 43.6
AUC_{∞}^{\ddagger} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	157.4 \pm 44.2*	157.0 \pm 45.1*	180.4 \pm 49.4
$t_{1/2}^{\text{c}, \ddagger}$ (h)	20.7*	20.1*	22.0

* Statistically significantly different from reference regimen (Regimen C, ANOVA, $p < 0.05$).

\ddagger N = 70.

c Harmonic mean; evaluations of $t_{1/2}$ were based on statistical tests for λ_z .

The bioequivalence/bioavailability results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
A vs. C	C _{max}	8.646	8.582	1.008	0.968 - 1.049
	AUC _t	148.47	170.49	0.871	0.852 - 0.890
	AUC _∞	151.69	176.03	0.862	0.843 - 0.881
B vs. C	C _{max}	8.399	8.582	0.979	0.940 - 1.019
	AUC _t	148.29	170.49	0.870	0.851 - 0.889
	AUC _∞	151.34	176.03	0.860	0.841 - 0.879

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Safety Results: Twenty-three (23/72, 31.9%) subjects reported at least one treatment-emergent adverse event. Adverse events reported by three or more subjects were abdominal pain (five subjects, 6.9%), pharyngitis (four subjects, 5.6%), headache (three subjects, 4.2%) and pain (three subjects, 4.2%). All remaining adverse events were reported by a maximum of 2.8% of subjects (two subjects).

The proportion of subjects reporting at least one treatment-emergent adverse event was for Regimen A (12.7%), Regimen B (13.9%) and Regimen C (14.1%). The majority of adverse events were assessed by the investigator as not related to study drug and mild in severity.

No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for laboratory variables, vital signs and ECGs were unremarkable for each regimen group.

Conclusions: Both test Regimens A and B (one 145 mg fenofibrate tablet and three 48 mg fenofibrate tablets, respectively) were bioequivalent to the reference Regimen C (one 200 mg fenofibrate capsule) because the 90% confidence intervals for log-transformed C_{max}, AUC_t and AUC_∞ were contained within the 0.80 to 1.25 range.

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study. There were no apparent differences among the regimens with regard to safety.

I	Individual Study Table Referring to Item of the Submission:	(For National Authority Use Only)
Name of Study Drug: Fenofibrate	Volume:	
Name of Active Ingredient: Fenofibric acid	Page:	
Title of Study: Food-Effect Bioavailability Study of Fenofibric Acid from a 145 mg tablet Formulation of Fenofibrate		
Investigator: J. Mulvaney, MBChB DCPSA		
Study Site:		
Publications: Not Applicable		
Studied Period (Years): Initiation Date: 10 March 2003 Completion Date: 07 May 2003	Phase of Development: 1	
Objectives: The primary objective was to determine the effect of food on the bioavailability of fenofibric acid from a 145 mg tablet formulation of fenofibrate. The secondary objective was to assess the general safety.		
Methodology: Open-label, randomized, single-dose, 3-way crossover design with at least 14 days of washout between each dosing day.		
Number of Subjects (Planned and Analyzed): Planned: 45; Analyzed for Pharmacokinetics: 44 and 45; Analyzed for Safety: 45		
Diagnosis and Main Criteria for Inclusion: Healthy male and female volunteers (18 – 45 years old).		
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: <u>Regimen A:</u> one 145 mg tablet formulation of fenofibrate administered under high-fat fed (HFF) conditions (50% fat – ca. 1000 kcal). <u>Regimen B:</u> one 145 mg tablet formulation of fenofibrate administered under low fat fed (LFF) conditions (30% fat – ca. 400 kcal). <u>Regimen C:</u> one 145 mg tablet formulation of fenofibrate administered under fasting conditions (reference).		
For Regimen A and Regimen B, breakfast was to start 30 minutes before study drug administration and to be consumed over 25 minutes. Regimen C was taken in fasting state. All treatments were administered orally with 240 mL of still mineral water. Tablet Batch Number: 03007, Clinical Batch Number: 306/02		

<p>Duration of Treatment: Three (3) single doses separated by at least a 14-day washout period.</p>
<p>Reference Therapy: <u>Regimen C</u> in fasting conditions, no food allowed for 10 hours before and 4 hours after study drug administration.</p>
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics:</p> <p>Blood samples were collected at time 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 48, 72, 96 and 120 hours post-dose (n = 63 for the three periods). A total of 315 mL of blood was collected per subject for pharmacokinetic purposes. Concentrations of fenofibric acid in plasma were determined using a validated HPLC/UV method (Lower Limit Of Quantification [LLOQ] = 0.03 µg/mL).</p> <p>Pharmacokinetic parameters: AUC_{∞}, AUC_t, C_{max}, T_{max} and $t_{1/2}$ determined using a non-compartmental method. AUC_{∞} and C_{max} were the primary variables for assessing the effect of food on the bioavailability of fenofibric acid. AUC_t, T_{max} and $t_{1/2}$ were secondary variables.</p> <p>Safety:</p> <p>General safety was assessed by means of physical examination, vital signs and EKG at screening, Day -1 and Day 2 of each period and at follow-up (Day 6 concurrent with the last blood sampling-time), and by laboratory investigations at screening, Day -1 of each period and at follow-up.</p>
<p>Statistical Methods:</p> <p>Pharmacokinetics</p> <p><u>Descriptive Statistics for Each Pharmacokinetic Parameter:</u> n, mean (SD), CV%, min, max and median, geometric mean for AUC_{∞}, AUC_t and C_{max}, harmonic mean for $t_{1/2}$.</p> <p><u>Comparative Statistics:</u> Log-transformation of exposure measurements prior to analysis. Analysis of variance (ANOVA) followed by calculation of the 90% confidence interval (CI) for the ratio of the geometric means between HFF and fasted regimens (Regimen A / Regimen C) as well as LFF and fasted regimens (Regimen B / Regimen C) for AUC_{∞}, AUC_t and C_{max}.</p> <p>According to the protocol, the statistical analysis was performed on the 44 subjects having completed the three treatment periods (PKS data). An additional analysis was performed on the 45 subjects (FAS data), since the subject who did not complete the three treatment periods had all the necessary data for the primary comparison (Regimen A versus Regimen C).</p> <p>The absence of food effect was concluded if the 90% CI of the relative mean for AUC_{∞} and C_{max} (HFF versus fasting) was included within the bioequivalence limits of 0.80 - 1.25.</p> <p>For additional information, the 90% CI between LFF and fasting conditions was calculated.</p> <p>Non-parametric Friedman's test was used for the comparisons of T_{max} and $t_{1/2}$.</p> <p>Safety</p> <p>Pre-, during and post-study data were recorded in tabular format and regarded as normal or abnormal values, and as clinically or not clinically significant for healthy subjects, in the judgment of the investigator. For categorical variables, n and % were to be calculated.</p>

Summary/Conclusions:**Analytical Results**

analytical runs were carried-out to analyze the study samples. Accuracy of Quality Controls (QCs) was always lower than 2%, and precision lower than 6%, irrespective of the plasma levels. For QC low (), all the experimental concentrations were between -15% and +10% of the theoretical concentration, for QC mid () and QC high (), most of the experimental concentrations were between -10% and +10% of the theoretical concentrations. No increasing or decreasing trends were observed throughout the assay period.

All the pre-dose samples showed concentrations of fenofibric acid below the LLOQ; most of the 120-hour post-dose samples showed concentrations below or close to the LLOQ.

Pharmacokinetic ResultsPharmacokinetic Parameters

Arithmetic mean (SD) and associated CV of pharmacokinetic parameters are presented below:

n = 44 (PKS)	Regimen A (HFF)	Regimen B (LFF)	Regimen C (Fasting)
AUC _∞ (µg/mL.h)	129.9 (36.4), 28%	125.1 (35.8), 29%	123.8 (35.7), 29%
AUC _t (µg/mL.h)	127.9 (35.4), 28%	123.2 (35.0), 28%	121.6 (34.2), 28%
C _{max} (µg/mL)	7.96 (1.47), 18%	7.96 (1.43), 18%	7.94 (1.59), 20%
T _{max} (h)	4.27 (1.94), 45%	3.56 (1.18), 33%	2.33 (0.73), 31%
t _{1/2} (h)	17.8 (4.1), 23%	18.7 (3.7), 20%	18.9 (4.7), 25%

Very close values of AUC, C_{max} and t_{1/2} were obtained following the different regimens. A slightly prolonged T_{max} was observed following HFF conditions, without any effect on mean C_{max}.

Statistical Comparisons

ANOVAs on log-transformed AUC_∞, AUC_t and C_{max}, accounting for differences between sequences, periods, subjects within sequences, and regimens, showed that there were no statistically significant differences between the sequences and the periods.

The Friedman's test showed a statistically significant difference between the regimens for T_{max} (p < 0.0001), and no difference for t_{1/2} (p = 0.1482).

The 90% CI results are presented below.

HFF versus Fasting

Parameter n = 44 (PKS)	Geometric Mean HFF (Regimen A)	Geometric Mean Fasting (Regimen C)	Point Estimate	90% CI
AUC _∞	124.8	118.5	1.052	1.018 - 1.088
AUC _t	123.0	116.5	1.054	1.020 - 1.090
C _{max}	7.82	7.77	1.007	0.963 - 1.054

The absence of food effect has been demonstrated as the 90% CI for the ratio of geometric means of HFF (Regimen A) versus fasting (Regimen C) falls within 0.80 - 1.25 for AUC and C_{max} with a point estimate of 1. The two regimens HFF and fasting are therefore bioequivalent.

LFF versus Fasting				
Parameter n = 44 (PKS)	Geometric Mean LFF (Regimen B)	Geometric Mean Fasting (Regimen C)	Point Estimate	90% CI
AUC _{0-∞}	119.8	118.5	1.012	0.978 – 1.046
AUC _t	118.1	116.5	1.013	0.981 – 1.047
C _{max}	7.84	7.77	1.009	0.964 – 1.055
<p>Geometric mean = least square mean.</p> <p>Similar results were obtained for the comparison between LFF (Regimen B) and fasting (Regimen C): the 90% CI for the geometric means of LFF (Regimen B) versus fasting (Regimen C) falls within 0.80 - 1.25 for AUC and C_{max} with a point estimate of 1. The two regimens LFF and fasting are therefore bioequivalent.</p> <p>Similar results were obtained when the statistical analysis was performed on the 45 subjects.</p>				
<p>Safety Results:</p> <p>No subjects withdrew prematurely for AEs, and none of the AEs were considered as serious. Eighty three (83) treatment-emergent AEs, most graded as mild, were reported by 31 subjects during the study; 19 of these AEs, in 9 subjects, were considered as possibly related to study treatment.</p> <p>Headache and digestive manifestations, generally graded as mild, were the most common symptoms considered by the investigator as possibly related to study treatment. Other AEs considered as possibly related to study treatment included leg discomfort, neck pain, postural dizziness and lethargy and dysphoria, in one subject each.</p> <p>Variations in hematology parameters were minor during the study; none of the abnormal values were considered to be clinically significant. Four subjects presented with abnormal transaminases values, which were considered as clinically significant in one of them (ASAT and ALAT: 3.5 and 2.3 times the Upper Normal Limit [UNL], respectively, concomitant with CK elevation) and not clinically significant in the other three. In three subjects, elevated transaminases were concomitant with elevated CK. As a whole, three subjects presented with elevated CK during the study, with abnormal values ranging between 8 and 27 times the UNL. Increased values were recorded on Day-1 of Period 2 in two subjects and on Day 6 of Period 3 in one. The subjects who had concomitant increase in transaminases and in CK reported doing physical exercise on the preceding days. The investigator considered all the elevations in CK and transaminases to be unlikely related to study treatment.</p> <p>No changes worth noting were observed in the other blood tests and in urinalysis.</p> <p>None of the abnormal vital signs values and none of the abnormal EKG assessments were considered to be clinically significant.</p> <p>Headache, digestive manifestations and other symptoms such as apathy and dizziness were slightly more frequent when the subjects received the study drug in fasting conditions than after breakfast.</p>				

Conclusions:

The 90% CI for the ratio of population geometric means between HFF and fasting regimens, based on log-transformed data, is contained in the equivalence limits of 0.80 - 1.25 for AUC and C_{max} .

In conclusion, the AUC and C_{max} obtained from this food-effect study involving administration of the new 145 mg tablet formulation of fenofibrate to healthy male and female subjects under fasting conditions and with a high-fat meal indicated that exposure to fenofibric acid is not affected by food. Therefore, the new 145 mg tablet formulation of fenofibrate may be taken without regard to meals.

The 145 mg tablet formulation of fenofibrate given as a single dose in this study was well tolerated.

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Fenofibrate (ABT-799)	Volume:	
Name of Active Ingredient: Fenofibric Acid	Page:	
Title of Study: Effect of Multiple Doses of Fenofibrate on the Multiple-Dose Pharmacokinetics of Pravastatin in Healthy Subjects		
Investigator: Hans-Ulrich Esslinger, MD		
Study Site: Clinical Pharmacology, Abbott GmbH & Co KG, Ludwigshafen, Germany		
Publications: Not applicable.		
Studied Period: First Screening Procedure: 28 Oct 2002 Date First Subject Dosed: 14 Nov 2002 (Cohort 1); 16 Nov 2002 (Cohort 2) Date Last Subject Completed Dosing: 30 Nov 2002 Date of Last Study Procedure: 01 Dec 2002		Phase of Development: 1
Objective: The objective of this study was to evaluate the effect of fenofibrate on the pharmacokinetics of pravastatin following administration of multiple doses of both drugs to healthy subjects under nonfasting conditions.		
<p>Methodology: This Phase I, multiple-dose, open-label study was conducted according to a sequential design. All subjects took pravastatin (one 40 mg tablet QD) on the mornings of Study Days 1 through 15. Fenofibrate (one 160 mg tablet QD) was co-administered with the pravastatin on the mornings of Study Days 6 through 15. Each dose of study drug was taken orally with approximately 240 mL of water 30 minutes after starting a low-fat breakfast.</p> <p>Blood samples (7 mL) for pravastatin and 3α-hydroxy-iso-pravastatin assay were collected into evacuated collection tubes containing EDTA within 5 minutes prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing on Study Days 5, 6 and 15. Sufficient blood was collected to provide approximately 3 mL plasma from each sample.</p> <p>Plasma concentrations of pravastatin and 3α-hydroxy-iso-pravastatin were determined using a validated liquid chromatography method with mass spectrometric detection at _____.</p> <p>_____ The lower limits of quantitation for pravastatin and 3α-hydroxy-iso-pravastatin were established at _____ respectively, using a 500 μL plasma sample. Samples were analyzed between the dates of 21 Dec 2002 and 24 Jan 2003.</p>		

Statistical Methods:

Pharmacokinetic: A paired t-test was performed for C_{max} , AUC, T_{max} and the elimination rate constant (λ_z) to assess the effect of fenofibrate co-administration. The comparison of each of Study Days 6 and 15 were made with Study Day 5. Additionally, a comparison of Study Day 15 with Study Day 6 was also performed.

In connection with the paired t-test for the logarithms of AUC and C_{max} , a point estimate and 90% confidence interval for the exposure during fenofibrate co-administration relative to the exposure for pravastatin alone was determined. A 90% confidence interval was also provided for the exposure on Study Day 15 relative to Study Day 6 (exposure of pravastatin and 3 α -hydroxy-iso-pravastatin with multiple doses of fenofibrate relative to a single dose of fenofibrate).

Safety: The number and percentage of subjects reporting adverse events were tabulated by COSTART V term and body system with a breakdown by study segment (pravastatin alone and co-administration of pravastatin and fenofibrate). Laboratory values and vital signs measurements that were identified as being potentially clinically significant according to predefined Abbott criteria were listed.

Summary/Conclusions:

Pharmacokinetic Results: Mean \pm standard deviation (SD) pharmacokinetic parameters of pravastatin and 3 α -hydroxy-iso-pravastatin from Study Day 5 (pravastatin alone), Study Day 6 (pravastatin plus single dose fenofibrate) and Study Day 15 (pravastatin plus multiple dose fenofibrate) are presented in the following table.

Pharmacokinetic Parameters (units)		Pravastatin Alone	Pravastatin with Single	Pravastatin with
		(Study Day 5)	Dose Fenofibrate	Multiple Dose
		(N = 24)	(Study Day 6)	Fenofibrate
			(N = 24)	(Study Day 15)
				(N = 23)
Pravastatin				
T _{max}	(h)	1.8 ± 0.4	2.0 ± 0.7	1.7 ± 0.5
C _{max}	(ng/mL)	24.8 ± 16.7	33.4 ± 29.7	34.2 ± 24.3*
AUC ₂₄	(ng•h/mL)	61.0 ± 33.7	76.2 ± 54.7*	79.8 ± 50.7*
t _{1/2} [‡]	(h)	2.31	2.07*	2.09
CL/F [†]	(L/h)	901 ± 533	781 ± 531	707 ± 395
3α-Hydroxy-Iso-Pravastatin				
T _{max}	(h)	2.0 ± 0.6	2.1 ± 0.6	2.0 ± 0.7
C _{max}	(ng/mL)	29.8 ± 19.9	38.7 ± 24.7	44.2 ± 28.0*
AUC ₂₄	(ng•h/mL)	71.6 ± 45.3	87.8 ± 48.8	97.9 ± 58.4*
t _{1/2} [‡]	(h)	1.54	1.45	1.41

* Statistically significantly different from Study Day 5 (paired t-test, p < 0.050).

‡ Harmonic mean; evaluations of t_{1/2} were based on statistical tests for λ_z.

† Parameter was not tested statistically.

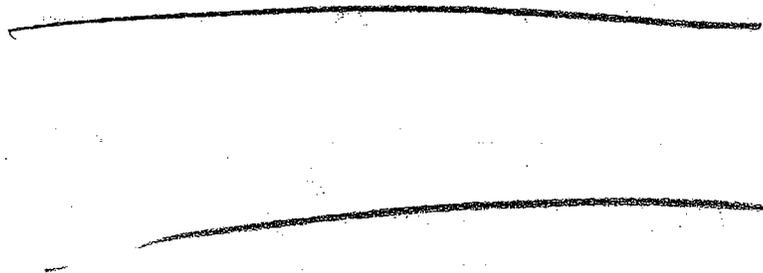
The point estimates and 90% confidence intervals for the ratios of central values on Study Day 6 (pravastatin with single dose fenofibrate) to those on Study Day 5 (pravastatin alone), for Study Day 15 (pravastatin with multiple dose fenofibrate) to those on Study Day 5 (pravastatin alone) and for Study Day 15 (pravastatin with multiple dose fenofibrate) to those on Study Day 6 (pravastatin with single dose fenofibrate) are listed in the following table for pravastatin and 3α-hydroxy-iso-pravastatin C_{max} and AUC₂₄.

Study Day Comparison	Pharmacokinetic Parameter	Central Values*		Relative Exposure	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
Pravastatin					
6 vs. 5	C _{max}	24.69	20.26	1.219	1.011 – 1.470
	AUC ₂₄	62.20	52.22	1.191	1.060 – 1.338
15 vs. 5	C _{max}	27.60	20.29	1.360	1.108 – 1.670
	AUC ₂₄	66.69	52.22	1.277	1.092 – 1.493
15 vs. 6	C _{max}	27.60	24.90	1.108	0.889 – 1.382
	AUC ₂₄	66.69	62.88	1.061	0.903 – 1.245
3α-Hydroxy-Iso-Pravastatin					
6 vs. 5	C _{max}	31.02	23.74	1.307	1.040 – 1.641
	AUC ₂₄	72.38	58.27	1.242	1.027 – 1.502
15 vs. 5	C _{max}	36.96	23.91	1.546	1.290 – 1.853
	AUC ₂₄	82.43	59.37	1.389	1.195 – 1.613
15 vs. 6	C _{max}	36.96	33.32	1.109	0.927 – 1.328
	AUC ₂₄	82.43	78.63	1.048	0.889 – 1.236
* Geometric Mean.					
+ Antilogarithm of mean differences of logarithms.					
<p>Safety Results: Overall, 21% (5/24) of subjects reported at least one treatment-emergent adverse event. All of the events occurred during the combination segment (pravastatin plus fenofibrate) of the study. The most frequently reported treatment-emergent adverse event (<i>i.e.</i>, events reported by three or more subjects in the study) was headache. All other treatment-emergent adverse events were reported by one subject. The investigator considered the adverse events as possibly related or not related to pravastatin plus fenofibrate and mild or moderate in severity.</p> <p>No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs and ECGs were unremarkable for each segment of the study.</p>					

Conclusions: Co-administration of 160 mg/day fenofibrate had relatively modest effects on the pharmacokinetics of 40 mg/day pravastatin in healthy male and female subjects. Increases in pravastatin exposures (36% or less, on average) and 3 α -hydroxy-iso-pravastatin exposures (less than 55%, on average) were observed upon co-administration. Increases in pravastatin exposures were not statistically significantly different following the first and tenth doses of fenofibrate.

Both pravastatin, administered at 40 mg QD for 15 days and fenofibrate, administered at 160 mg QD for 10 days, were generally well tolerated by the subjects. No clinically significant vital signs or laboratory measurements related to study drug administration were observed during the course of the study.

Name of Sponsor/Company: 	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product: LIPANTHYL® 160 TAHOR®	Volume:	
Name of Active Ingredient: Fenofibric acid Atorvastatin	Page:	
Title of Study: Investigation of a possible pharmacokinetic interaction between fenofibrate and atorvastatin following multiple dose administration in healthy male volunteers		
Investigator: "Leiter der klinischen Prüfung" according to § 40 German Drug Law (Principal Investigator):  For a list and description of investigators and other important participants in the study, including their role in the study and brief CVs please refer to Appendix 16.1.4.		
Study center: 		
Publication (reference): Not applicable.		
Studied period: Date of first enrollment: 09.01.2003 Date of last completed: 16.04.2003	Phase of development: Phase 1	
Objectives: The primary objective of this study was to investigate a possible pharmacokinetic interaction of atorvastatin on fenofibrate as well as of fenofibrate on atorvastatin. The secondary objective was to monitor the general safety in particular when fenofibrate and atorvastatin are co-administered.		
Methodology: Open, randomized, three-way cross-over, multiple dose design. All subjects received in a randomized manner 160 mg of fenofibrate, 20 mg of atorvastatin and the combination of both drugs in fed condition once daily on 10 consecutive days. Dosing was performed in the evening after a dinner. The wash-out period between the treatments was 12 days.		
Number of subjects (planned and analyzed): Number of subjects planned: 24 Number of subjects completed: 22 Number of subjects analyzed: 22		
Diagnosis and main criteria for inclusion: Healthy, male, smoking (≤ 10 cigarettes) and non-smoking subjects, Caucasian, aged between 18 and 45 years, inclusive.		
Test drug, dose and mode of administration, batch number: Fenofibrate 160 mg, tablet for oral administration, batch number: 72197 Atorvastatin 20 mg, tablet for oral administration, batch number: 0384082		
Duration of treatment: Treatment A: Fenofibrate 160 mg tablet, once daily in the evening on 10 consecutive days. Treatment B: Atorvastatin 20 mg tablet, once daily in the evening on 10 consecutive days. Treatment C: Fenofibrate 160 mg tablet and atorvastatin 20 mg tablet, once daily in the evening on 10 consecutive days.		

<u>Name of Sponsor/Company:</u> 	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
<u>Name of Finished Product:</u> LIPANTHYL [®] 160 TAHOR [®]	<u>Volume:</u>	
<u>Name of Active Ingredient:</u> Fenofibric acid Atorvastatin	<u>Page:</u>	
Reference drug, dose and mode of administration, batch number: Not applicable.		
Criteria for evaluation: Pharmacokinetics: All main PK parameters were determined - AUC_{ss} , $AUC(0-24)$, C_{max} , t_{max} , C_{min} , V_d , CL and $t_{1/2}$. The main endpoint for assessment of the interaction was AUC_{ss} . Blood samples for determinations of fenofibric acid concentrations in plasma were collected on: Days 1, 8, 9: 0 (pre-dose) Days 10 - 15: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, 96 and 120 hours post last dose Plasma fenofibric acid levels were determined using an _____ method (LLOQ = _____) Blood samples for determinations of atorvastatin concentrations in plasma were collected on: Days 1, 8, 9: 0 (pre-dose) Days 10 - 15: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post last dose Plasma atorvastatin levels were determined using an _____ method (LLOQ = _____) Safety: Adverse events, vital signs, ECG and laboratory tests (including creatine kinase (CK), creatinine, and liver function tests):		
Statistical methods: Summary statistics were calculated for all pharmacokinetic parameters. Mixed effects analysis of variance with sequence, subject within sequence, period and treatment effects was applied to AUC_{ss} , $AUC(0-24)$, C_{max} and $t_{1/2}$ of fenofibric acid and atorvastatin after log-transformation, subject effects considered as random. Nonparametric analysis of t_{max} . Estimation of the treatment ratios (with vs without co-administration) with 90% confidence intervals.		
SUMMARY - CONCLUSIONS ANALYTICAL RESULTS: 		

Name of Sponsor/Company: 	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: LIPANTHYL® 160 TAHOR®	Volume:	
Name of Active Ingredient: Fenofibric acid Atorvastatin	Page:	

PHARMACOKINETIC AND STATISTICAL RESULTS:

For fenofibrate

The most important pharmacokinetic parameters for fenofibric acid were as follows (citing medians and differences for t_{max} , nonparametric evaluation):

The statistical results did not show any effect of atorvastatin on fenofibrate, as confirmed by the bioequivalence between Treatment C and A.

Parameter	Unit	Treatment A Fenofibrate alone	Treatment C Fenofibrate + Atorvastatin	Point estimate ratio C/A	90% Confidence Interval
		geom. mean	geom. mean		
AUC ₀₋₂₄	h·µg/mL	166.83*	162.35*	0.977*	0.92 : 1.04
C _{max}	µg/mL	11.88*	11.38*	0.96*	0.91 : 1.02
t _{max}	h	3.0*	3.0*	±0*	-1 : +1
t _{1/2}	h	21.68*	20.96*	0.967*	0.92 : 1.01

*N = 22

For atorvastatin

Concentrations of atorvastatin in a few cases were not quantifiable for a full 24-hour interval, and in consequence, λ_{z2} , $t_{1/2}$ and AUC₀₋₂₄ could not be estimated for all 22 subjects. The most important pharmacokinetic parameters for atorvastatin were as follows (citing medians and differences for t_{max} , nonparametric evaluation).

The statistical results failed to show a bioequivalence between Treatments C and B. The co-administration of fenofibrate led to a comparable C_{max} but a slightly lower exposure based on AUC₀₋₂₄ (-14%).

Parameter	Unit	Treatment B Atorvastatin alone	Treatment C Fenofibrate + Atorvastatin	Point estimate ratio C/B	90% Confidence Interval
		geom. mean	geom. mean		
AUC ₀₋₂₄	h·ng/mL	37.31 (N=21)	32.30 (N=19)	0.86* (N=19) #	0.76 : 0.95* #
AUC(0-24)	h·ng/mL	36.20*	29.98*	0.83*	0.74 : 0.93
C _{max}	ng/mL	3.96*	3.97*	1.00*	0.85 : 1.18
t _{max}	h	1.25*	1.75*	+0.5**	±0 : +1.25*
t _{1/2}	h	13.89 (N=18)	11.50 (N=18)	0.83 (N=15)	0.71 : 0.97

*N = 22 * nonparametric evaluation

AUC₀₋₂₄ Mixed model: Point estimate=0.83 with 90% CI [0.73 ; 0.95]

SAFETY RESULTS:

All treatments were well tolerated. No serious adverse event was reported and none of the subjects withdrew due to an adverse event. The frequency of drug-related adverse events was low. In total, 68 post-dose adverse events were reported, 33 of them were considered to be possibly or remotely drug-related. During Treatment A (fenofibrate) 9 subjects experienced 18 adverse events, during Treatment B (atorvastatin) 8 subjects experienced 24 adverse events and during Treatment C (fenofibrate/atorvastatin) 11 subjects experienced 26 adverse events. Most of the adverse events were mild in intensity. The following possibly/remotely drug-related adverse events were reported:

Treatment A:

- headache (4 episodes in 4 subjects), a pressure over the epigastric region (1 episode) and stomach cramps, diarrhoea and nausea (1 episode in the same subject).

Treatment B:

- headache (3 episodes in 3 subjects), dizziness (1 episode) and pain in the right hand and thumb with numbness at the other 4 fingers (1 episode).

<u>Name of Sponsor/Company:</u> 	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
<u>Name of Finished Product:</u> LIPANTHYL® 160 TAHOR®	<u>Volume:</u>	
<u>Name of Active Ingredient:</u> Fenofibric acid Atorvastatin	<u>Page:</u>	
<u>Treatment C:</u> — headache (12 events in 9 subjects), pain in the stomach (3 events in 3 subjects), diarrhoea, nausea and dizziness (1 episode in the same subject), muscular pain (1 episode; CK value was within normal range) and lumbalgia (1 episode). Concerning laboratory tests, only single values outside the reference range were observed without obvious trend or pattern. None of these deviations was clearly attributed to co-administration of fenofibrate with atorvastatin. Physical examinations, vital signs and ECGs were without clinically relevant findings.		
<u>CONCLUSION:</u> All treatments, i.e. fenofibrate, atorvastatin and fenofibrate/atorvastatin were well tolerated. No serious adverse event was reported. Drug-related adverse events were rare and most of them were mild in intensity. Regarding laboratory tests, only single values outside the reference range were observed without obvious trend or pattern. Finally, physical examinations, vital signs and ECGs were without clinically significant findings. The comparative statistical evaluation revealed that atorvastatin co-administration has no effect on the pharmacokinetics of fenofibric acid: the bioequivalence has been demonstrated at steady state between the two treatments including fenofibrate (160 mg fenofibrate tablet alone and co-administered with 20 mg atorvastatin tablet). Co-administration of fenofibrate had a slight effect on the pharmacokinetics of atorvastatin at steady-state. A decrease in atorvastatin exposure of 14% on average for AUC _{ss} was observed upon co-administration while C _{max} was comparable and met the requirements for demonstrating bioequivalence. In conclusion, the results of this study do not identify any increase in fenofibric acid or in atorvastatin concentrations when the two products are given together.		
<u>Date of the Final Report:</u> August 28, 2003		

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-656	Brand Name	Tricor®	
OCPB Division (I, II, III)	II	Generic Name	Fenofibrate	
Medical Division	510	Drug Class	Lipid lowering	
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Type II, IV, and V hyperlipidemia	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	tablets	
Related IND(s)		Dosing Regimen	48 and 145 mg	
Date of Submission	Oct. 29, 2003	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	Abbott Laboratories	
PDUFA Due Date	Aug. 30, 2004	Priority Classification	standard	
Division Due Date	July 30, 2004			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:		1		
Mutual:		1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Meta Analysis:				
PD:				
Phase 2:				

On Oct. 29, 2003, Abbott Laboratories submitted an original NDA for fenofibrate tablets, 48 mg and 145 mg for the treatments of Type II, IV and V hyperlipidemia.

There were 5 PK studies conducted in support of this application. In addition, dissolution data for the 48 mg and 145 mg tablets and analytical validation reports were included.

1. **M02-558** Single dose definitive BE trial comparing one 145 mg or three 48 mg NanoCrystal fenofibrate tablets with one 200 mg micronized fenofibrate capsule under low fat fed condition
2. **KLF 178P 02 06 KH** Food effect on single dose of 145 mg tablet
3. **K 178P 02 05 KH** pilot food effect study
4. **M02-514** Effects of fenofibrate on the pharmacokinetics of pravastatin
5. **K 178 02 01 KH** Drug-drug interaction between fenofibrate and atorvastatin

The pharmacokinetic results of Tricor ~~are~~ are summarized as follows:

1. The bioavailability of fenofibric acid following administration of one 145 mg or three 48 mg NanoCrystal fenofibrate tablets was equivalent to that for one 200 mg micronized fenofibrate capsule under low-fat meal conditions.
2. The absence of food effect was documented via 90% confidence intervals for C_{max} and AUC_{inf} which are contained within the required range of 0.80 to 1.25.
3. Fenofibrate coadministration increased pravastatin and 3 α -hydroxy-iso-prvastatin exposure by 36% and 55%, respectively.
4. Atorvastatin co-administration had no effect on the pharmacokinetics of fenofibric acid. Fenofibrate co-administration decreased AUCs of atorvastatin by 14%.

The following dissolution method was proposed:

Apparatus: USP Dissolution Apparatus 2

Rotation: _____

Medium: 25 mM Sodium Dodecyl Sulfate (SDS)

3 Page(s) Withheld

x § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Wei Qiu
8/4/04 02:01:25 PM
BIOPHARMACEUTICS

Hae-Young Ahn
8/4/04 03:13:19 PM
BIOPHARMACEUTICS

12/5/03

**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information
NDA Number	21-656	Brand Name	Tricor®
OCBP Division (I, II, III)	II	Generic Name	Fenofibrate
Medical Division	510	Drug Class	Lipid lowering
OCBP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Type II, IV, and V hyperlipidemia
OCBP Team Leader	Hae-Young Ahn	Dosage Form	tablets
Related IND(s)		Dosing Regimen	48 and 145 mg
Date of Submission	Oct. 29, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Abbott Laboratories
PDUFA Due Date	Aug. 30, 2004	Priority Classification	standard
Division Due Date	July 30, 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:		1		
Mutual:		1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Meta Analysis:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:	x			
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm ?				
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Relative bioavailability compared with Tricor micronized capsules 2. Dosage form equivalence 3. Food effect 4. Drug-drug interaction with pravastatin and atorvastatin 		
Other comments or information not included above		<p>Since no clinical trial was conducted with the subject of this NDA submission, it is desirable to conduct DSI inspection on the pivotal BE study.</p> <p>Protocol M02-558</p> <p>Title of Study: A Comparative Study of the Bioavailability of Fenofibric Acid from Two Fenofibrate Tablet Dosage Strengths (145 and 48 mg) Relative to that from a Reference 200 mg Fenofibrate Capsule</p> <p>Clinical Site: Patrick T. Horn, MD, Ph.D., Abbott Clinical Research Unit, Victory Memorial Hospital, 1324 North Sheridan Road, Waukegan, IL 60085</p> <p>Analysis Site: Dept. R46W, 1 _____, Abbott Laboratories, 100 Abbott Park Road, Abbott, IL 60064 Phone: (847) 937-0889</p>		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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The following dissolution method was proposed:

Apparatus: USP Dissolution Apparatus 2 _____

Rotation: _____

Medium: 25 mM Sodium Dodecyl Sulfate (SDS)

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/s/

Wei Qiu
12/2/03 10:13:23 AM
BIOPHARMACEUTICS

Hae-Young Ahn
12/5/03 09:13:17 AM
BIOPHARMACEUTICS