CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-203

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-203**	**Brand Name**	**Tricor®**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Fenofibrate tablets**
Medical Division	**510**	**Drug Class**	**Lipid lowering**
OCPB Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Adjunctive therapy to diet for Primary hypercholesterolemia, mixed dyslipidemia and Types IV and V hypertriglyceridemia**
OCPB Team Leader	**Hae-Young Ahn, Ph.D.**	**Dosage Form**	**tablet**
		Dosing Regimen	
Date of Submission	**03-05-01**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Abbott**
PDUFA Due Date	**09-05-01**	**Priority Classification**	
Division Due Date	**07-15-01**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) - Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	3		

CC: NDA 21-203, HFD-850(Electronic Entry or Lee), HFD-510(Simoneau), HFD-870(Ahn, Malinowski, Hunt)

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA # 21-203	**SUBMISSION DATE: 05-March-01**
BRAND NAME:	**Tricor®**
GENERIC NAME:	**Fenofibrate Tablet**
REVIEWER:	**Wei Qiu, Ph.D.**
SPONSOR:	**Abbott Laboratories**
TYPE OF SUBMISSION:	**Amendment of a pending application**

TERMS AND ABBREVIATIONS:

AUC0-t ..... area under the plasma-concentration-time curve from time 0 to time of last measurable concentration
AUC0-∝ ..... area under the plasma concentration-time curve from time 0 to infinity
BA..... ..... Bioavailability
BE..... ..... Bioequivalence
Cmax .. .. Maximum observed drug concentration
DMEDP..... Division of Metabolic and Endocrine Drug Products
DSI..... ..... Division of Scientific Investigation
NDA .... New Drug Application
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
QC .... Quality control
SD..... ..... Standard deviation
T1/2..... ..... Terminal phase elimination half-life
Tmax... ..... Time to reach maximum observed drug concentration

SYNOPSIS:

Abbott Laboratories submitted an amendment to pending NDA 21-203 for TRICOR® (fenofibrate tablets) 54 mg, [redacted] and 160 mg tablets on 05-March-01

Tricor® (fenofibrate capsules) is an approved marketed drug product as 67mg, 134 mg, and 200 mg strengths. Abbott has developed a new [redacted] tablet formulation as 54 mg, [redacted] and 160 mg strengths. Since there were no clinical trials conducted with this new formulation to support the safety and efficacy, in the original submission (10-NOV-99) the sponsor attempted to generate a concentration-response (PK-PD) relationship to seek approval. However, the concentration-effect analysis (CFEN-8802) presented by the sponsor was found inadequate to confirm the concentration-effect relationship. Two pharmacokinetic studies were also included in the original submission. A pharmacokinetic study M98-961 was a comparative BA study for comparing the 54 mg tablet and the 67 mg capsule under fed condition. The results of this study showed that the two formulations were comparable under fed condition. The other pharmacokinetic study (M98-962) showed that the 160 mg tablet and three 67 mg capsules were comparable under fed condition. However, a comparative PK study was not conducted to compare the 160 mg tablet and the 200 mg capsule. Since the sponsor did not conduct a BE study under fasting conditions as directed by the Agency, a two-way crossover bioequivalence study that compares the 160 mg tablet with the 200 mg capsule under fasting conditions was recommended. In addition, the in vitro

dissolution information including only one dissolution condition was found incomplete to the Agency. Additional dissolution studies were requested.

This amendment included two bioequivalence studies and some dissolution data. A pilot bioequivalence study (24 subjects) and a pivotal bioequivalence study (160 subjects) compared the 160 mg tablet with the 200 mg capsule under fasting conditions. In both studies the 160 mg tablet met the requirement for demonstrating bioequivalence to the 200 mg capsule with respect to AUC0-∞, but the Cmax from the tablet was higher than that from the capsule. The dissolution results using paddle speed of [redacted]

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-203 submitted on 05-03-01 and finds it acceptable provided that the DSI audit results are appropriate. In addition, the following dissolution method and specification is recommended. This recommendation and the labeling comments (p. 10) should be sent to the sponsor as appropriate.

Appraratus	USP Apparatus 2 (Paddle)
Agitation	[redacted]
Medium	0.05 M Sodium Dodecyl Sulfate
Volume of Medium	1000 mL
Assay	[redacted]
Tolerance	Not less than [redacted] (Q) in 30 minute

Table of Contents

BACKGROUND:

Fenofibrate is a lipid-regulating agent indicated as adjunctive therapy to diet for the treatment of adult patients with primary hypercholesterolemia, mixed dyslipidemia and Types IV and V hypertriglyceridemia.

The activity of fenofibric acid, the active metabolite of fenofibrate, appears to be due to activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma. Activation of PPARα also induces an increase in the synthesis of HDL-cholesterol.

Currently, fenofibrate is marketed as TRICOR® in 67, 134, and 200 mg capsule strengths. Fenofibrate absorption is markedly improved more than 30% when the drug is given with food. The approved labeling states that TRICOR capsules should be administered once daily with a meal.

In adults, the recommended initial dose of fenofibrate is 67 to 200 mg per day. For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 200 mg per day. For adult patients with hypertriglyceridemia, the initial dose is 67 to 200 mg per day.

STUDY SUMMARY INDEX

DISSOLUTION:

Q: Is the dissolution method and specification acceptable?

In the original NDA submission the sponsor used the approved dissolution method for capsule (Table 1) which was found to be unacceptable for tablets. Additional dissolution data was requested at paddle speed of

This amendment contained dissolution data (n = 12) from three lots of each strength (54 mg, and 160 mg), tested at paddle speeds of . Mean dissolution profiles comparing the rpm data from each lot are presented in Table 2 and Figure 1. The release was fast and complete at both . On average, more than of the claimed drug dissolved in The dissolution rate was faster at , with the exception of one 54 mg tablet from lot 47800AL, which released slower than the other tablets tested from the same lot at either agitation rate. The sponsor concluded that the results presented for lot 47800AL confirmed that the paddle speed method was able to discriminate slower releasing tablets. However, it should be recognized that at paddle speed of this slow tablet would exhibit slower dissolution rate compared to paddle speed of Therefore, the data presented for lot 47800AL can not be used to justify agitation rate.

Overall, with the facts that on average more than of the label-claim drug product of all strengths dissolved in and the dissolution rate was slower using , it was recommended by the Agency that the dissolution method with specification of not less than s using paddle speed of is appropriate for this product (Table 1).

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

ANALYTICAL METHODOLOGY:

Q. Have the analytical methods been adequately validated?

Table 3. Summary of Analytical Methods

Assay method
Clinical Study
Sensitivity (LOQ)
Linearity
Internal standard
Standards
Precision
Accuracy

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Bioequivalence

Q: Was the bioequivalence between 160 mg tablet and 200 mg capsule established?

In the original NDA submission, a comparative bioavailability study between 160 mg tablet and three 67 mg capsules, and between 54 mg tablet and 67 mg capsule were conducted under fed condition. The analyses of log-transformed Cmax and AUC0-∞ showed that the 160 mg fenofibrate tablet and three 67 mg reference fenofibrate capsules were comparable under fed condition. It was also shown that the 54 mg tablet was comparable to the 67 mg capsule under fed condition (Table 4).

Table 4. Comparison of bioavailabilities of tablets and capsules under fed condition

Study	Regimens Test vs. Reference	PK parameters	Relative Bioavailability	
			Point Estimate*	90% CI
M98-962	160 mg Tablet (N = 36) vs. 3×67 mg Capsules (N = 36)	Cmax	0.955	0.887-1.028
		AUC0-∞	0.900	0.864-0.937
M98-961	54 mg Tablet (N = 38) vs. 67 mg Capsule (N = 38)	Cmax	0.922	0.871-0.975
		AUC0-∞	0.854	0.826-0.882

*. Antilogarithm of the difference (tablet minus capsule for nonfasting bioequivalence evaluation) of the least squares means for logarithms.

Two BE studies were conducted to compare, in fasting state, the bioavailability of fenofibric acid from one

160 mg tablet and one 200 mg capsule, taken as reference. Both studies were Phase I, single-dose, two-way cross-over, open label, and randomized study. Doses in the two periods were separated by 14 days. In the pivotal study (M00-253), 160 subjects participated in the study and 153 subjects were included in the primary statistical analyses of the pharmacokinetic parameters. In the pilot study (K 178 00 03 KH 01 02), a total of 25 healthy Caucasian male volunteers were enrolled, 24 of which completed the study.

Summary of fenofibric acid pharmacokinetic parameters are provided (Table 5). The bioavailability of the test formulation relative to that of the reference formulation was assessed by the two one-sided tests procedure via 90% confidence intervals. Both studies demonstrated that the 160 mg tablet was bioequivalent to the 200 mg capsule with respect to AUC0-∞ since the 90% confidence intervals limits were within 0.80 – 1.25, the Cmax being higher for tablet about 36%.

Table 5. Summary (mean ± SD) of the pharmacokinetic results

Study	M00-253		K 178 00 03 KH 01 02	
Regimen	160 mg Tablet	200 mg Capsule	160 mg Tablet	200 mg Capsule
Tmax (hr)	6.4 ± 7.4	8.8 ± 11.2	-	-
Cmax (µg/mL)	3.55 ± 2.10	2.72 ± 2.11	3.08 ± 1.11	2.21 ± 1.03
AUC0-t (µg/mL.h)	110.9 ± 38.2	98.3 ± 40.3	90.79 ± 34.32	78.30 ± 31.30
AUC0-∞ (µg/mL.h)	116.8 ± 43.1	106.6 ± 47.2	96.09 ± 39.03	85.33 ± 40.57
T1/2 (hr)	20.7	21.8	23.58 ± 9.73	26.02 ± 10.94
	Relative Bioavailability		**Relative Bioavailability**	
	Point Estimate* (Tablet/Capsule)	90% CI	Point Estimate* (Tablet/Capsule)	90% CI
Cmax	1.358	1.257-1.468	1.42	1.29-1.57
AUC0-∞	1.127	1.083-1.173	1.15	1.07-1.23

* Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

Food Effect: The food effect studies showed similar increases in absorption in terms of AUC values for 67 mg capsule (35%), 200 mg capsule (37%), and 160 mg tablet (35%). Therefore, the food effect on capsule and tablet are comparable. However, the fenofibric acid Cmax was about 2.5 fold and 2 fold higher when fenofibrate was administered with food for 200 mg capsule and 160 mg tablet, respectively.

Inter-Subject Variability: The inter-subject variabilities for both Cmax and AUC values were smaller in tablets compared to capsules under fasting conditions. In contrast, under fed conditions, capsules and tablets exhibited similar inter-subject variabilities. In addition, food decreased the variability for both capsules and tablets greatly (Table 6).

Table 6. Comparison of inter-subject variability between Tablet and Capsule.

	Tablet		Capsule		
	160 mg		200 mg		3×67 mg
	Fast	Fed	Fast	Fed	Fed
Cmax %CV	42%[b] 59%[c]	21%[b]	76%[a] 78%[c]	25%[a]	29%[b]
AUC0-∞ %CV	40%[b] 37%[c]	32%[b]	38%[a] 44%[c]	42%[a]	32%[b]

[a]: Study M98-874
[b]: Study M98-962
[c]: Study M00-253

Comments:

1. In this NDA submission, fasting BE studies were conducted between 160 mg tablet and 200 mg capsule (RLD). The results showed that the 160 mg tablet was bioequivalent to the 200 mg capsule in terms of AUC0-∞ but had 36% higher Cmax than the 200 mg capsule under fasting conditions. However, the Cmax of tablets under fasting condition is much lower than that under fed condition. Therefore, there is no safety concern for higher Cmax of tablets.
2. A comparative BA study showed that the 54 mg tablet and 67 mg capsule were equivalent under fed condition. In addition, the 160 mg tablet and three 67 mg capsules were equivalent under fed conditions.
3. Theoretically, food increases the solubility of the poorly soluble fenofibrate. Subsequently, food increased the bioavailability of tablets and capsules to the same extent about 35%.
4. Labeling insert stated that both tablets and capsules should be taken with meals.
5. Therefore, the Agency agreed that tablets and capsules are therapeutically equivalent.
6. The sponsor should not have conducted a BE study with 160 subjects. A pilot BE study showed that the Cmax value of the 160 mg tablet was about 40% higher than that of the 200 mg capsule. The 90% confidence interval showed that higher Cmax was not due to inter-subject variability. Thus, increasing the number of subjects would not make the Cmax values equivalent.

[redacted] . The

LABELING COMMENTS:

(~~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

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under [redacted] conditions to 67 mg and 200 mg capsules, respectively

Absorption

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

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

Distribution

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

Metabolism

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

Appendix 1. Study Summaries

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

2.0 Synopsis

Abbott Laboratories **Name of Study Drug:** Fenofibrate (ABT-799) **Name of Active Ingredient:** Fenofibric Acid	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only):**
Title of Study: Comparison of the Bioavailability of Fenofibric Acid from a 160 mg Tablet Formulation of Fenofibrate with that from a 200 mg Capsule Formulation of Fenofibrate under Fasting Conditions		
Investigator: [redacted]		
Study Site:		
Publication (Reference): not applicable		
Studied Period: **Study Initiation Date:** 26 September 2000 **Date First Subject Dosed:** 13 October 2000 **Date Last Subject Completed Dosing:** 03 November 2000 **Study Completion Date:** 08 November 2000	**Phase of Development:** 1	
Objective: The objective of this study was to compare the bioavailability of fenofibric acid following administration of a 160 mg fenofibrate tablet relative to that following administration of a 200 mg fenofibrate capsule under fasting conditions		
Methodology: This Phase I, single-dose, fasting, open-label, single-center, randomized study was conducted according to a two-period, crossover design. Subjects received a single dose of study drug once in each period under fasting conditions. For each cohort of subjects (N = 80), a washout interval of 14 days separated the doses in the two study periods. Blood samples (approximately 7 mL) were collected into evacuated collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 12, 18, 24, 48, 72, 96 and 120 hours after the dose in each study period. Plasma concentrations of fenofibric acid were determined [redacted] Samples were analyzed between the dates of 14 November 2000 and 08 January 2001.		
Number of Subjects: Planned: 160; Entered: 160; Completed: 152; Received both formulations: 154; Evaluated for Safety: 160; Evaluated for Pharmacokinetics: 153 For the 160 subjects who participated in the study, the mean age was 36.9 years (range of 18 to 51 years), the mean weight was 69.8 kg (range of 50.9 to 100.5 kg) and the mean height was 165.7 cm (range of 147.3 to 190.5 cm). For the 153 subjects who were included in the primary statistical analyses of the		

pharmacokinetic parameters, the mean age was 36.8 years (range of 18 to 51 years), the mean weight was 69.8 kg (range of 50.9 to 100.5 kg) and the mean height was 165.7 cm (range of 147.3 to 190.5 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were to be male and female volunteers between 18 and 50 years of age, inclusive. Subjects in the study were judged to be in general good health based on the results of a medical history, physical examination, laboratory profile and electrocardiogram (ECG). Females were postmenopausal, sterile or if of childbearing potential, were not pregnant or nursing and were practicing an acceptable method of birth control.

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

	A (Test)	B (Reference)
Dosage Form	Tablet	Capsule
Strength (mg)	160	200
Mode of Administration	Oral	Oral
Bulk Product Lot Number	69-447-2E	69-417-2E-21
Bulk [redacted]	[redacted]	NA
Potency (% of Label Claim)	100.9	97.8
Manufacturing Site	Laboratories Fournier*	Laboratories Fournier*
Batch Size	[redacted]	[redacted]
Finishing Sublot Number	70-096-S2	NA
[redacted]	[redacted]	NA
Expiration/Retest Date	31 October 2001	01 October 2002

NA = Not Applicable.

Duration of Treatment: A single dose (one 160 mg tablet or one 200 mg capsule) was administered under fasting conditions in each of two periods.

Criteria for Evaluation:

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

Safety: Safety was evaluated based on adverse event, physical examination, vital signs and laboratory tests assessments.

Statistical Methods: Analyses of variance (ANOVAs) were performed for T_{max}, and the natural logarithms of C_{max}, AUC_t and AUC_∞. The model included fixed effects for cohort, sequence, period, formulation and interactions of cohort with each of sequence, period and formulation, and random effects for subject nested within cohort-sequence combination.

The bioavailability of the test formulation relative to that of the reference formulation was assessed by the two one-sided tests procedure via 90% confidence intervals. Bioequivalence between the test

formulation and the reference formulation was to be 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.

The number and percentage of subjects reporting adverse events were tabulated by COSTART term and body system. Laboratory values that were identified as being Very Low or Very High according to predefined Abbott criteria were flagged and evaluated for clinical significance.

Summary/Conclusions:

Pharmacokinetic Results: Mean ± SD pharmacokinetic parameters are listed in the following table.

Pharmacokinetic Parameters		Formulation A: 160 mg Tablet (Test) (N = 153)	Formulation B: 200 mg Capsule (Reference) (N = 153)
T_{max}	(h)	6.4 ± 7.4*	8.8 ± 11.2
C_{max}	(µg/mL)	3.55 ± 2.10*	2.72 ± 2.11
AUC_t	(µg•h/mL)	110.9 ± 38.2*	98.3 ± 40.3
AUC_∞	(µg•h/mL)	116.8 ± 43.1*	106.6 ± 47.2
$t_{1/2}$$	(h)	20.7	21.8

* Statistically significantly different from reference (Formulation B, ANOVA, $p < 0.05$).
$ Harmonic mean, parameter was not tested statistically

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

Formulations Test vs Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
A vs B	C_{max}	3.114	2.293	1.358	1.257 – 1.468
	AUC_t	104.43	90.50	1.154	1.111 – 1.199
	AUC_∞	109.18	96.85	1.127	1.083 – 1.173

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

Safety Results: Thirteen (13/160) of the subjects reported at least one treatment-emergent adverse event (event with onset after the first dose of study drug) during the study. The most commonly reported treatment-emergent adverse event was headache, reported by three subjects (1.9%) receiving Formulation A and by two subjects (1.3%) receiving Formulation B. All other treatment-emergent adverse events were reported by at most one subject with either the test or reference formulation.

The total number of subjects reporting treatment-emergent adverse events by formulation was as follows: Formulation A (6 subjects, 3.8%) and Formulation B (8 subjects, 5.1%). All adverse events were rated by the investigator as mild or moderate in severity.

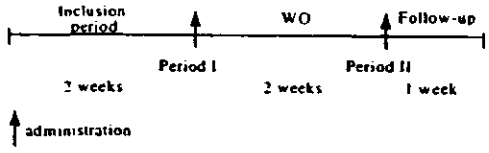
Adverse events that were found by the investigator to be possibly or probably drug related were reported by four subjects (2.5%) receiving Formulation A and four subjects (2.5%) receiving Formulation B.

Conclusions: The two one-sided tests procedure based on the analyses of log-transformed AUC_{∞} showed that the 160 mg fenofibrate tablet formulation (Formulation A) met the bioequivalence criterion relative to the reference 200 mg fenofibrate capsule formulation (Formulation B) since the 90% confidence interval for AUC_{∞} was within the 0.80 to 1.25 range. However, the 90% confidence interval for C_{max}, comparing Formulation A to Formulation B, exceeded the 0.80 to 1.25 range, with the tablet formulation having a higher central value.

Both formulations tested were generally well tolerated by the subjects. No clinically significant physical examination results, vital signs, laboratory measurements or adverse event profiles were observed during the course of the study. All of the adverse events were considered mild or moderate in severity and resolved quickly. There were no apparent differences between the formulations with respect to safety

Date of Report: 27 February 2001

2. SUMMARY

NAME OF STUDIED PRODUCT	Fenofibrate
TITLE	COMPARATIVE BIOAVAILABILITY STUDY OF ONE TABLET CONTAINING 160 MG OF FENOFIBRATE Ter VERSUS ONE CAPSULE CONTAINING 200 MG OF MICRONISED FENOFIBRATE. AFTER SINGLE ADMINISTRATION IN FASTING STATE, IN 24 HEALTHY SUBJECTS
INVESTIGATOR	[redacted]
STUDY LOCATION	[redacted]
START AND END OF STUDY	Start: October 05, 2000 End: November 16, 2000
AIM OF THE STUDY	To compare, in fasting state, the bioavailability of fenofibric acid from one tablet containing 160 mg of fenofibrate Ter and one capsule containing 200 mg of micronised fenofibrate.
CLINICAL PHASE	I
EXPERIMENTAL DESIGN	Open, randomized, 2-way cross-over design with at least a two-week wash-out period between each administration day.  WO: wash-out
NUMBER OF SUBJECTS	24
INCLUSION CRITERIA	Healthy male volunteers (18 - 55 years old)
TEST TREATMENT DOSAGE	**Treatment A:** one tablet containing 160 mg of fenofibrate Ter administered in fasting state (test) **Treatment B:** one capsule containing 200 mg of micronised fenofibrate administered in fasting state (reference) All treatments were administered in fasting state, orally with exactly 200 ml of mineral water.
REFERENCE TREATMENT, DOSAGE	Treatment B: 200 mg of micronised fenofibrate in fasting state

TREATMENT DURATION	2 treatment days separated by a two-week wash-out period
EVALUATION CRITERIA	**PRIMARY CRITERIA** **Pharmacokinetics** From fenofibric acid plasma levels determined: at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 48, 72, 96 and 120 h after each administration (n = 38 ; i.e. 190 ml blood volume per subject), determined using an validated [redacted]. The method is fully described in the analytical report K 178 00 06 KHA 00 02 presented in Appendix B-4. Pharmacokinetic parameters: AUC_t, AUC_∞, C_{max}, t_{max}, $t_{1/2}$, λ_z **SECONDARY CRITERIA** **Safety and tolerability** • adverse events, • laboratory tests (pre-, on and post-treatment periods), • vital signs, ECG.
STATISTICAL METHODS	**Pharmacokinetics** Descriptive analysis for each parameter: mean ± SD, max and min. Statistical analysis: – ANOVA on log transformed data (AUCt, AUC∞ and Cmax) for the comparison of the 2 treatments. – The 90% confidence interval was calculated on log transformed data (AUCt, AUC∞ and Cmax) for the comparison of treatment A with treatment B (taken as reference). Bioequivalence of the formulations was to be concluded if the 90% confidence intervals of the relative mean AUC∞ and Cmax (test/reference) were included within 80-125% limits. – Non parametric test (WILCOXON test) for tmax comparisons. **Safety and tolerability** Summary statistics (mean ± SD, max and min) determined in the 24 subjects who completed both periods and were used for bioequivalence analysis and in the all subjects who participated in the study.
RESULTS	
STUDY SUBJECTS	A total of 25 healthy caucasian male volunteers were enrolled, 24 of which completed the study. All subjects were non-smokers or smoked less than 10 cigarettes a day. One subject (No. 005) withdrawn one day after dosing on period 1 for personal reasons. This subject was replaced by Subject No. 105. All volunteers were male and Caucasian, the mean age was 32 ± 9 years (MIN 21 years, MAX 52 years), the mean weight was 74 ± 8 kg (MIN 60 kg, MAX 91 kg) and the mean height was 177 ± 8 cm (MIN 162 cm, MAX 194 cm) at inclusion.

ANALYTICAL METHODS

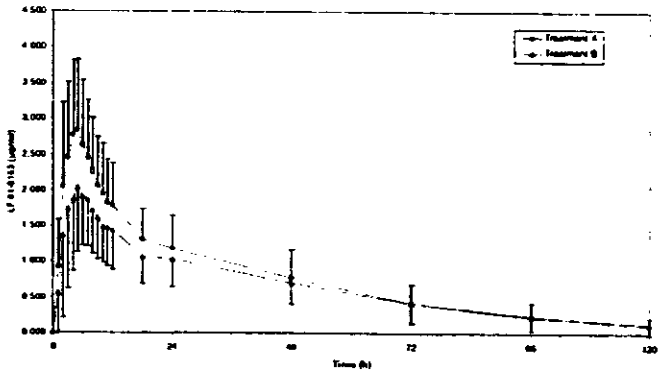
The quality control results obtained throughout the study are as follows:

CALIBRATION CURVES	Mean slope (n = 11): 0.18815, CV = 3.8% Mean coefficient of determination: 0.99987 , CV = 0.009%			
QUALITY CONTROLS	**µg/ml**	**n**	**PRECISION %**	**ACCURACY %**
QC1	0.05	28		
QC2	4.5	28		
QC3	9.0	28		

Following successful pre-analysis validation, quality control results determined during the study demonstrate that, after column and pre-column problems solving, the method is reliable and provides a good level of confidence in the accuracy and precision of the plasma level results obtained for pharmacokinetic analysis.

FENOFIBRIC ACID PLASMA LEVELS

Mean (SD) fenofibric acid plasma curves obtained following the two treatments (A: 160 mg of fenofibrate Ter tablet and B: 200 mg of micronised fenofibrate capsule)



FENOFIBRIC ACID PLASMA PHARMACOKINETICS

STATISTICAL RESULTS

The following table presents the geometric mean values for the pharmacokinetic parameters, the 90% CI and the point estimates used for the bioequivalence test :

	Treatment A 160 mg fenofibrate ter Tablet *In fasting state*	**Treatment B** 200 mg micronised fenofibrate Capsule *In fasting state* = **Reference**	**90% Confidence interval*** (log-transformed) Lower : Upper
AUC_t (µg/ml.h)	**85.24**	**72.98**	**1.10 : 1.24** Point estimates = 1.17
AUC (µg/ml.h)	**89.38**	**77.94**	**1.07 : 1.23** Point estimates = 1.15
Cmax (µg/ml)	**2.90**	**2.04**	**1.29 : 1.57** Point estimates = 1.42

SAFETY	**SAFETY AND TOLERABILITY** Five (5) adverse events occurred during the study in 4 subjects: one episode of myalgia and one episode of epistaxis under treatment A, one episode of headache, one episode of myalgia and one episode of rhinitis under treatment B. The relationship of these AEs to the study drug was judged by the investigator as not related, unlikely or possible. Some subjects presented out-of-range vital sign and ECG values but none of them were judged by the investigator as clinically significant. **BIOLOGICAL TOLERANCE** Some out of range laboratory values were observed during the study but none of them were considered by the investigator as clinically significant.
CONCLUSION	This study was performed to compare, in fasting state, the bioavailability of fenofibric acid from one tablet containing 160 mg of fenofibrate Ter (treatment A) and one capsule containing 200 mg of micronised fenofibrate (treatment B), taken as reference. For both AUCt and AUC∞, the 90% confidence intervals of the relative mean AUC and Cmax (test/reference) were included within 0.80-1.25 limits. For Cmax, however, the 90% confidence intervals limits were outside 0.80 – 1.25 limits. For Tmax, the difference between means was not statistically significant. Therefore, although the bioequivalence between the tested formulation and the reference cannot be formally concluded, it appears that these treatments are equivalent in terms of AUC, the Cmax being higher with 160 mg of fenofibrate Ter in fasting conditions. The intersubject variability is lower for AUC and Cmax following 160 mg fenofibrate Ter. The overall safety of the 2 treatments was good during the study.

Formulation of 54 mg [redacted], and 160 mg tablets

Component	Amount per Tablet (mg)		Function
	54 mg Strength	160 mg Strength	
Fenofibrate	54.0	160.0	Active
Sodium Lauryl Sulfate			Wetting
Lactose, Monohydrate			Diluent
Povidone			Binder
Microcrystalline Cellulose			Compress
Colloidal Silicon Dioxide			Glidant
Crospovidone			Disintegrant
Sodium Stearyl Fumarate			Lubricant
[redacted]			
Total weight			

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 15

❖❖❖

Draft Labeling
(not releasable)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wei Qiu
7/13/01 02:27:26 PM
PHARMACOLOGIST

Hae-Young Ahn
7/13/01 04:10:46 PM
BIOPHARMACEUTICS

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

General Information About the Submission

	Information		Information
NDA Number	21-203	Brand Name	Tricor®
OCPB Division (I, II, III)	II	Generic Name	Fenofibrate tablets
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Adjunctive therapy to diet for Primary hypercholesterolemia, mixed dyslipidemia and Types IV and V hypertriglyceridemia
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	tablet
		Dosing Regimen	
Date of Submission	03-05-01	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Abbott
PDUFA Due Date	09-05-01	Priority Classification	
Division Due Date	07-15-01		

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:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
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 -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	3		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?	**Yes.**	The following items are requested: CD-ROM disk containing overall summary of human PK studies, study synopsis (2-3 pages), and a summary table of analytical method validation studies in Word format.
QBR questions (key issues to be considered)	**1. Is the 160 mg tablet bioequivalent with the 200 mg Tricor capsule conducted under fasting conditions?** **2. Is the dissolution method acceptable?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Done T. Cox 4/30/01

CC: NDA 21-203, HFD-850(Electronic Entry or Lee), HFD-510(Simoneau), HFD-870(Ahn, Malinowski, Hunt)

Content:

Abbott Laboratories were asked to submit a BE study under fasting condition and additional dissolution data. Two BE protocols were submitted-identical but the number of subjects to be enrolled were different (24 subjects vs. 160 subjects). Twenty-four subjects would not be adequate due to the high variability seen with this drug under fasting condition. OCPB suggested that a higher number subjects would have a better chance for success. In this submission, the sponsor submit two BE studies including one BE study under fasting condition in 160 subjects and a supporting BE study under fasting condition in 24 subjects. In terms of dissolution data, the sponsor agreed to submit additional dissolution data with 3 lots at —. In this application, the dissolution data (n=12) from three lots of each strength (54, —, 160 mg) tested at — rpm were submitted.

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-203	**Relevant NDAs:**	19-304 S001 – S005
Brand Name:	TRICOR™ Tablets	**Generic Name:**	Fenofibrate Tablets
Strength(s):	54 mg, [redacted], 160 mg		
Sponsor:	Abbott Laboratories, 100 Abbott Park Road, D491, AP6B-1SW, Abbott Park, IL 60064-6108		
Submission Date:	10-NOV-99		
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		
PM Reviewer:	Sam H. Haidar, R.Ph, Ph.D.		

Terms and Abbreviations

Agency	Food and Drug Administration
AUC	Area under the plasma-concentration-time curve
BA	Bioavailability
BE	Bioequivalence
CPB	Clinical Pharmacology and Biopharmaceutics
C_{max}	Maximum drug concentration
DMEDP	Division of Metabolic and Endocrine Drug Products
FD&C	Food, Drug, and Cosmetic (Act)
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
NDA	New Drug Application
T_{max}	Time of maximum drug concentration
$t_{1/2}$	Drug elimination half-life

Synopsis

Abbott Laboratories has submitted NDA 21-203 for TRICOR™ (fenofibrate) 54 mg, [redacted], and 160 mg tablets. This is the second major formulation change for this product. The original product, Lipidil™ 100 mg capsule, was approved by the Agency on 31-DEC-93, but never marketed in the United States. The second product, TRICOR™ Micronized 67 mg capsule, was determined to be bioequivalent to the Lipidil™ 100 mg capsule and was approved on 12-FEB-98. Both of these approvals were granted under NDA 19-304. Subsequent supplemental applications, filed under NDA 19-304, have led to the approval of two additional strengths of TRICOR™ Micronized Capsules: 134 mg and 200 mg. The 67 mg TRICOR™ capsule is the reference listed drug in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) drug list (see **Equivalence Table below**).

Actual and Theoretical Equivalence Table				
1 x 100 mg standard capsule	=	1 x 67 mg micronized capsule	≠	1 x 54 mg tablet
2 x 100 mg standard capsule	=	1 x 134 mg micronized capsule	≠	[redacted]
3 x 100 mg standard capsule	=	1 x 200 mg micronized capsule	≠	1 x 160 mg tablet

In the pre-NDA meeting for TRICOR™ Tablets, held on 7-SEP-99, the sponsor agreed to the following three conditions: 1) the NDA would be filed under section 505(b)(2) of the FD&C Act as a stand alone NDA; 2) the sponsor was to generate a concentration-response relationship; and 3) approvability of the NDA would be based on the concentration-response (PK-PD) relationship and not on a bioequivalence claim. These conditions were required of the sponsor because they (the sponsor) did not show bioequivalence between the new tablet formulation and the reference listed product under fasting conditions. There were no clinical trials conducted with this new formulation. As such, the sponsor submitted the following in an attempt to support the safety and efficacy of the new tablet formulation:

1. Demonstration of a concentration-effect (PK/PD) relationship of plasma fenofibric acid levels and hyperlipidemia efficacy parameters;

2. Demonstration that the plasma concentrations of fenofibric acid from the tablet dosage form are comparable to the plasma concentrations from the original clinical trials used for the approval of fenofibrate for evaluation of efficacy; and
3. Demonstration that the plasma fenofibric acid levels from the tablet formulation do not exceed the plasma concentrations of the original trials for the evaluation of safety.

In an effort to confirm the sponsor's demonstration of concentration-effect relationship, a pharmacometrics consult from the Office of Clinical Pharmacology and Biopharmaceutics was requested. Results of that consult state that the concentration-effect analysis presented by the sponsor was not adequate to confirm the relationship. There were also several issues raised concerning the E_{max} model that was fitted to the fenofibrate data (see **Appendix – PM Review**). As a result of the failure to establish a reasonable concentration-effect relationship, the second and third "demonstration" points listed above are unsubstantiated.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-203 submitted 10-NOV-99. The overall Clinical Pharmacology and Drug Interactions Sections are **not acceptable** to OCPB as presented in this application. Please convey **Comments to Firm** to the sponsor as appropriate.

Table of Contents

Appendix Index

Background

TRICOR™ Micronized Capsules are currently indicated as adjunctive therapy to diet for the reduction of cholesterol (LDL-C and Total-C), triglycerides, and Apo-B. The mechanism by which fenofibrate achieves these benefits is thought to be due to the activation of peroxisome proliferator activated receptor α

(PPAR-α). Specifically, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from the plasma by activating apoprotein C-III, an inhibitor of lipoprotein lipase activity. This reduces triglyceride levels, which results in a modification in the size and composition of low density lipoproteins, from small, dense particles, to larger buoyant particles that have a higher affinity for cholesterol receptors and are readily catabolized.

The starting dose of TRICOR™ tablets is 160 mg/day for adult patients with primary hypercholesterolemia or mixed hyperlipidemia, and 54 mg/day for those with hypertriclyceridemia. TRICOR™ tablets are administered once daily with a meal.

Drug Formulation
Is the composition of each strength tablet similar?

TRICOR™ tablet compositions are proportionally similar between strengths and differ only in their respective multiples and color coatings.

Components and Composition					
Component	Compendial Grade	54 mg Amount Per Tablet (mg)		160 mg Amount Per Tablet (mg)	Function
Fenofibrate	In-house	54.0		160.0	Active
Sodium Lauryl Sulfate	NF 18				Wetting
Lactose, Monohydrate	NF18				Diluent
Povidone	USP 23				Binder
Purified Water[1]	Eur. Pharm.				Solvent
Microcrystalline Cellulose	NF 18				Compress.
Colloidal Silicon Dioxide	NF 18				Glidant
Crospovidone	NF 18				Disintegrant
Sodium Stearyl Fumarate	NF 18				Lubricant
Sub-Total					
Purified Water[1]	Eur. Pharm.				Solvent
Total		245.3		722.0	

1. Removed from the product during the manufacturing process.

Dissolution
Has the sponsor proposed appropriate dissolution methods and specifications?
Was sufficient data submitted for evaluation of the dissolution methods and specifications?
Was a profile comparison made between the previous capsule and new tablet formulations?

Dissolution Methods	
Apparatus:	
Speed:	
Medium:	
Volume:	
Units Tested:	12

Time Points:	10, 20, 30, and 40 minutes
Specifications:	NLT [redacted]

Dissolution Results				
Clinical Study:	*	*	*	M98-962
Bulk Lot #:				
Strength:				
10 min	[redacted]			
20 min				
30 min				
40 min				

* Biowaiver request for the [redacted] strength tablets – not used in clinical studies; Mean (SD)

There was insufficient data provided to evaluate the method and specifications for TRICOR™ Tablets. Although this method is useful for the micronized capsules and perhaps when comparing the relative rates of dissolution between the micronized capsules and the new tablet formulation (see below table), it is not an acceptable method for providing quality control assessment of the tablets (see ***Comments to Firm***).

Comparison of Dissolution of the 54 mg Tablet and 67 mg Capsule Formulations	
Strength:	
10 min	
20 min	
30 min	
40 min	
60 min	
Amount Released (%) ± SD	

Analytical Methodology
Have the analytical methods been sufficiently validated for the two PK studies?

Human plasma samples were analyzed for fenofibric acid using a validated HPLC method and was found to be acceptable. Results of the assay validation reports are provided in the following table:

Study #:	M98-961	M98-962
UQL (µg/mL):		
LLQ (µg/mL):		
Calibration (µg/mL):		
Precision (%RSD):		
Accuracy (%):		

Human Pharmacokinetics Studies
– Concentration-Effect Relationship –
Was an adequate PK/PD relationship established for TRICOR™?
Was the new PK data generated from studies M98-961 and M98-962 applied to the PK/PD model?

The answer to both of these questions is no. In an attempt to establish a concentration-effect relationship between fenofibric acid (fenofibrate is hydrolyzed in the blood and cannot be reliably measured) and pharmacodynamic endpoints (e.g., triglycerides, total cholesterol, LDL cholesterol, etc.) the sponsor used a phase III clinical trial (CFEN-8802) that compared the efficacy of the fenofibrate standard formulation (3 x 100 mg QD) with TRICOR™ micronized capsules (1 x 200 mg QD). CFEN-8802, was a three-way, placebo controlled, parallel design study, with 41 to 46 type IIa or IIb hyperlipidemia patients per arm (see **Appendix** for full study summary and **PM Review**). Results of PK-PD analysis were then to be applied to the PK data generated from the to-be-marketed tablet formulation studies, M98-961 and M98-962. There was no new pharmacodynamic data submitted for the to-be-marketed tablet formulation.

Essentially, the sponsor used the data from study 8802 to determine a range of effective drug concentrations for fenofibric acid. They then defined the minimum effective concentration of fenofibric acid at — a value where there was a ≥ 15% change in the respective pharmacodynamic endpoints from baseline. Since the C_{max} for the 160 mg TRICOR™ tablet (8.02 µg/mL ± 1.70) was — after a single dose, under fed conditions, it was concluded that the new formulation would be effective. Extrapolations of the new tablet formulation PK data to determine C_{max}, C_{avg}, and C_{min} at steady-state for the 54 mg and 160 mg strengths were not made.

Two major issues were immediately identified concerning the data used to create the model and the model itself. First, the sampling and dosing times were not recorded for study 8802, which prevented a temporal relationship from being defined for the plasma drug levels and the PD endpoint, and second, the E_{max} model is inappropriate because of fenofibrate's mechanism of action and the fact that E_{max} has not been established.

Also, when a model is generated for one set of data, with the intent of allowing for the prediction of some unknown endpoint from a second set of data, it is customary to apply the second data set to the model so that a predictive measurement is obtained. The model should also be validated in some way. These items were perhaps overlooked by the sponsor.

– Single Dose Bioequivalence –

Was bioequivalence established between TRICOR™ tablets and TRICOR™ micronized capsules? Was dosage form proportionality established between the to-be-marketed formulations?

Two pharmacokinetic studies were submitted in this application. The first study, M98-961, was a two-way crossover design in normal healthy subjects, and evaluated the bioequivalence between TRICOR™ 54 mg tablets and TRICOR™ 67 mg capsules under fed conditions. The second study, M98-962, was a three-way crossover design in normal healthy subjects, and evaluated the dosage form proportionality between TRICOR™ 160 mg tablets and TRICOR™ 67 mg capsules under fed conditions. This study also included a food-effect appraisal that will be discussed under the – Food Effect – section. Results of the bioequivalence and dosage form proportionality portions of these two studies are presented in the following table.

Parameters	Study M98-961		Study M98-962	
	1 x 54 mg Tablet (test)	1 x 67 mg Capsule (reference)	1 x 160 mg Tablet (test)	3 x 67 mg Capsules (reference)
N	38	38	36	36
T_{max} (h)	3.7 ± 0.8*	4.6 ± 1.4	4.0 ± 0.9*	4.6 ± 0.9
C_{max} (µg/mL)	2.81 ± 0.53*	3.05 ± 0.59	8.02 ± 1.70	8.59 ± 2.50
AUC_{0-t} (µg*h/mL)	50.0 ± 15.6*	58.8 ± 19.5	129.6 ± 39.6*	142.7 ± 43.9
AUC_{0-inf} (µg*h/mL)	51.1 ± 16.3*	60.3 ± 20.6	132.5 ± 42.0*	147.1 ± 47.0
$t_{1/2}$ (h) [1,2]	18.4 ± 5.0*	19.1 ± 4.8	19.2 ± 5.7	20.3 ± 7.3
Cl/F (L/h) [3]	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	1.5 ± 0.5

* Statistically significantly different from the respective reference product ($p < 0.05$).
[1] Harmonic Mean ± Psuedo Standard Deviation.
[2] Evaluations of $t_{1/2}$ were based on statistical tests for β.
[3] Parameter was not tested statistically.

Relative bioavailability evaluations (i.e., point estimates and 90% confidence intervals) were also included in the application for both PK studies and are presented in the following table. However, because the sponsor failed to conduct these studies under fasting conditions as directed by the Agency, and because this application was based solely on the establishment of a PK-PD relationship, they are not considered to add relevant information to this review.

Regimens (test vs Reference)	Pharmacokinetic Parameters	Relative Bioavailability	
		Point Estimate	90% Confidence Interval
Study M98-961			
1 x 54 mg tablets vs. 1 x 67 mg capsules	C_{max}	0.922	0.871 – 0.975
	$AUC_{0-\infty}$	0.854	0.826 – 0.882
Study M98-962			
1 x 160 mg tablets vs. 3 x 67 mg capsules	C_{max}	0.955	0.887 – 1.028
	$AUC_{0-\infty}$	0.900	0.864 – 0.937

Dosage form proportionality was never directly established between the to-be market formulations. Rather, it appears that the sponsor was using the following rationale: if the 54 mg tablets were considered bioequivalent to the 67 mg capsules, and the 160 mg tablets were bioequivalent to 3 x 67 mg capsules, then dosage form proportionality between the to-be-marked products is implied. This novel approach is not considered acceptable.

– Food Effect –

What effect does food have on TRICOR™ Tablets?

Historical data for TRICOR™ Capsules suggest that when administered with food, the extent of absorption is increased by approximately 25% to 35%. In study M98-962 for TRICOR™ Tablets, a similar event was noted, with $AUC_{0-\infty}$ increasing to 32% under fed conditions. This information is included in the product labeling. TRICOR™ is indicated to be administered with food.

– Biowaivers –

Can the biowaiver request be granted ——— , strength tablet not used in the PK biostudies?

In order to grant a biowaiver for a drug product, three criteria must be met:

1. Are the individual strength tablets proportional?
2. Does dosage form proportionality span the range of the to-be-marketed strengths?
3. Does each strength tablet exhibit a similar dissolution profile?

The individual strength tablets are proportional. However, dosage form proportionality and dissolution information submitted in this application were insufficient to make a determination. Therefore, a biowaiver cannot be granted for ——— strength tablet at this time.

Labeling Comments

Labeling comments will be addressed with the subsequent submission. It is premature to discuss labeling at this time.

Comments to Firm

Concentration-Response Model

The concentration-response relationship, as described by the data submitted in this application, does not support the approval of this application for the following reasons:

1) Sampling and dosing times were not recorded for CFEN-8802, thus preventing the time-course of the effect relative to that of the PK from being defined.
2) Since a single dose, and its equivalent, were evaluated in the PK-PD analysis, the accuracy of the E_{max} estimates is questionable.
3) The model assumes no effect when drug concentration equals zero. However, data indicate that some subjects had a clinically significant response with placebo treatment. Therefore, normal fluctuations in the PD endpoints, which was not accounted for in the model, could have a significant effect on the precision of the estimated parameters.
4) The EC_{50} values were poorly estimated, as reflected by the large confidence intervals around the estimates, often containing zero, and the large intersubject variability.

Solution –

Further exploration of this path for approval is not recommended given the nature of the available data.

Bioequivalence

Bioequivalence has not been established between the TRICOR™ micronized capsules and TRICOR™ tablets.

Solution –

For approval of TRICOR™ Tablets, OCPB recommends conducting a 2-way crossover bioequivalence study that compares the 160 mg TRICOR™ Tablet with the 200 mg TRICOR™ Capsule under <u>fasting</u> conditions.

Dosage Form Proportionality

The indirect approach of establishing dosage form proportionality (DFP) as presented in this application is not acceptable. However, if the "solution" for bioequivalence is followed, a biowaiver for the two lower strengths can be considered which would make the DFP a non-issue for TRICOR™ Tablets.

Dissolution

The dissolution method that was submitted in this application is incomplete, thereby preventing the evaluation of the method and specifications. The method presented is perhaps useful when comparing the relative rates of dissolution between the tablet and micronized capsule formulations, but it is not appropriate for establishing a quality control measure for the new tablet formulation.

Solution –

Please submit alternative dissolution methods for fenofibrate tablets over the range of physiologic pH values, with and without sodium lauryl sulfate, as appropriate, for each of the to-be-marketed formulations.

/S/ 9.5.2000

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II

Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 24-AUG-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: /S/ 9/5/00

OCPB Briefing on: 31-AUG-00

Briefing Attendees:

Ahn, Hae-Young
Chen, Mei-Ling
Haidar, Sam H.
Huang, Shiew-Mei
Hunt, John
Johnson, Steven B.
Lee, Peter
Lesko, Larry
Mehta, Mehul
Orloff, David
Parks, Mary
Patnaik, Robbie
Selen, Arzu
Shore, Robert
Simoneau, Peggy
Sun, He
Wei, Xiao-Xiong "Jim"

CC: NDA 21-203 (orig., 1 copy), HFD-510 (Simoneau), HFD-870 (AhnH, HuangS, JohnsonST, HaidarS), HFD-850 (LeeP), CDR

Code: AE

APPEARS THIS WAY
ON ORIGINAL

2.0 Study Synopsis

Abbott Laboratories	*(For National Authority Use Only):*
Investigational Product: Fenofibrate (Tricor™)	
Active Ingredient: Fenofibrate	**Phase of Development:** Phase I

Title of Study: A Comparative Study of the Effect of Food on the Bioavailability of Fenofibric Acid from a 160-mg Tablet Formulation of Fenofibrate with that from a Capsule Formulation of Fenofibrate

Investigator: Robert O'Dea, PhD, MD

Study Site: Abbott Clinical Pharmacology Research Unit
Victory Memorial Hospital, Waukegan, Illinois

Publication (reference): N/A

Studied Period: 50 days

Study Day -1 (day prior to dosing): January 25, 1999

Date of last dose administration: March 10, 1999

Date of last scheduled study procedure: March 15, 1999

Objective(s): To compare the bioavailability of fenofibric acid from a 160-mg tablet formulation of fenofibrate with that from a capsule formulation of fenofibrate, both administered with food. The bioavailability of fenofibric acid from the tablet formulation administered under nonfasting and fasting conditions was also compared.

Study Design: Single-dose, open-label, randomized, three-period, crossover, single-center study. Subjects were confined to the research unit for approximately 7 days in each period. The doses in the three periods were separated by 14 days.

Subjects received a single dose of Regimen A, Regimen B or Regimen C in each period. The dose in Regimen A was administered under fasting conditions. The doses in Regimens B and C were administered 30 minutes after starting a breakfast. All doses were also administered with 180 mL of water.

Number of Subjects: Planned: 39 Entered: 39 Completed: 36 Evaluated for Safety: 39 Evaluated for Pharmacokinetics: 36

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

Investigational Product: Fenofibrate

Dose/strength/concentration: one, 160-mg tablet under fasting conditions (Regimen A)
one, 160-mg tablet with food (Regimen B)
three, 67-mg capsule with food (Regimen C)

Mode of administration: oral

Lot number: Bulk Lot No.: 47-813-AL; Finishing Lot No.: 48-036-S2 (160-mg tablet)
Bulk Lot No.: 41-032-3T-21 (67-mg capsule)

Duration of treatment: Subjects were dosed once on Study Day 1 of each period.

Criteria for Evaluation:

Pharmacokinetics: The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}) and the area under the plasma concentration time curve (AUC) of fenofibric acid.

Safety: Vital signs measurements, physical examination, laboratory tests assessment and adverse events assessments.

Statistical Methods: Linear mixed effects analysis was performed for T_{max}, β, $\ln(C_{max})$, $\ln(AUC_{0-t})$ and $\ln(AUC_{0-\infty})$. The model included fixed effects for sequence, period and regimen, and random effect for subject nested. Within sequence within the framework of the linear mixed effects model for $\ln(AUC_{0-\infty})$ and $\ln(C_{max})$, the bioavailability of fenofibric acid under nonfasting conditions of the 160 mg tablet relative to that of three 67 mg capsules was assessed by the two one-sided tests procedure via 90% confidence intervals. The bioavailability of fenofibric acid under fasting conditions (Regimen A) relative to that under nonfasting conditions (Regimen B) was also assessed by the two one-sided tests procedure.

Summary:

Pharmacokinetic results: A summary (mean ± SD) of the pharmacokinetic parameters of fenofibric acid is presented in the following table.

Pharmacokinetic Parameter	Regimen£ A (N = 36)	B (N = 36)	C (N = 36)
T_{max} (h)	5.5 ± 3.7*	4.0 ± 0.9+	4.6 ± 0.9
C_{max} (µg/mL)	2.87 ± 1.21*	8.02 ± 1.70	8.59 ± 2.50
AUC_{0-t} (µg·h/mL)	95.8 ± 37.2*	129.6 ± 39.6+	142.7 ± 43.9
$AUC_{0-\infty}$ (µg·h/mL)	100.6 ± 40.1*	132.5 ± 42.0+	147.1 ± 47.0
$t_{1/2}$ (h)‡,§	20.9 ± 6.5*	19.2 ± 5.7	20.3 ± 7.3
CL/F (L/h)†	1.9 ± 0.8	1.3 ± 0.5	1.5 ± 0.5

£ Regimen A: 1 × 160-mg fenofibrate tablet (fasting conditions).
Regimen B: 1 × 160-mg fenofibrate tablet (nonfasting conditions).
Regimen C: 3 × 67-mg fenofibrate capsule (nonfasting conditions).
* Statistically significantly different from Regimen B ($p < 0.05$).
\+ Statistically significantly different from Regimen C ($p < 0.05$).
‡ Harmonic Mean ± Pseudo Standard Deviation.
§ Evaluations of $t_{1/2}$ were based on statistical tests for β.
† Parameter was not tested statistically.

The mean T_{max}, C_{max}, AUC and $t_{1/2}$ values of fenofibric acid were statistically significantly ($p < 0.05$) different for Regimen A compared to the corresponding values for Regimen B. Only the mean T_{max} and AUC values were statistically significantly different when Regimen B was compared to Regimen C.

For the two one-sided tests procedure based on analyses of $\ln(AUC_{0-\infty})$ and $\ln(C_{max})$ of fenofibric acid, the 90% confidence intervals for evaluating food effect and bioequivalence, and the corresponding point estimates of relative bioavailability are listed in the following table:

Pharmacokinetic Parameter	Regimen Comparison£	Relative Bioavailability: Point Estimate*	Relative Bioavailability: 90% Confidence Interval
Food Effect Evaluation			
C_{max}	A *vs.* B	0.334	0.300 – 0.372
$AUC_{0-\infty}$	A *vs.* B	0.742	0.694 – 0.792
Bioequivalence Evaluation			
C_{max}	B *vs.* C	0.955	0.887 – 1.028
$AUC_{0-\infty}$	B *vs.* C	0.900	0.864 – 0.937

£ Regimen A: 1 × 160-mg fenofibrate tablet (fasting conditions).
Regimen B: 1 × 160-mg fenofibrate tablet (nonfasting conditions).
Regimen C: 3 × 67-mg fenofibrate capsule (nonfasting conditions).
* Antilogarithm of the difference (A minus B for food effect evaluation and B minus C for bioequivalence evaluation) of the least squares means for logarithms.

The 90% confidence intervals of the ratio of central values (fasting relative to nonfasting conditions) for fenofibric acid C_{max} and $AUC_{0-\infty}$ fell entirely outside the equivalence ranges of 0.70 – 1.43 and 0.80 – 1.25, respectively, indicating a food effect.

Regimen B was bioequivalent to Regimen C as the 90% confidence intervals of the ratio of central values (Regimen B relative to Regimen C) for C_{max} and $AUC_{0-\infty}$ of fenofibric acid were contained entirely within the 0.80 – 1.25 equivalence range.

Safety results:

Thirty-four treatment-emergent adverse events (events with onset after the first dose of study drug) were reported during the study by 17 subjects. All adverse events were rated mild in severity.

The number and percentage of subjects reporting any treatment-emergent adverse events were nine (24.3%) after administration of one 160-mg fenofibrate tablet under fasting conditions (Regimen A), eight (21.1%) after administration of one 160-mg fenofibrate tablet with food (Regimen B) and five (13.2%) after administration of three 67-mg fenofibrate capsules (total dose, 210-mg) with food (Regimen C). The most frequently reported (reported by at least three subjects with any regimen) adverse event was headache (three subjects, 8.1% with Regimen A, one subject, 2.6% with Regimen B and four subjects, 10.5% with Regimen C).

Conclusions:

Under nonfasting conditions, one 160-mg fenofibrate tablet was bioequivalent to three 67-mg fenofibrate capsules. The extent of absorption of fenofibric acid from the 160-mg fenofibrate tablet administered under nonfasting conditions was increased by 35% relative to that under fasting conditions. The 160-mg fenofibrate tablet, like the approved 67-mg fenofibrate capsule, should be taken with food. Fenofibrate was generally well tolerated by the subjects.

Date of the report: August 3, 1999

2.0 Study Synopsis

Abbott Laboratories	*(For National Authority Use Only):*
Investigational Product: Fenofibrate (Tricor™)	
Active Ingredient: Fenofibrate	**Phase of Development:** Phase I

Title of Study: Comparison of the Bioavailability of Fenofibric Acid from a 54-mg Tablet Formulation of Fenofibrate with that from a 67-mg Capsule Formulation of Fenofibrate

Investigator: Thao Doan, MD

Study Site: Abbott Clinical Pharmacology Research Unit at Victory Memorial Hospital, Waukegan, Illinois

Studied Period: 27 days

Study Day -1 (day prior to dosing): January 12, 1999

Date of last dose administration: February 2, 1999

Date of last scheduled study procedure: February 7, 1999

Objective: To compare the bioavailability of fenofibric acid from a 54-mg tablet formulation of fenofibrate with that from a 67-mg capsule formulation of fenofibrate.

Study Design: Single-dose, open-label, crossover, two-period, randomized, single-center study. Subjects were confined to the research unit for approximately 7 days in each period. The doses of the two periods were separated by 14 days.

Subjects received a single dose of Regimen A or Regimen B in each period. All doses were administered with 180 mL of water and 30 minutes after starting a low fat breakfast.

Number of Subjects:

Planned: 42 Entered: 41 Completed: 38 Evaluated for Safety: 41 Evaluated for Pharmacokinetics: 38

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

Investigational Product: Fenofibrate

Dose/strength/concentration: one 54-mg tablet (Regimen A, test)
one 67-mg capsule (Regimen B, reference)

Mode of administration: oral

Lot numbers: Bulk Lot No. 47-800-AL; Finishing Lot No. 48-993-S2 (54-mg tablet)
Bulk Lot No. 47-032-3T-21; NDC No. 0074-4342-90 (67-mg capsule)

APPEARS THIS WAY
ON ORIGINAL

Duration of treatment: Each subject was dosed once on Study Day 1 in each period.

Criteria for Evaluation:

Pharmacokinetic: The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}) and the area under the plasma concentration-time curve (AUC) of fenofibric acid.

Safety: Vital signs measurements, physical examination, laboratory tests assessment, and adverse events assessments.

Statistical Methods: Analyses of variance (ANOVAs) were performed for T_{max}, β and the natural logarithms of C_{max} and AUC. In these analyses, the sources of variation in the model were sequence, subject nested within sequence, period, and regimen. Within the framework of the analyses of the logarithms of C_{max} and $AUC_{0-\infty}$, relative bioavailability was assessed by the two one-sided tests procedure via a 90% confidence interval.

Summary:

Pharmacokinetic results: A summary (mean ± SD) of the pharmacokinetic parameters of fenofibric acid after administration of each of the two regimens are shown in the following table.

Pharmacokinetic Parameters	Regimens£	
	A (N = 38)	B (N = 38)
T_{max} (h)	3.7 ± 0.8*	4.6 ± 1.4
C_{max} (µg/mL)	2.81 ± 0.53*	3.05 ± 0.59
AUC_{0-t} (µg*h/mL)	50.0 ± 15.6*	58.8 ± 19.5
$AUC_{0-\infty}$ (µg*h/mL)	51.1 ± 16.3*	60.3 ± 20.6
$t_{1/2}$ (h)‡§	18.4 ± 5.0*	19.1 ± 4.8
CL/F (L/h)††	1.2 ± 0.4	1.2 ± 0.4

£ Regimen A: 1 × 54-mg test fenofibrate tablet.
Regimen B: 1 × 67-mg reference fenofibrate capsule.
‡ 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 from Regimen B ($p < 0.05$).

The mean T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$ of fenofibric acid after administration of the 54-mg test fenofibrate tablet formulation (Regimen A) were statistically significantly ($p < 0.05$) smaller than those obtained after a single oral administration of the 67-mg reference fenofibrate capsule (Regimen B).

For the two one-sided tests procedure based on analyses of $\ln(AUC_{0-\infty})$ and $\ln(C_{max})$ of fenofibric acid, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are listed in the following table:

Regimens Test *vs.* Reference[£]	Pharmacokinetic Parameters	Relative Bioavailability	
		Point Estimate[*]	90% Confidence Interval
A *vs.* B	C_{max}	0.922	0.871 – 0.975
	$AUC_{0-\infty}$	0.854	0.826 – 0.882

£ Regimen A: 1 × 54-mg test fenofibrate tablet.
Regimen B: 1 × 67-mg reference fenofibrate capsule.
* Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Regimen A was bioequivalent to Regimen B as the 90% confidence interval for relative bioavailability was within the range of 0.8 - 1.25.

Safety results:

Eleven treatment-emergent adverse events (events with onset after the first dose of study drug) were reported during the study by seven subjects. Two adverse events were rated severe (scalp laceration and pain in one subject) and nine were mild in severity. One adverse event was considered by the investigator to be probably not related, and ten not related to the study drug.

The number and percentage of subjects reporting any treatment-emergent adverse events were two (5.3%) after administration of Regimen A (one 54-mg fenofibrate tablet) and six (14.6%) after administration of Regimen B (one 67-mg fenofibrate capsule). The most frequently reported (reported by at least two subjects with any regimen) adverse events were headache (no subjects in Regimen A and two subjects, 4.9% with Regimen B) and pharyngitis (one subject, 2.6% in Regimen A and two subjects, 4.9% in Regimen B).

One subject was prematurely discontinued due to a serious adverse event (hospitalization following an automobile accident).

Conclusions: Under nonfasting conditions, one 54-mg fenofibrate test tablet was bioequivalent to one 67-mg fenofibrate reference capsule. Fenofibrate was generally well tolerated by the subjects.

Date of the report: May 11, 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
Division of Pharmaceutical Evaluation II

NDA:	**21-203**
Generic	**Fenofibrate**
(Brand®)	**Tricor®**
Submission Date:	**November 10, 1999**
Sponsor:	**Abbott Laboratories**
Consult:	**Pharmacokinetics-Pharmacodynamics (PK-PD) Analysis**
Pharmacometrics Scientist:	**Sam H. Haidar**

Background

NDA 21-203 for fenofibrate (Tricor®) ——— tablets was submitted on November 10, 1999, by Abbott Laboratories. Tricor is currently marketed as a micronized capsule formulation, and the sponsor seeks approval for ——— tablet formulation that has greater bioavailability relative to the capsule. Tricor is indicated for the treatment of Type II, IV, and V hyperlipidemia

Included in this submission is a bioequivalency study between the to-be-marketed ——— tablet, and the approved micronized capsule. However, the study was conducted under fed conditions, which was not acceptable to the Division of Metabolic and Endocrine Drug Products (DMEDP). The sponsor is seeking approval of this NDA on the basis of PK-PD analysis of data obtained from a clinical trial conducted with micronized capsules and standard (non-micronized) capsules. No PD data were submitted for the to-be-marketed formulation.

This pharmacometric consult evaluated the PK-PD analysis performed on data from a Phase III Clinical trial (Study 8802, France). The study design was double-blind, placebo-controlled, parallel group, and multicenter. The objectives were to compare the efficacy of two formulations of fenofibrate (standard 100 mg capsule, t.i.d, and Tricor 200 mg micronized capsule, QD with evening meal). Treatment was started after a 2-month run-in phase, and continued for 3 months. Blood samples were collected prior to initiating treatment, at 1-month and at 3-months of treatment. The primary efficacy parameters were plasma cholesterol and triglycerides. Secondary efficacy parameters were plasma concentrations of LDL-cholesterol, HDL-cholesterol, and apolipoproteins A1 and B. In addition to the efficacy markers, the blood samples were analyzed for fenofibric acid levels. According to the sponsor, the time a blood sample was obtained, the time of dosing, and the proximity of dosing to a meal (and content) were not recorded in the study. Therefore, a plasma level of fenofibric acid may be a peak concentration, a trough concentration, or anywhere in between.

A retrospective PK-PD modeling was performed using fenofibrate plasma levels and the efficacy parameters listed above. A simple E_{max} model was used, which according to the sponsor provided the best fit:

$$E = E_{max}(C)/(EC_{50} + C)$$

where E (effect) is % change from baseline, E_{max} is the estimated maximum effect, C is fenofibric acid plasma concentration, EC_{50} is fenofibric acid plasma concentration leading to 50% of maximum effect. Non-linear regression fitting was performed using WinNonlin Standard Edition.

Results:

Plots of the data and model fits are shown below.

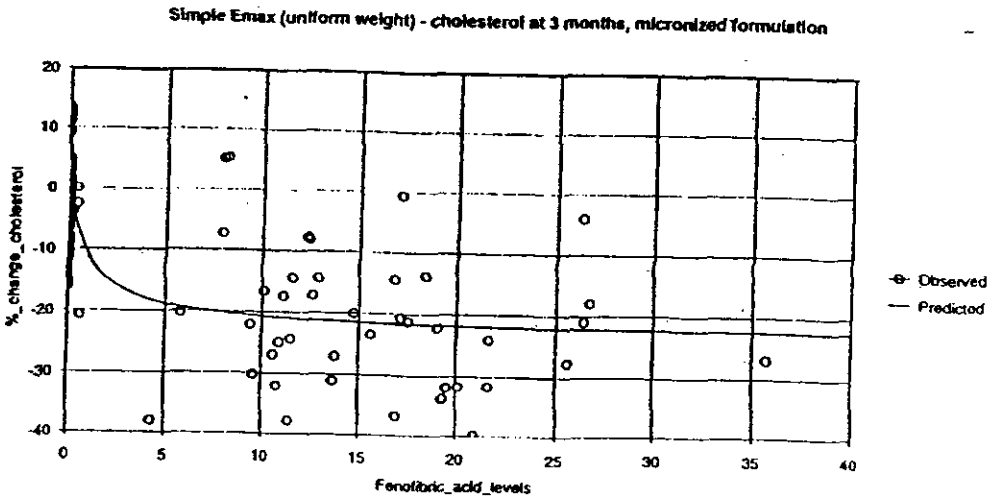


Figure 1. Observed and model predicted % change from baseline for total cholesterol following 3 months of treatment with Tricor micronized capsules, 200 mg, QD with evening meal.

APPEARS THIS WAY ON ORIGINAL

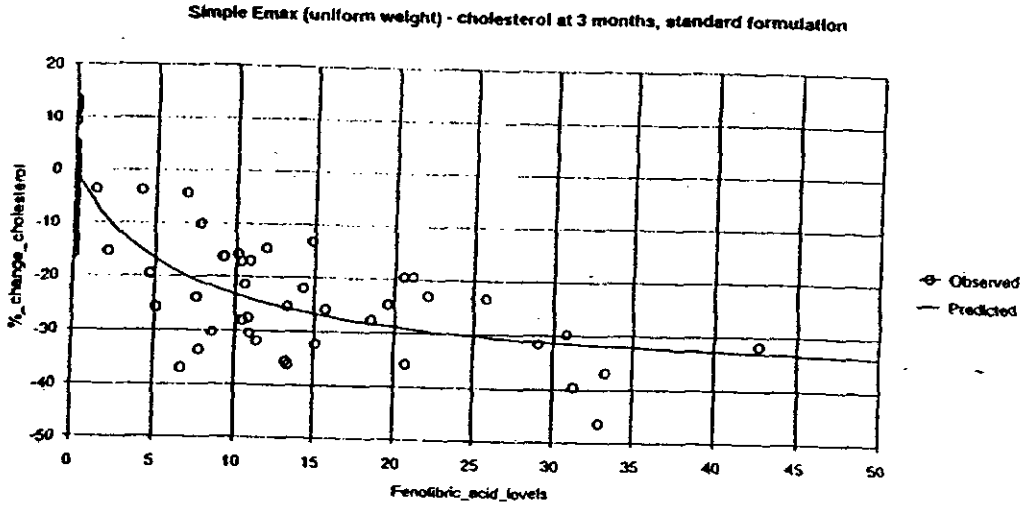


Figure 2. Observed and model predicted % change from baseline for total cholesterol following 3 months of treatment with fenofibrate standard capsules, 100 mg, TID.

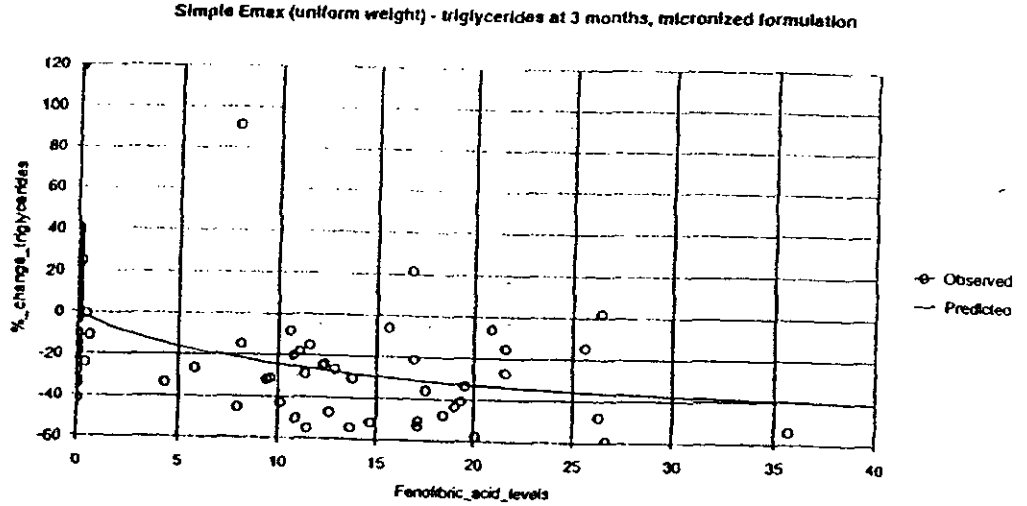


Figure 3. Observed and model predicted % change from baseline for triglycerides following 3 months of treatment with Tricor micronized capsules, 200 mg, QD with evening meal.

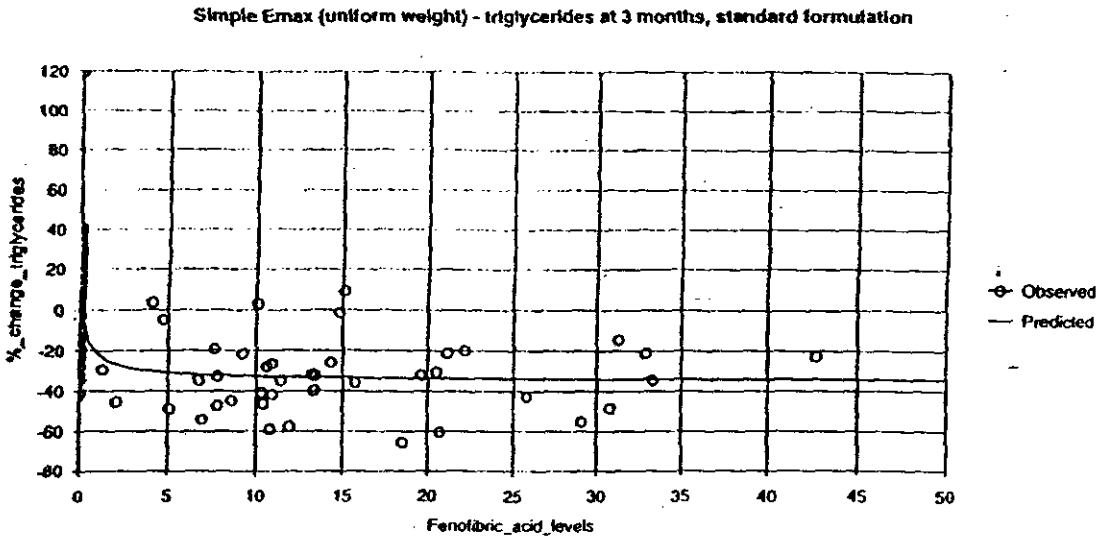


Figure 4. Observed and model predicted % change from baseline for triglycerides following 3 months of treatment with fenofibrate standard capsules, 100 mg, TID.

APPEARS THIS WAY
ON ORIGINAL

Efficacy Parameter	Fenofibrate Form	Month from Baseline	E_{max} Parameter Estimate	E_{max} %CV	EC_{50} Parameter Estimate	EC_{50} %CV
LDL:HDL	standard	1	-51.1	16.0	4.9	62.4
LDL:HDL	micronized	1	-40.7	14.9	2.3	96.4
LDL:HDL	standard	3	-48.8	12.3	3.4	55.6
LDL:HDL	micronized	3	-61.6	29.5	11.7	69.1
LDL	standard	1	-58.5	17.5	11.3	43.4
LDL	micronized	1	-42.5	18.1	6.5	59.4
LDL	standard	3	-49.3	13.8	6.0	45.1
LDL	micronized	3	-43.6	27.5	7.6	81.4
Triglycerides	standard	1	-42.1	38.6	2.5	239.3
Triglycerides	micronized	1	-32.8	30.0	0.9	375.0
Triglycerides	standard	3	-34.7	18.1	0.6	256.4
Triglycerides	micronized	3	-52.0	65.9	11.3	156.7
Cholesterol	standard	1	-47.5	18.0	13.2	41.5
Cholesterol	micronized	1	-29.4	15.1	4.7	59.8
Cholesterol	standard	3	-38.1	14.0	6.3	44.5
Cholesterol	micronized	3	-23.2	11.6	1.2	109.1
Apolipoprotein B	standard	1	-49.9	12.6	7.2	39.3
Apolipoprotein B	micronized	1	-34.3	12.6	2.4	78.8
Apolipoprotein B	standard	3	-46.2	11.1	5.0	40.0
Apolipoprotein B	micronized	3	-41.6	22.0	6.5	71.1

Table I. Parameter estimates and CV% for the different pharmacodynamic (clinical endpoints) evaluated at 1 month and 3 months in Study 8802.

Reviewer's Comments:

The PK-PD analysis of Study 8802 is not adequate as basis for approval of NDA 21-203. The to-be-marketed formulation ———) is different from those evaluated in Study 8802 (micronized capsule and standard capsule); and no PD information is available for the ——— to allow for a comparison of the dose-response relationships between the different formulations. Additionally, there are several issues of concern regarding the selection and use of the E_{max} model to fit fenofibrate data. These are listed below:

1. Because sample times and dosing times were not recorded during the study, the time-course of the effect relative to the time-course of the PK of the drug could not be

determined (the temporal relationship between drug levels in the plasma and PD effect was not defined).

2. Based on fenofibrate's mechanism of action, an indirect PK-PD model is more appropriate than an E_{max} model, which relates drug concentrations (actual or theoretical) at the effect site to a PD measurement.
3. Given that a single strength (and its equivalent) was evaluated in the PK-PD analysis, it is difficult to conclude with a reasonable degree of accuracy that E_{max} was achieved for the various PD endpoints.
4. The model assumes no effect at zero drug concentration, yet data indicate that some subjects had a clinically significant response (e.g. 15% decrease in cholesterol levels) with placebo treatment. Therefore, normal fluctuations in the PD endpoints, which are not accounted for by the model, could have a significant effect on the precision of the estimated parameters.
5. EC_{50} values were poorly estimated. This is reflected by the large confidence intervals around the estimates, which often contained zero. Additionally, the estimates showed large intersubject variability.

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

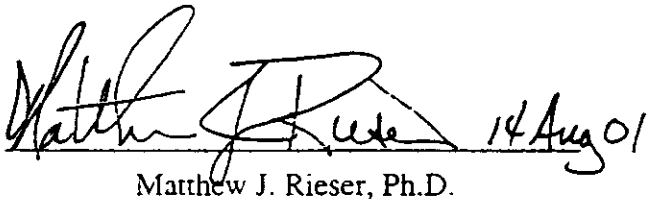
Peer reviewed by He Sun, Ph.D.

cc:
NDA 21-203
HFD-870 (Huang S-M, Johnson S, Ahn H-Y, Sun H, Haidar S)
HFD-850 (Lee P.)
CDR (Barbara Murphy For Drug)

APPEARS THIS WAY
ON ORIGINAL

Supplemental Stability Data Submitted in Support of the Analytical Method for Fenofibric Acid (Abbott-52799 Free Acid) in Human Plasma

Prepared by:



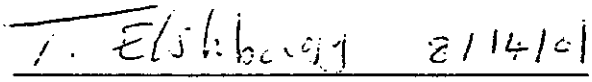
14 Aug 01

Matthew J. Rieser, Ph.D.
Senior Scientist, Drug Analysis

Contributors

William K. LaBeau B.S., Drug Analysis
Brendan Swaine. B.S., Drug Analysis

Reviewed and Approved by:



Tawakol El-Shourbagy, Ph.D.
Director. Drug Analysis

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

Table 1. Back-Calculated Concentrations µg/mL and % of Theory for Fenofibric Acid Standard Curves and Fit Parameters

	Back Calculated Concentrations and % Theory					
Batch	3357.6	% Theory	1647.2	% Theory	671.5	% Theory
Autosampler Day 0	3027.8	90.2	1574.4	95.6	724.0	107.8
Autosampler Day 4	3116.8	92.8	1496.4	90.8	705.0	105.0
Freeze-thaw Fresh	2877.5	85.7	1613.0	97.9	708.7	105.5
Freeze-thaw (cycles)	3200.2	95.3	1598.5	97.0	698.4	104.0
Mean	3055.6	91.0	1570.6	95.4	709.0	105.6
SD	138.0		51.9		10.9	
%CV	4.5		3.3		1.5	
High						
Low						
N	4		4		4	

	Back Calculated Concentrations and % Theory					
Batch	268.6	% Theory	65.9	% Theory	34.3	% Theory
Autosampler Day 0	285.2	106.2	65.4	99.3	35.1	102.5
Autosampler Day 4	288.6	107.4	66.2	100.4	37.0	107.9
Freeze-thaw Fresh	285.0	106.1	68.6	104.0	35.7	104.2
Freeze-thaw (cycles)	280.3	104.3	65.2	99.0	34.5	100.8
Mean	284.8	106.0	66.3	100.7	35.6	103.9
SD	3.4		1.5		1.0	
%CV	1.2		2.3		2.9	
High						
Low						
N	4		4		4	

	Back Calculated Concentrations and % Theory				
Batch	16.8	% Theory	Intercept	Slope	r
Autosampler Day 0	16.5	98.5	0.0015	0.0011	0.9975
Autosampler Day 4	16.1	95.5	0.0005	0.0010	0.9966
Freeze-thaw Fresh	16.2	96.5	0.0013	0.0010	0.9963
Freeze-thaw (cycles)	16.7	99.6	0.0012	0.0008	0.9992
Mean	16.4	97.5	0.0011	0.0010	0.9974
SD	0.3				
%CV	1.9				
High					
Low					
N	4		4	4	4

All calculations performed prior to rounding.

Table 2. Summary of Fenofibric Acid Stability After Freeze-Thaw

Number of Cycles	Measured Concentration ng/mL and % Theory					
	QC High		QC Mid		QC Low	
	2735.9	% Theory	175.1	% Theory	35.0	% Theory
fresh		96.1		112.8		108.3
fresh		88.3		103.1		107.7
fresh		92.4		108.5		106.0
fresh		86.2		105.4		107.0
fresh		87.7		110.5		104.3
fresh		90.8		98.7		93.3
Mean	2469.4	90.3	186.5	106.5	36.6	104.4
SD	100.0	3.7	9.1	5.2	2.0	5.6
1 cycle		102.7		108.2		106.9
1 cycle		97.1		104.5		104.9
1 cycle		97.7		110.0		106.3
1 cycle		99.2		107.7		104.1
1 cycle		98.6		106.3		108.0
1 cycle		93.9		106.6		108.1
Mean	2686.4	98.2	187.7	107.2	37.3	106.4
SD	78.2	2.9	3.3	1.9	0.6	1.6
3 cycles		95.2		110.2		107.8
3 cycles		98.7		107.5		105.7
3 cycles		99.6		107.7		104.7
3 cycles		96.8		107.2		104.5
3 cycles		95.4		109.4		105.9
3 cycles		96.9		109.7		105.5
3 cycles		97.7		107.7		107.6
3 cycles		95.8		107.6		107.5
3 cycles		98.9		111.5		106.5
3 cycles		100.0		110.6		109.2
3 cycles		97.4		103.6		101.4
3 cycles		97.0		103.6		98.1
Mean	2666.2	97.5	189.2	108.0	36.9	105.4
SD	43.6	1.6	4.4	2.5	1.1	3.0

All calculations performed prior to rounding.

Table 2. Summary of Fenofibric Acid Stability After Freeze-Thaw (Cont.)

	Measured Concentration ng/mL and % Theory					
Number	QC High		QC Mid		QC Low	
of Cycles	2735.9	% Theory	175.1	% Theory	35.0	% Theory
4 cycles		95.6		98.6		95.5
4 cycles		100.8		100.9		98.4
4 cycles		100.0		101.2		101.0
4 cycles		93.4		104.5		108.2
4 cycles		94.0		104.4		101.5
4 cycles		94.2		106.7		102.5
Mean	2635.7	96.3	179.8	102.7	35.4	101.2
SD	88.9	3.3	5.2	3.0	1.5	4.3
5 cycles		89.5		98.9		104.8
5 cycles		96.1		115.5		115.1
5 cycles		92.4		107.7		105.8
5 cycles		96.0		108.3		100.7
5 cycles		93.2		108.7		102.9
5 cycles		90.2		104.7		108.5
Mean	2541.6	92.9	187.9	107.3	37.2	106.3
SD	76.5	2.8	9.5	5.4	1.8	5.0
6 cycles		88.2		98.6		101.0
6 cycles		89.1		105.9		101.9
6 cycles		89.1		106.3		100.7
6 cycles		91.7		109.6		107.7
6 cycles		88.7		105.5		108.3
6 cycles		88.2		107.3		105.4
Mean	2439.3	89.2	184.8	105.5	36.5	104.2
SD	35.3	1.3	6.5	3.7	1.2	3.4
7 cycles		92.2		106.6		96.5
7 cycles		91.3		102.7		103.8
7 cycles		90.0		101.9		99.5
7 cycles		95.6		103.4		100.1
7 cycles		94.4		105.4		98.8
7 cycles		92.3		113.5		107.3
Mean	2534.6	92.6	184.9	105.6	35.4	101.0
SD	55.8	2.0	7.5	4.3	1.4	3.9

All calculations performed prior to rounding.

Table 3. Summary of Autosampler Stability Data

	Analytical Recoveries on Day 0			Analytical Recoveries on Day 4 (Freshly Extracted Curve)	
Sample	Theoretical Concentration	Calculated Concentration	% Theory	Calculated Concentration	% Theory
QC High	2735.9	2382.5	87.1	2953.0	107.9
QC High	2735.9	2474.6	90.4	2786.3	101.8
QC High	2735.9	2530.5	92.5	2647.8	96.8
QC High	2735.9	2631.3	96.2	2506.6	91.6
QC High	2735.9	2827.6	103.4	2437.6	89.1
QC High	2735.9	2935.2	107.3	2476.9	90.5
Mean		2630.3	96.1	2634.7	96.3
SD		213.3	7.8	202.3	7.4
QC Mid	175.1	169.1	96.6	186.3	106.4
QC Mid	175.1	172.9	98.7	186.2	106.3
QC Mid	175.1	174.9	99.9	195.5	111.7
QC Mid	175.1	186.3	106.4	177.1	101.1
QC Mid	175.1	189.4	108.2	177.7	101.5
QC Mid	175.1	202.4	115.6	182.4	104.2
Mean		182.5	104.2	184.2	105.2
SD		12.5	7.2	6.8	3.9
QC Low	35.0	32.7	93.4	37.8	107.8
QC Low	35.0	33.6	96.0	37.3	106.5
QC Low	35.0	35.3	100.7	37.5	107.1
QC Low	35.0	35.7	102.0	35.5	101.4
QC Low	35.0	38.2	109.1	35.9	102.5
QC Low	35.0	38.5	110.0	37.1	106.1
Mean		35.7	101.9	36.8	105.2
SD		2.4	6.7	0.9	2.6

All calculations performed prior to rounding.

Sources of Data

Item for Validation	Date Extracted	Notebook Reference	Generated by
Autosampler Day 0	July 31, 2001	29980:91	W. K. LaBeau
Autosampler Day 4	August 4, 2001	29980:95	W. K. LaBeau
Freeze-thaw (fresh)	July 23, 2001	29980:85-87	B. Swaine
Freeze-thaw (cycles)	August 2, 2001	29980:93	B. Swaine

This study was conducted by the staff of Department 46W, Abbott Laboratories at the Abbott Park facilities located in Abbott Park, Illinois. This data will be archived with supporting data for the study M00-253 according to the departmental standard operating procedures.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

8 pgs