

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-418

PHARMACOLOGY REVIEW(S)

4/30/09



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-418
SERIAL NUMBER: 0000
DATE RECEIVED BY CENTER: 8/15/08
PRODUCT: fenofibric acid tablets
INTENDED CLINICAL POPULATION: Adult subjects with hypercholesterolemia,
hypertriglyceridemia
SPONSOR: Mutual Pharmaceutical Company, Inc.
DOCUMENTS REVIEWED: Vol. 000
REVIEW DIVISION: Division of Metabolism and Endocrinology
Products (HFD-510)
PHARM/TOX REVIEWER: C. Lee Elmore
PHARM/TOX SUPERVISOR: Karen Davis-Bruno
DIVISION DIRECTOR: Mary Parks
PROJECT MANAGER: Kati Johnson

Date of review submission to Division File System (DFS): April 30, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Recommend approval.

B. Recommendation for nonclinical studies

No additional non-clinical studies are required.

C. Recommendations on labeling

Labeling should be identical to that of the reference listed drug (Tricor[®], e.g. 21-656), without exception.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Mutual performed two comparative pharmacokinetic studies (one in rats and another in dogs) after a single oral dose of Mutual's fenofibrate drug substance (prodrug similar to Tricor[®]) and approximate equimolar amounts of Mutual's fenofibric acid drug substance (2.6% and 10% greater molar amounts of fenofibric acid in rat and dog studies, respectively).

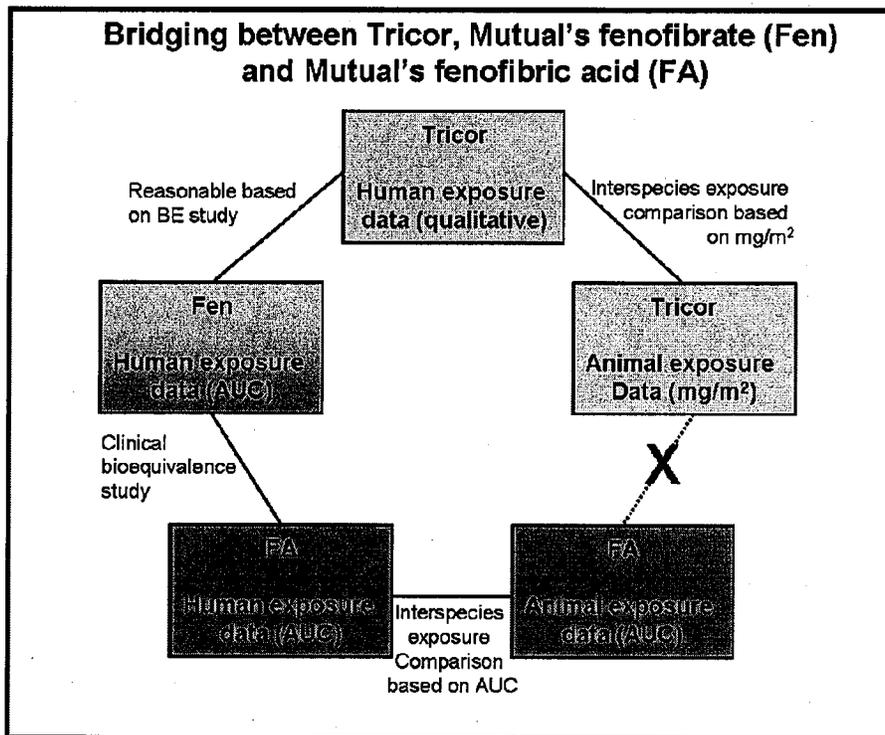
Data from the rat study demonstrated that animals administered equimolar fenofibrate or fenofibric acid showed similar plasma exposure to the common active moiety, fenofibric acid. While this does not provide direct bridging toxicokinetic data in rats, it does indicate that studies described in the approved labeling for the reference listed drug (Tricor[®]), administered here as Mutual's fenofibrate, were likely to have similar exposure to fenofibric acid as rats administered approximately equimolar doses of Mutual's fenofibric acid.

In addition to a single-dose pharmacokinetic study in rats, Tricor[®] 145 mg and Mutual's fenofibric acid 105 mg were demonstrated by Mutual to be bioequivalent in humans. The Agency's CMC review team indicated that, according to information provided by the sponsor, there are no impurities or degradants present in Mutual's fenofibric acid drug substance or drug product that would require qualification via bridging non-clinical toxicology studies based on ICH Q3A and Q3B guidances. Furthermore, there are no novel excipients present in the drug product that would require non-clinical qualification. No direct non-clinical bridging studies between the reference listed drug (Tricor[®]) and Mutual's fenofibric acid were submitted to NDA 22-418. However, data submitted do provide a minimal bridge between exposure of Mutual's fenofibrate (similar to

Tricor[®]) and exposure to Mutual's fenofibric acid in a single non-clinical species (rats). This provides a comparison between non-clinical exposures in rats with Mutual's fenofibrate and fenofibric acid and the human bioequivalence study conducted and evaluated by Mutual that utilized the reference listed drug Tricor[®].

A single-dose pharmacokinetic study in dogs was performed. Exposure to fenofibric acid (as measured by AUC_{0-last}) after administration of Mutual's fenofibric acid drug substance was 90% greater than that measured after administration of approximately equimolar doses of Mutual's fenofibrate drug substance. Total exposure, as measured by $AUC_{0-\infty}$, were more similar between drug substances than AUC_{0-last} . Therefore, dogs described in the approved labeling for the reference listed drug (Tricor[®]) were likely exposed to less fenofibric acid on average than were dogs administered Mutual's fenofibric acid, but exposures fell within the high end of the range of exposures measured with Mutual's fenofibrate (similar to Tricor[®]).

Mutual provided reports for three toxicokinetic studies designed to allow estimation of exposure (AUC) that may have occurred after administration of the fenofibrate in studies described in approved labeling for the reference listed drug (Tricor[®]). Mutual's toxicokinetic assays were performed with Mutual's fenofibrate alone and did not utilize Mutual's to-be-marketed fenofibric acid or the reference listed drug (Tricor[®]). Since no direct comparison was made, no bridge between Mutual's fenofibric acid drug substance and the reference listed drug (Tricor[®]) was established. Therefore, Mutual's labeling should be identical to that of the reference listed drug (Tricor[®]).



B. Pharmacologic activity

Fenofibric acid is the active form of the prodrug fenofibrate. Fenofibric acid activates the peroxisome proliferator activated receptor, sub-type alpha (PPAR α), and leads to reductions in total cholesterol, apolipoprotein B, total triglycerides and triglyceride-rich lipoprotein (VLDL). Fenofibric acid also lowers serum uric acid levels by increasing uric acid excretion by the kidney.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW**2.6.1 INTRODUCTION AND DRUG HISTORY**

NDA number: 22-418

Review number: 1

Sequence number/date/type of submission: 0000/August 15, 2008/original application 505(b)(2)

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Mutual Pharmaceutical Company, Inc., Philadelphia, PA, USA.

Manufacturer for drug substance: _____ b(4)

Reviewer name: C. Lee Elmore, Ph.D.

Division name: Metabolism and Endocrinology Products

HFD #: 510

Review completion date: May 1, 2009

Drug:

Trade name: Not yet assigned (sponsor proposed Fibracor™ and _____) b(4)

Generic name: fenofibric acid tablets

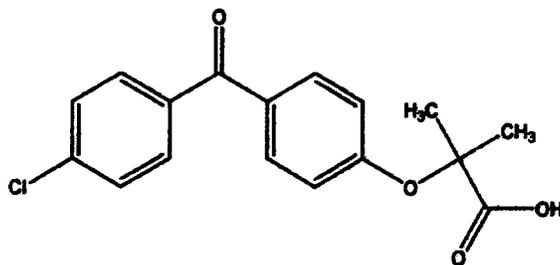
Code name: N/A

Chemical name: 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid

CAS registry number: 42017-89-0

Molecular formula/molecular weight: C₁₇H₁₅ClO₄/318.75

Structure:

**Relevant INDs/NDAs/DMFs:**

NDA 21-656 (Tricor®, Abbott—US)

NDA 21-203 (Tricor®, Abbott—US)

NDA 19-304 (Tricor®, Abbott—US)

NDA 21-612 (Lipofen®, Cipher Pharmaceutical, Inc.)

NDA 21-695 (Antara® capsules, Oscient)

NDA 21-350 (Triglide® tablets, Skyepharma)

IND 76,749 (fenofibric acid, Mutual Pharmaceutical Company, Inc.)

IND 70,345 (fenofibric acid, Abbott—US)
IND 65,886 (Tricor® + pravastatin, Abbott—US)
DMF _____

b(4)

Drug class: fibrate (PPARα agonist, lipid lowering agent for the treatment of dyslipidemia)

Intended clinical population: Treatment of hyperlipidemia, including familial hypercholesterolemia and combined hyperlipidemia (Fredrickson Types IIa and IIb, respectively) and hypertriglyceridemia (Fredrickson Types IV/V hyperlipidemia) (compare to Tricor label.)

Clinical formulation:

Table 3.2.P.1
Composition of Fenofibric Acid Tablets Intended for Commercialization

Ingredient	% w/w	Tablet Strength	
		35 mg	105 mg
		mg/ Tablet	
Fenofibric acid		35.0	105.0
Microcrystalline cellulose, NF			
Copovidone, NF			
Croscopovidone, NF			
Magnesium stearate, NF			
Total			

b(4)

(Sponsor)

Table 3.2.P.2
Composition of Fenofibric Acid Tablets
(Additional Strengths with Supportive Stability Data)

Ingredient	% w/w	Tablet Strength	
		mg/ Tablet	
Fenofibric acid			
Microcrystalline cellulose, NF			
Copovidone, NF			
Croscopovidone, NF			
Magnesium stearate, NF			
Total			

b(4)

(Sponsor)

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-418 are owned by Mutual Pharmaceutical Company, Inc. or are data for which Mutual Pharmaceutical Company, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-418 that Mutual Pharmaceutical Company, Inc. does not own or

have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Mutual Pharmaceutical Company, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-418.]

Studies reviewed within this submission:

- MPC-025-08-0004 "Pharmacokinetics of fenofibrate and fenofibric acid in rat following a single oral gavage dose"
- MPC-028-08-0005 "Pharmacokinetics of fenofibrate and fenofibric acid in dog following a single oral gavage dose"
- MPC-028-08-0001 "Toxicokinetics of fenofibric acid in the male mouse following dietary administration of fenofibrate for up to 4 weeks"
- MPC-028-08-0002 "Toxicokinetics of fenofibric acid in two strains of male rats following dietary administration of fenofibrate for up to 4 weeks"
- MPC-028-08-0003 "Toxicokinetics of fenofibric acid in the male rabbit following oral gavage administration of fenofibrate for 4 weeks"

Studies not reviewed within this submission:

b(4)

2.6.2 PHARMACOLOGY

No new pharmacology studies were conducted for this 505(b)(2) submission.

2.6.2.1 Brief summary

Fenofibric acid is a member of the fibrate class of drugs. Fenofibric acid is an agonist of the nuclear transcription factor peroxisome proliferator activated receptor alpha (PPAR α). Fenofibric acid is the pharmacologically active form of the FDA-approved fenofibrate (Tricor[®]), a prodrug that is esterified in the intestines and blood forming fenofibric acid. Fenofibrate is not observed in blood, being poorly soluble and resistant to absorption in the acidic lumen of the stomach. Fenofibrate absorption is variable, depending on food. Fenofibric acid is water soluble and absorbed in the acidic environment of the stomach, increasing bioavailability. Higher bioavailability and smaller overall drug mass allows for reduction of the dose administered, which are the primary reasons for the marketing of fenofibric acid proposed by the sponsor. Mutual submitted a 505(b)(2) NDA application for approval of their 105 mg fenofibric acid tablets based on findings of safety and efficacy for the reference listed Tricor[®] drug products (NDA 21-656, NDA 21-203, NDA 19-304), and requested a biowaiver for the 35 mg fenofibric acid tablet based on linearity of pharmacokinetics over the proposed dose range.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Fenofibric acid is an agonist of the nuclear transcription factor, peroxisome proliferator activated receptor, sub-type alpha (PPAR α). <[This produces reductions in total cholesterol, LDL cholesterol, and apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with [fenofibric acid] results in increases in [HDL] cholesterol and [apolipoproteins] apoAI and apoAII.>*

*<Duplicated> from the approved label for Tricor[®] (NDA 21-656), except when modified where [indicated].

Drug activity related to proposed indication: <[Activation of PPAR α] increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of [apoCIII] (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the synthesis of [apoAI and apoAII], and HDL-cholesterol. Fenofibric acid also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.>*

*<Duplicated> from the approved label for Tricor[®] (NDA 21-656, NDA 21-203, or NDA 19-304), except when modified where [indicated].

2.6.2.3 Secondary pharmacodynamics

No new secondary pharmacodynamic studies were conducted for this 505(b)(2) submission.

2.6.2.4 Safety pharmacology

No new safety pharmacology studies were conducted for this 505(b)(2) submission.

2.6.2.5 Pharmacodynamic drug interactions

No new pharmacodynamic drug interaction studies were conducted for this 505(b)(2).

2.6.3 PHARMACOLOGY TABULATED SUMMARY

This 505(b)(2) NDA relies on the already approved product label for Tricor[®] (NDA 21-656, NDA 21-203, NDA 19-304), as it pertains to safety and efficacy.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Two comparative pharmacokinetic studies were conducted in support of this 505(b)(2) new drug application. The pharmacokinetics of fenofibrate and fenofibric acid were evaluated in rats and dogs following a single oral gavage dose. The Agency can rely on its previous decision of safety for Tricor[®] (NDA 21-656, NDA 21-203, NDA 19-304), with this new fenofibric acid product. Extensive toxicology studies were performed in support of marketing Tricor[®] NDAs (NDA 21-656, NDA 21-203, NDA 19-304). No new extensive non-clinical toxicology studies were submitted to NDA 22-418.

Three toxicokinetic studies were conducted for this 505(b)(2) new drug application. The toxicokinetics of fenofibric acid was analyzed in 1) male mice following dietary administration for up to 4 weeks, 2) two strains of male rats following dietary administration of fenofibrate for up to 4 weeks, and 3) male rabbits following oral gavage administration of fenofibrate for 4 weeks. The sponsor attempted to establish an accurate measurement of the fenofibric acid exposure (AUC) after administration of fenofibrate that may have occurred in the original studies conducted by the original innovator (Abbott). These studies may relate to fenofibric acid exposure in human subjects, but did not bridge to the rodent data for labeling Tricor[®] (NDA 21-656, NDA 21-203, NDA 19-304). Therefore, the non-clinical study information with fenofibrate available in labeling for Tricor[®] (NDA 21-656, NDA 21-203, NDA 19-304) upon which this NDA rely, should be used for labeling Mutual's fenofibric acid product *verbatim*.

2.6.4.2 Methods of Analysis

Fenofibric acid, reduced fenofibric acid, fenofibric acid glucuronide, and reduced fenofibric acid glucuronide concentrations in plasma were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

2.6.4.3 Absorption

No absorption studies were conducted for this 505(b)(2) submission.

2.6.4.4 Distribution

No new distribution studies were conducted for this 505(b)(2) submission.

2.6.4.5 Metabolism

No new metabolism studies were conducted for this 505(b)(2) submission.

2.6.4.6 Excretion

No new excretion studies were conducted for this 505(b)(2) submission.

2.6.4.7 Pharmacokinetic drug interactions

No new pharmacokinetic drug interaction studies were conducted for this 505(b)(2) submission.

2.6.4.8 Other Pharmacokinetic Studies

MPC-028-08-0004 – Pharmacokinetics of Fenofibrate and Fenofibric Acid in Rat Following a Single Oral Gavage Dose

Key findings: (Note: Bioavailability of fenofibrate in rats is ~64%, from Mogi et al., 1995a, Jpm Pharmacol Ther, 23.) Mean AUC, C_{max} , and T_{max} for fenofibric acid exposure after administration of fenofibrate (14 mg/kg) and fenofibric acid (12 mg/kg) were within a range (20%) that constitutes bioequivalence. The sponsor showed that exposures to metabolites of fenofibric acid after administration of fenofibric acid are similar to those observed after administration of equimolar fenofibrate.

Background: Bridging pharmacokinetic analyses were performed to establish that levels of exposure to fenofibric acid after administration of fenofibric acid (manufactured by _____) were bioequivalent to the level of exposure to fenofibric acid measured after administration of fenofibrate (also manufactured by _____). Male Sprague-Dawley rats (_____) CD(SD) were utilized for this study, and pharmacokinetic analyses with the approved fenofibrate product (Tricor[®]) also utilized male Sprague-Dawley rats (_____) CD(SD). Fenofibrate (14 mg/kg) or fenofibric acid (12 mg/kg) was administered to adult male rats by oral gavage. The dose volume was 1.0 mL/kg. There were 18 rats per drug for a total of 36 rats.

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Blood was drawn at Time 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in groups of 3 rats/time-point, staggered over time (6 groups/drug) for a total of two blood draws per animal. Fenofibrate and fenofibric acid (as well as major metabolites, including reduced fenofibric acid, fenofibric acid glucuronide, and reduced fenofibric acid glucuronide) were measured.

BATCH ANALYSES

7.1. Test Article 1	
Identity:	Fenofibrate
Description:	white crystalline powder
Lot number:	RD060190
Chemical purity:	99.5%
Retest date:	07 February 2009
Storage conditions:	room temperature, with adequate ventilation
Supplier:	_____ via URL/Mutual Pharmaceutical Company
7.2. Test Article 2	
Identity:	Fenofibric Acid
Description:	white powder
Lot number:	RD060130
Chemical purity:	100.1%
Retest date:	02 August 2008
Storage conditions:	room temperature
Supplier:	_____ via URL/Mutual Pharmaceutical Company

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(Sponsor)

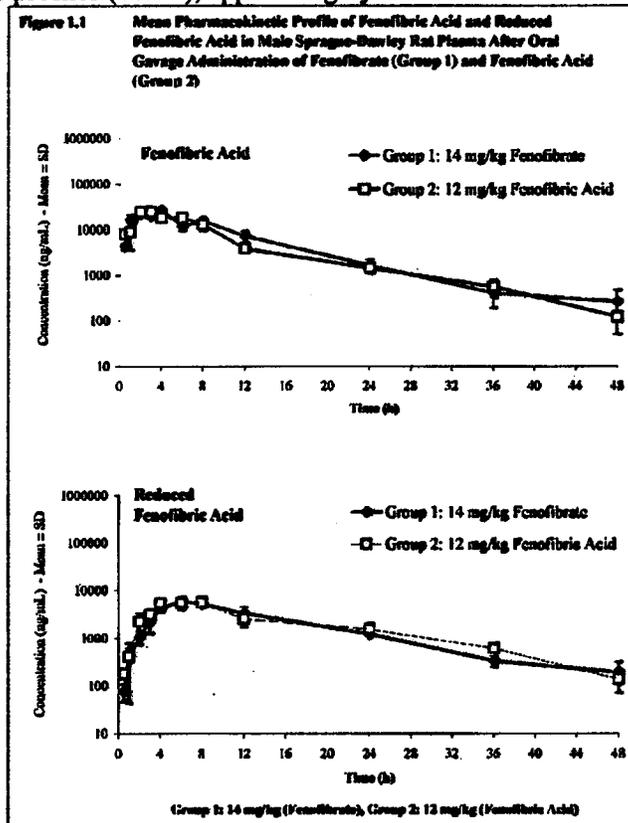
Results: Upon administration of a single-dose of 14 mg/kg fenofibrate or 12 mg/kg fenofibric acid to male rats by oral gavage, time-to-maximum plasma concentration (T_{max}), elimination constants (K_{el}), and half-lives of elimination ($T_{1/2}$) for fenofibric acid and reduced fenofibric acid were similar (see sponsor Table 2.1 below). The data appear to represent reliable data assessments, as evidenced by high R^2 values. The plasma concentration of the reduced fenofibric acid metabolite concentration in male rats, after either fenofibrate administration or fenofibric acid administration, is approximately 20% of the parent fenofibric acid levels in plasma.

Table 2.1 Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid and Reduced Fenofibric Acid in Male Sprague-Dawley Rat Plasma After Oral Gavage Administration of Fenofibrate (Group 1) and Fenofibric Acid (Group 2)

Day 1							
Group	Dose Level	Analyte	T _{max}	T _{1/2}	K _e	R ²	T _{1/2}
No.	(mg/kg)		(h)	(h)	(1/h)		(h)
1 Fenofibrate	14	Fenofibric Acid	4	48	0.11	0.97	6.48
		Reduced Fenofibric Acid	6	48	0.09	0.99	8.12
2 Fenofibric Acid	12	Fenofibric Acid	3	48	0.09	0.99	7.33
		Reduced Fenofibric Acid	8	48	0.10	0.98	6.86

(Sponsor)

Exposure to fenofibric acid and reduced fenofibric acid, based on observation of mean pharmacokinetic profiles (below), appears highly similar.



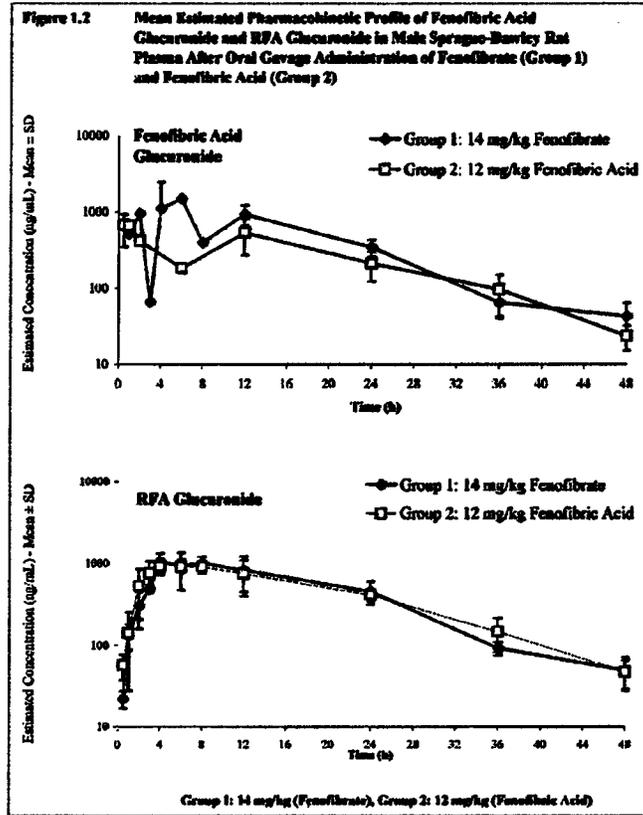
(Sponsor)

The primary route of elimination of fenofibric acid and reduced fenofibric acid is by glucuronidation and subsequent excretion in the urine. The plasma concentrations of the metabolites of fenofibrate/fenofibric acid, fenofibric acid glucuronide and reduced fenofibric acid glucuronide, were measured after administration of a single dose of 14 mg/kg fenofibrate or 12 mg/kg fenofibric acid. The glucuronidated metabolites of fenofibric acid and reduced fenofibric acid are present at approximately 3-5% of the levels of the parent fenofibric acid levels in plasma. The elimination constants (K_{el}) and half-lives of elimination ($T_{1/2}$) for fenofibric acid glucuronide and reduced fenofibric acid glucuronide were highly similar (see sponsor Table 2.2 below). The values representing the T_{max} were the exception, because the data for reduced fenofibric acid glucuronide produced a double-peak in the exposure curve; the second time point was likely due to an outlier in the data leading to an artificially shortened T_{max} . The shapes of the exposure curves are otherwise quite similar. The fits for these two curves were also quite strong (high R^2 values) indicating a likelihood that these data represent a reliable exposure assessment.

Table 2.2 Estimated Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid Glucuronide and RFA Glucuronide in Male Sprague-Dawley Rat Plasma After Oral Gavage Administration of Fenofibrate (Group 1) and Fenofibric Acid (Group 2)

Day 1							
Group	Dose Level		T_{max}	T_{last}	K_{el}	R^2	$T_{1/2}$
No.	(mg/kg)	Analyte	(h)	(h)	(1/h)		(h)
1 Fenofibrate	14	Estimated Fenofibric Acid Glucuronide	6	48	0.09	0.96	7.60
		Estimated RFA Glucuronide	4	48	0.08	0.97	8.66
2 Fenofibric Acid	12	Estimated Fenofibric Acid Glucuronide	0.5	48	0.08	0.98	8.17
		Estimated RFA Glucuronide	4	48	0.09	1.00	7.66

(Sponsor)



(Sponsor)

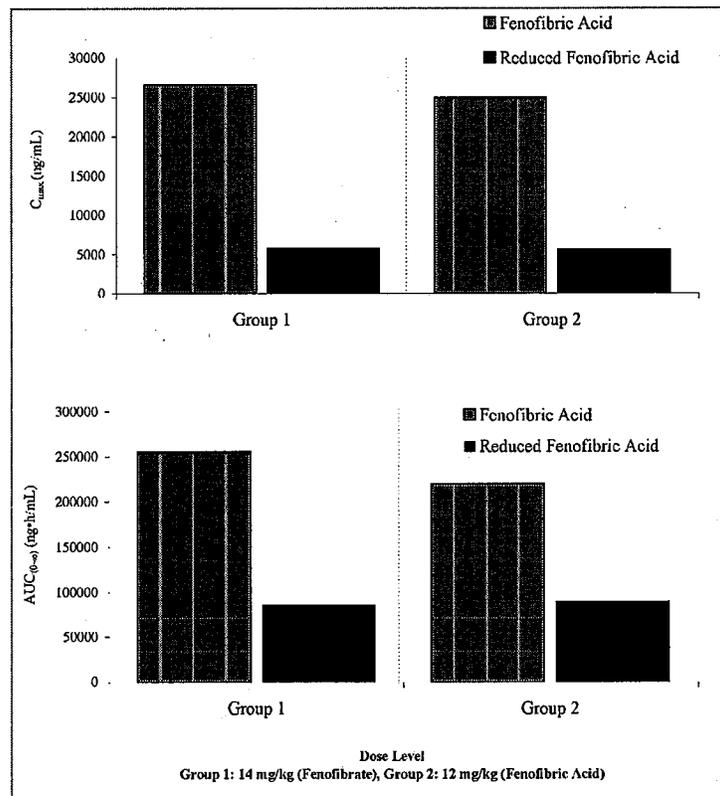
Exposure to fenofibric acid and reduced fenofibric acid after administration of 14 mg/kg of fenofibrate or 12 mg/kg fenofibric acid was comparable, as the maximum observed plasma concentration (C_{max}) and the values representing total exposure ($AUC_{(0-last)}$ and $AUC_{(0-\infty)}$) between the two compounds were less than 20% different (see Table 3.1, below and figure, below).

Table 3.1 Pharmacokinetic Exposure Parameters of Fenofibric Acid and Reduced Fenofibric Acid in Male Sprague-Dawley Rat Plasma After Oral Gavage Administration of Fenofibrate (Group 1) and Fenofibric Acid (Group 2)

Day 1

Group No.	Dose Level (mg/kg)	Analyte	C _{max} (ng/mL)	AUC _(0-last) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-∞) /Dose
1 Fenofibrate	14	Fenofibric Acid	26519	252258	254700	0.96	1894	18193
		Reduced Fenofibric Acid	5757	83157	85391	2.62	411	6099
2 Fenofibric Acid	12	Fenofibric Acid	24854	218056	219337	0.58	2071	18278
		Reduced Fenofibric Acid	5546	88242	89588	1.50	462	7466

(Sponsor)



(Sponsor)

The exposure parameters of fenofibric acid glucuronide and reduced fenofibric acid glucuronide after administration of 14 mg/kg fenofibrate or 12 mg/kg fenofibric acid were similar for reduced fenofibric acid glucuronide, but not for fenofibric acid glucuronide. The plasma fenofibric acid glucuronide concentration after administration of fenofibric acid was lower than expected base upon the fenofibric acid glucuronide

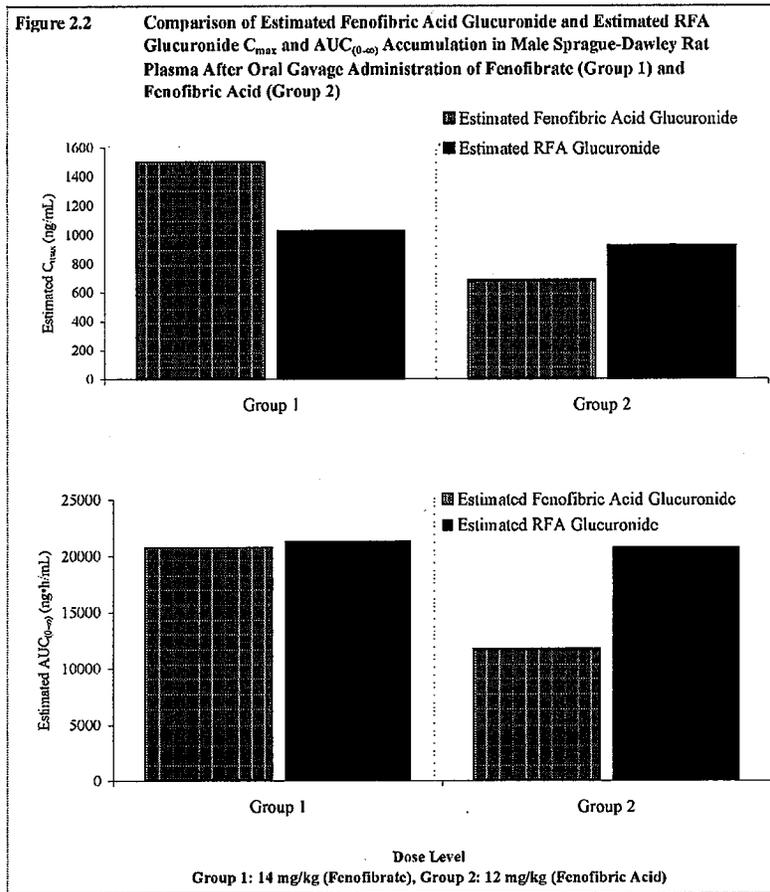
concentration data obtained after administration of fenofibrate; C_{max} was ~45% of that expected and $AUC_{(0-\infty)}$ was ~57% of that expected).

Table 3.2 Estimated Pharmacokinetic Exposure Parameters of Fenofibric Acid Glucuronide and RFA Glucuronide in Male Sprague-Dawley Rat Plasma After Oral Gavage Administration of Fenofibrate (Group 1) and Fenofibric Acid (Group 2)

Day 1								
Group No.	Dose Level (mg/kg)	Analyte	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·h/mL)	$AUC_{(0-\infty)}$ (ng·h/mL)	AUC%	$C_{max}/Dose$	$AUC_{(0-\infty)}/Dose$
1 Fenofibrate	10	Estimated Fenofibric Acid Glucuronide	1497	20289	20756	2.23	107	1483
		Estimated RFA Glucuronide	1027	20754	21364	2.86	73.3	1526
2 Fenofibric Acid	12	Estimated Fenofibric Acid Glucuronide	681	11496	11775	2.36	56.7	981
		Estimated RFA Glucuronide	922	20274	20792	2.49	76.8	1733

(Sponsor)

Note: Error-bars were omitted from the bar graph comparisons between analytes (below).



(Sponsor)

Summary: In order to rely upon the FDA’s prior judgment of safety and efficacy for the approved reference drug Tricor[®], the sponsor demonstrated comparability between exposures (i.e. pharmacokinetic profiles) of fenofibrate and fenofibric acid. The sponsor administered 14 mg/kg of fenofibrate (Mutual) and 12 mg/kg of fenofibric acid (Mutual) to adult male rats. The results of these pharmacokinetic assays have shown that administration of fenofibric acid yields exposure to fenofibric acid, reduced fenofibric acid, and reduced fenofibric acid glucuronide that is comparable to the exposure observed after administration of fenofibrate. The raw pharmacokinetic data, after administration of fenofibric acid, generated for fenofibric acid glucuronide and reduced fenofibric acid glucuronide were highly similar to that observed after administration of fenofibrate. One difference, which consisted of lower exposure to fenofibric acid glucuronide, likely occurred due to low levels of this metabolite in plasma and the error that this introduces upon measurement. Though the absolute means of pharmacokinetic parameters were different for fenofibric acid glucuronide, the exposure profiles observed for fenofibric acid glucuronide after fenofibric acid administration were well within the range of data observed after fenofibrate administration.

MPC-028-08-0005 – Pharmacokinetics of Fenofibrate and Fenofibric Acid in Dog Following a Single Oral Gavage Dose

Key findings: (Note: bioavailability of fenofibrate is ~19% in dogs, from Mogi et al., 1995b, Jpm Pharmacol Ther, 23.) Mean AUC, C_{max}, and T_{max} for fenofibric acid exposure after administration of fenofibrate (5 mg/kg) and fenofibric acid (4 mg/kg) were outside the 20% range that constitutes bioequivalence. However, the sponsor showed that exposures to metabolites of fenofibric acid after administration of fenofibric acid are in the range of and qualitatively similar to those observed after administration of (~10% lower than) equimolar amounts of fenofibrate.

Background: Pharmacokinetic analyses were performed to measure the fenofibric acid exposures observed after administration of fenofibric acid to that exposure measured after fenofibrate administration. The dog was utilized for this study because pharmacokinetic analyses with the approved fenofibrate product were also performed in dogs.

Fenofibrate (5 mg/kg) or fenofibric acid (4 mg/kg) was administered to adult male Beagle dogs by oral gavage. The dose volume was 1.0 mL/kg. There were three dogs per drug for a total of 6 dogs.

The animals were assigned to the study groups as follows:

Group Number	Test Article	Dose Level (mg/kg)	Concentration (mg/mL)	Animal Numbers
				Males
1	Fenofibrate	5	5	101-103
2	Fenofibric Acid	4	4	201-203

(Sponsor)

Blood was drawn predose and at 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose. Exposure after administration of fenofibrate and fenofibric acid was measured as fenofibric acid in plasma. Major metabolites (reduced fenofibric acid, fenofibric acid glucuronide, and reduced fenofibric acid glucuronide) were measured.

BATCH ANALYSES

7.2. Test Article 1	
Identity	Fenofibrate
Description	White crystal powder
Lot number	RD060190
Chemical purity	99.5%
Retest date	07 February 2009
Storage conditions	Store at room temperature with adequate ventilation
Supplier	_____ via URL/Mutual Pharmaceuticals Company
7.3. Test Article 2	
Identity	Fenofibric Acid
Description	White powder
Lot number	RD060130
Chemical purity	100.1%
Retest date	02 August 2008
Storage conditions	Store at room temperature with adequate ventilation
Supplier	_____ via URL/Mutual Pharmaceuticals Company

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(Sponsor)

Results: The elimination constants (K_{el}) and elimination time half-lives ($T_{1/2}$) for fenofibric acid were similar between male dogs administered 5 mg/kg fenofibrate or 4 mg/kg fenofibric acid. T_{max} data collected for fenofibric acid were similar after administration of fenofibrate or fenofibric acid. The curve fit for data from which the fenofibric acid exposure T_{max} was determined was poor ($R^2=0.58$); one dog in the fenofibrate-administered group showed an unusually long period to reach T_{max} (12 hours). This was considered an outlier. Otherwise T_{max} was 1 hr for all dogs studied.

The elimination constants (K_{el}) and elimination time half-lives ($T_{1/2}$) for reduced fenofibric acid were similar between male dogs administered 5 mg/kg fenofibrate or 4 mg/kg fenofibric acid. T_{max} data collected for reduced fenofibric acid were very different after administration of fenofibrate or fenofibric acid (8 hours versus 1 hour, respectively).

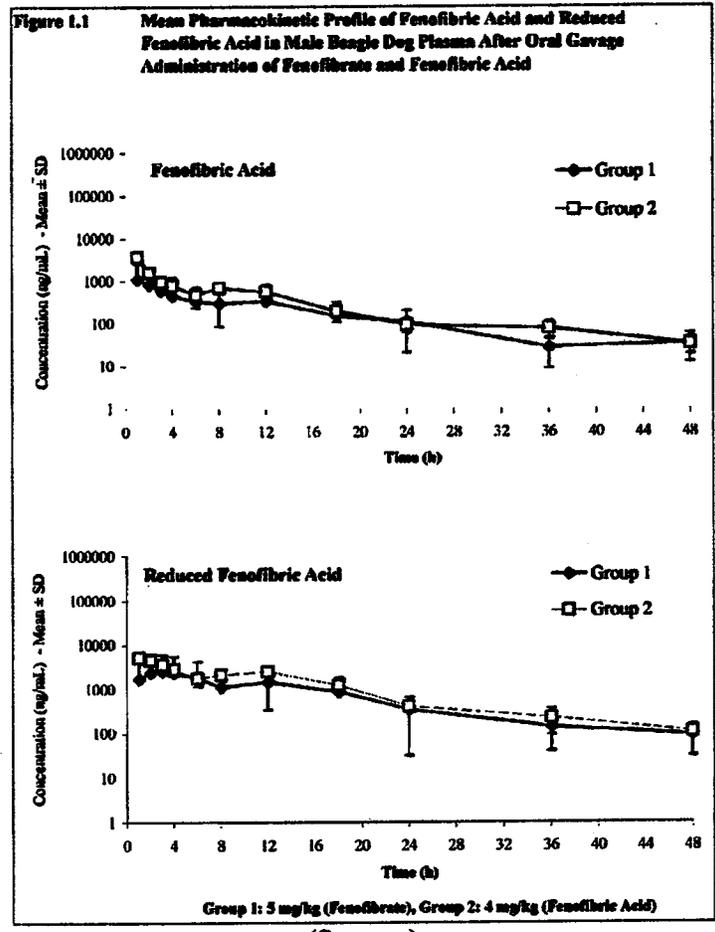
Table 3.1 Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid and Reduced Fenofibric Acid in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

Fenofibric Acid							
Group No.	Dose Level (mg/kg)	Animal No.	T _{max} (h)	T _{1/2α} (h)	K _d (1/h)	R ²	T _{1/2} (h)
1	5	101	12	48	0.08	0.84	9.21
		102	1	48	0.08	0.89	8.32
		103	1	48	b	0.58	b
		Mean ^a	1	48	0.08		8.77
		SD			c		c
2	4	201	1	48	0.09	0.90	7.74
		202	1	48	0.06	0.93	10.8
		203	1	48	0.07	0.91	10.2
		Mean ^a	1	48	0.07		9.56
		SD			0.01		1.60
Reduced Fenofibric Acid							
Group No.	Dose Level (mg/kg)	Animal No.	T _{max} (h)	T _{1/2α} (h)	K _d (1/h)	R ²	T _{1/2} (h)
1	5	101	12	48	0.08	0.94	8.43
		102	3	48	0.06	1.00	12.0
		103	8	48	b	0.72	b
		Mean ^a	8	48	0.07		10.2
		SD			c		c
2	4	201	1	48	0.09	0.96	7.44
		202	1	48	0.08	0.93	8.32
		203	1	48	0.08	0.92	8.90
		Mean ^a	1	48	0.08		8.22
		SD			0.01		0.73

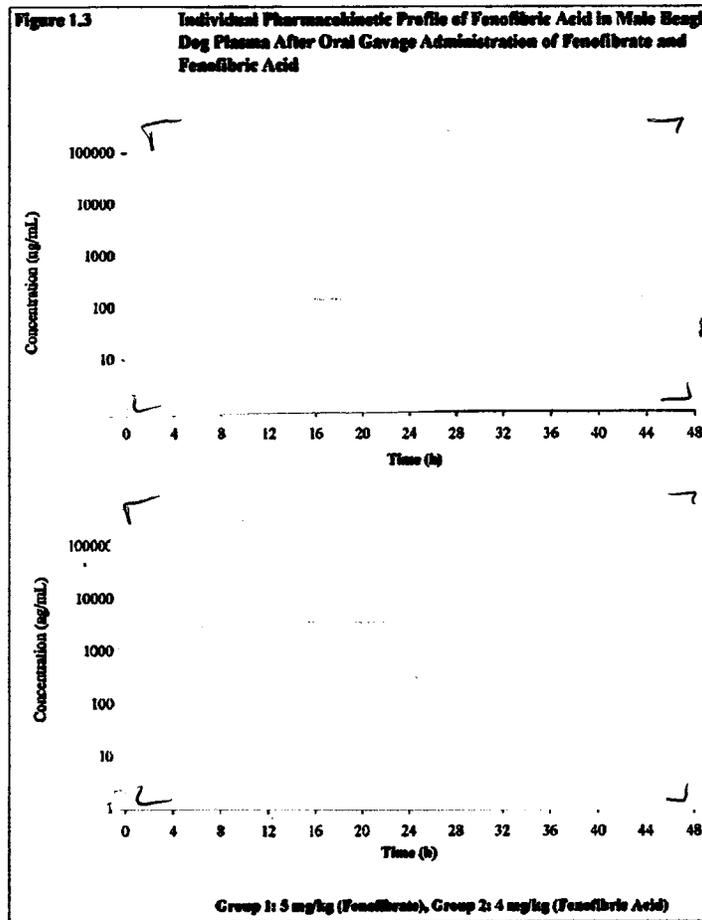
^a Median value reported for T_{max} and T_{1/2α}.
^b Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
^c Standard deviation is not calculated.

(Sponsor)

The mean fenofibric acid and reduced fenofibric acid exposure profiles after administration of fenofibrate or fenofibric acid appeared similar (see sponsor Figures 1.1, 1.3, and 1.4, below). However, the exposure data recorded after fenofibric acid administration were higher and showed less variability than those recorded after fenofibrate administration. This is likely due to the improved and more predictable absorption of the fenofibric acid, compared to the less well-absorbed fenofibrate comparator (Mutual). The mean exposure profiles for fenofibric acid after administration of fenofibric acid were basically identical to exposures detected after administration of fenofibrate.



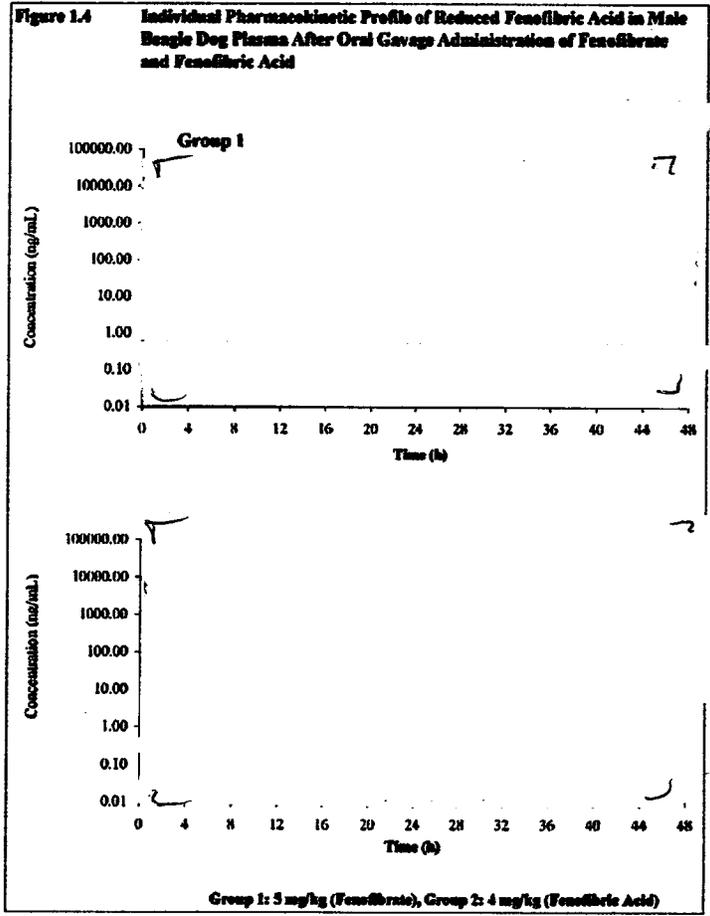
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(Sponsor)

Time to reach maximum plasma drug concentration (T_{max}) of fenofibric acid glucuronide and reduced fenofibric acid glucuronide were dissimilar; however, the actual exposure curves were similar. Differences were due to inherent variability in the data, whereby transient upticks in metabolite concentrations were measured at 2, 4, or 12 hours post-administration. It is unlikely that these differences in T_{max} are biologically relevant.

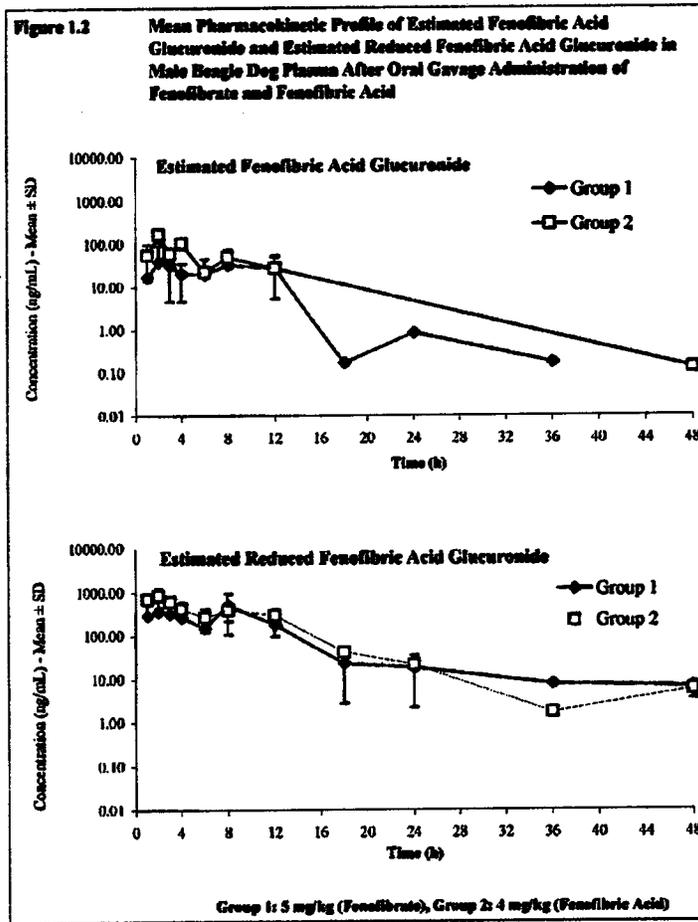
The exposure data recorded after fenofibric acid administration were largely higher and showed less variability than those recorded after fenofibrate administration. This is likely due to the improved and more predictable absorption of fenofibric acid, compared to fenofibrate (Mutual). The mean exposure profiles for fenofibric acid glucuronide and reduced fenofibric acid glucuronide after administration of fenofibric acid were within the range of exposures detected after administration of fenofibrate.

Table 3.2 Pharmacokinetic Observed and Secondary Parameters of Estimated Fenofibric Acid Glucuronide and Estimated Reduced Fenofibric Acid Glucuronide in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

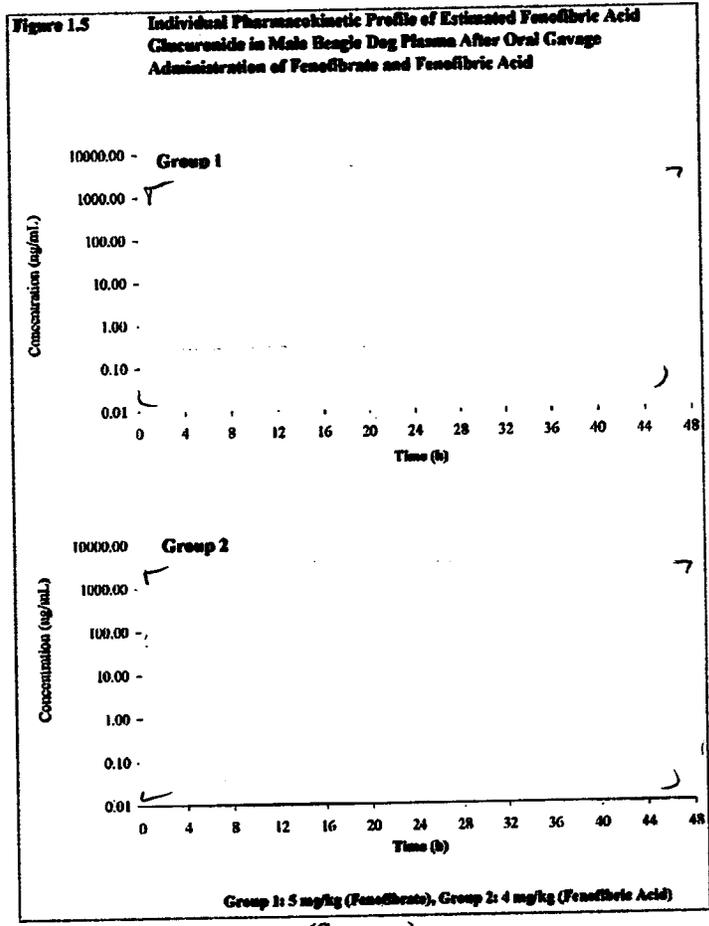
Estimated Fenofibric Acid Glucuronide							
Group No.	Dose Level (mg/kg)	Animal No.	T_{max} (h)	$T_{1/2}$ (h)	K_{el} (1/h)	R^2	$T\%$ (h)
1	5	101	12	36	b	b	b
		102	2	24	b	b	b
		103	12	36	b	b	b
		Mean ^a	12	36	-	-	-
		SD	-	-	-	-	-
2	4	201	2	12	b	b	b
		202	2	48	b	b	b
		203	4	12	b	b	b
		Mean ^a	2	12	-	-	-
		SD	-	-	-	-	-
Estimated Reduced Fenofibric Acid Glucuronide							
Group No.	Dose Level (mg/kg)	Animal No.	T_{max} (h)	$T_{1/2}$ (h)	K_{el} (1/h)	R^2	$T\%$ (h)
1	5	101	8	48	0.05	0.97	13.9
		102	2	24	0.19	0.88	3.62
		103	12	48	c	0.12	c
		Mean ^a	8	48	0.12	-	8.76
		SD	-	-	d	-	d
2	4	201	2	48	0.13	0.86	5.29
		202	3	48	0.13	0.90	5.34
		203	2	48	0.12	0.80	5.63
		Mean ^a	2	48	0.13	-	5.42
		SD	-	-	0.00	-	0.18

^a Median value reported for T_{max} and $T_{1/2}$.
^b Insufficient data to characterize the terminal phase.
^c Values are not reported because the $AUC_{0-\infty}$ was extrapolated by more than 20% or R^2 is <0.8.
^d Standard deviation is not calculated.
 - Not calculated.

(Sponsor)



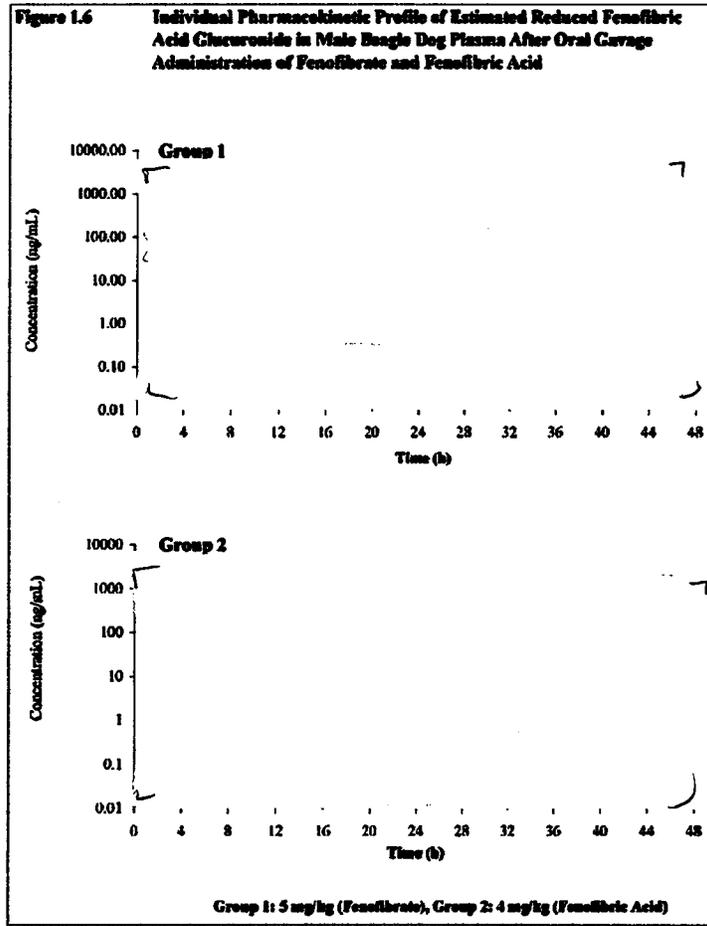
(Sponsor)



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(Sponsor)



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b(4)

(Sponsor)

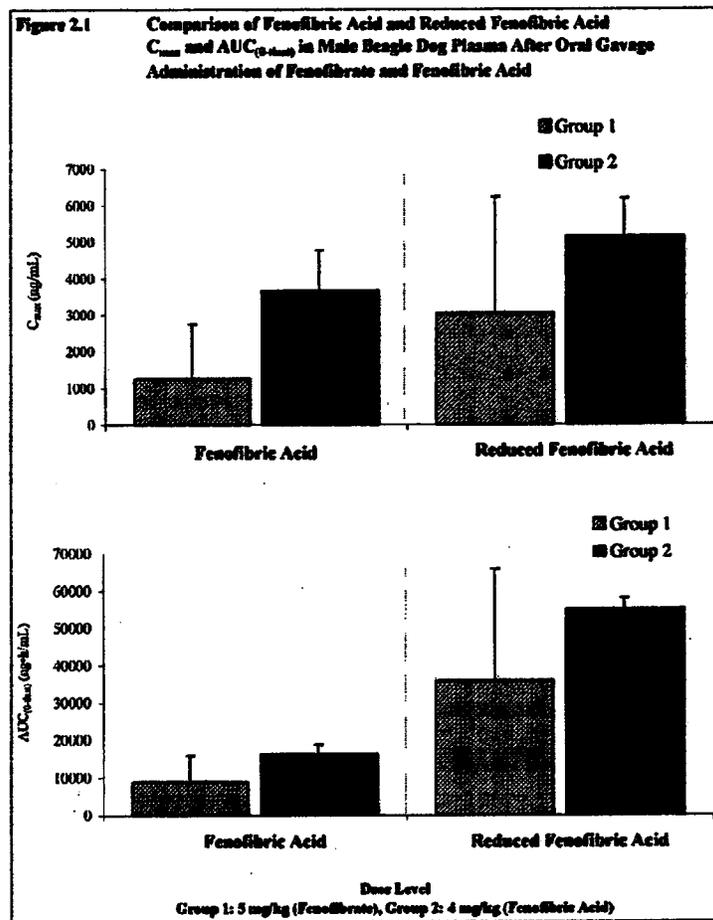
Mean pharmacokinetic exposure parameters measured for fenofibric acid in plasma of male Beagle dogs were higher after administration fenofibric acid than after administration of fenofibrate: C_{max} (↑193%), $AUC_{(0-t_{last})}$ (↑90%), and $AUC_{(0-\infty)}$ (↑26%). Mean pharmacokinetic exposure parameters measured for reduced fenofibric acid in plasma of male Beagle dogs were higher after administration of fenofibric acid than after administration of fenofibrate: C_{max} (↑69%), $AUC_{(0-t_{last})}$ (↑54%), and $AUC_{(0-\infty)}$ (↑6%).

Table 4.1 Pharmacokinetic Exposure Parameters of Fenofibric Acid and Reduced Fenofibric Acid in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

Fenofibric Acid								
Group	Dose Level	Animal	C_{max}	$AUC_{(0-t_{last})}$	$AUC_{(0-\infty)}$	AUC%	$C_{max}/$	$AUC_{(0-t_{last})}/$
No.	(mg/kg)	No.	(ng/mL)	(ng·h/mL)	(ng·h/mL)	(t _{last} -∞)	Dose	Dose
1	5	101	704	10736	11516	6.60	141	2151
		102	2946	14686	15102	2.76	589	2937
		103	111	1037	a	20.8	22.1	207
		Mean	1254	8826	13309	10.1	251	1765
		SD	1495	7026	b	9.51	299	1405
2	4	201	4923	17033	17367	1.80	1231	4264
		202	3223	13654	13989	2.40	806	3413
		203	2884	18340	19046	3.70	721	4583
		Mean	3676	16330	16801	2.63	919	4087
		SD	1093	2422	2576	0.97	273	605
Reduced Fenofibric Acid								
Group	Dose Level	Animal	C_{max}	$AUC_{(0-t_{last})}$	$AUC_{(0-\infty)}$	AUC%	$C_{max}/$	$AUC_{(0-t_{last})}/$
No.	(mg/kg)	No.	(ng/mL)	(ng·h/mL)	(ng·h/mL)	(t _{last} -∞)	Dose	Dose
1	5	101	2315	39260	41161	4.62	463	7852
		102	6538	63848	65380	2.34	1308	12770
		103	251	4107	a	12.7	50.3	821
		Mean	3035	35738	53270	6.56	607	7148
		SD	3205	30026	b	5.46	641	6005
2	4	201	6004	53261	54311	1.93	1501	13315
		202	5456	53828	55145	2.39	1364	13457
		203	4009	58382	59972	2.63	1002	14596
		Mean	5136	55137	56476	2.32	1289	13789
		SD	1031	2807	3056	0.36	258	702

a Values are not reported because the $AUC_{(0-\infty)}$ was extrapolated by more than 20% or R^2 is <0.8.
b Standard deviation is not calculated.

(Sponsor)



(Sponsor)

Mean pharmacokinetic exposure parameters for fenofibric acid glucuronide measured in plasma of male Beagle dogs were higher after administration of fenofibric acid than after administration of fenofibrate: C_{max} ($\uparrow 213\%$) and $AUC_{(0-t_{last})}$ ($\uparrow 67\%$). The exposure parameter $AUC_{(0-\infty)}$ was not calculated due to insufficient data. Mean pharmacokinetic exposure parameters for reduced fenofibric acid glucuronide measured in plasma of male Beagle dogs after administration of fenofibric acid were higher than after administration of fenofibrate: C_{max} ($\uparrow 42\%$), $AUC_{(0-t_{last})}$ ($\uparrow 45\%$), and $AUC_{(0-\infty)}$ ($\uparrow 1\%$).

Table 4.2 Pharmacokinetic Exposure Parameters of Estimated Fenofibric Acid Glucuronide and Estimated Reduced Fenofibric Acid Glucuronide in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

Estimated Fenofibric Acid Glucuronide

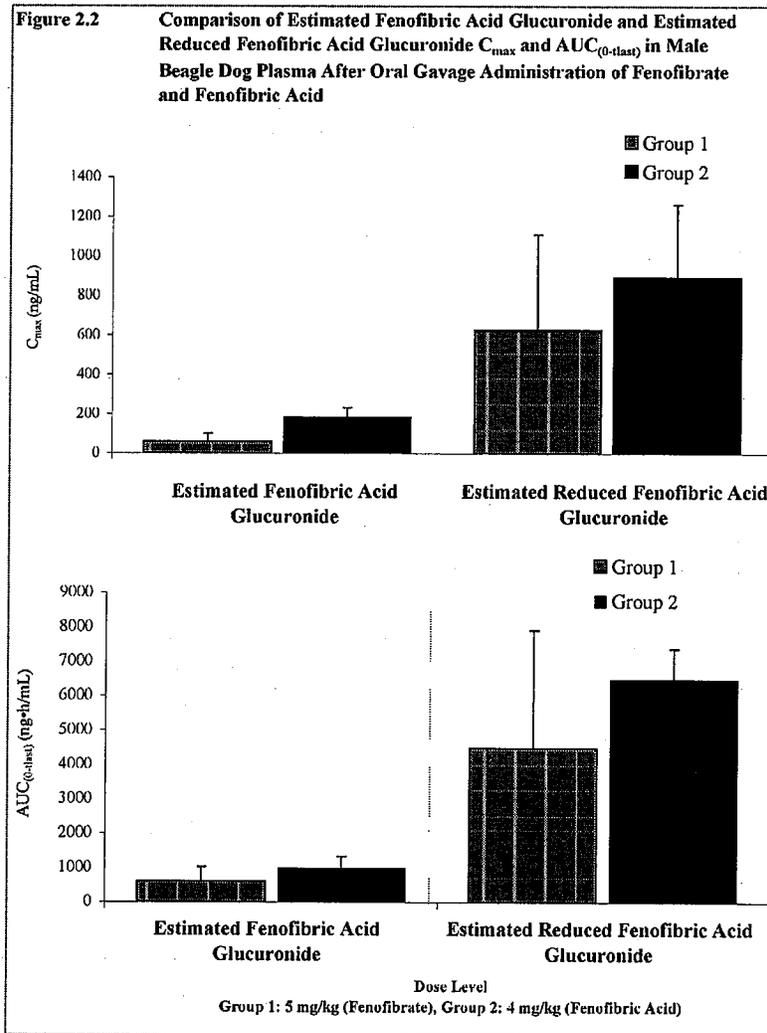
Group No.	Dose (mg/kg)	Level No.	Animal No.	C _{max} (ng/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC%	C _{max} /Dose	AUC _(0-12h) /Dose	AUC _(0-12h) /Dose
1	5		101	59.2	970	259	a	a	11.8	194	51.8
			102	101	677	622	a	a	20.1	135	124
			103	14.8	132	82.7	a	a	2.97	26.3	16.5
			Mean	58.2	593	321	-	-	11.6	119	64.3
			SD	42.8	425	275	-	-	8.57	85.1	55.0
2	4		201	233	651	651	a	a	58.3	163	163
			202	136	1327	518	a	a	34.1	332	129
			203	177	997	997	a	a	44.2	249	249
			Mean	182	992	722	-	-	45.6	248	180
			SD	48.6	338	248	-	-	12.2	84.6	61.9

Estimated Reduced Fenofibric Acid Glucuronide

Group No.	Dose (mg/kg)	Level No.	Animal No.	C _{max} (ng/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC%	C _{max} /Dose	AUC _(0-12h) /Dose	AUC _(0-12h) /Dose
1	5		101	783	5099	-	5307	3.91	157	1020	-
			102	1011	7555	-	7683	1.67	202	1511	-
			103	82.9	769	-	b	6.29	16.6	154	-
			Mean	626	4474	-	6495	3.96	125	895	-
			SD	484	3436	-	c	2.31	96.7	687	-
2	4		201	1317	6990	-	7006	0.79	329	1737	-
			202	649	5498	-	5522	0.43	162	1374	-
			203	718	7064	-	7123	0.83	179	1766	-
			Mean	894	6504	-	6550	0.69	224	1626	-
			SD	367	873	-	893	0.22	91.8	218	-

a Insufficient data to characterize the terminal phase.
 b Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
 c Standard deviation is not calculated.
 - Not calculated.

(Sponsor)



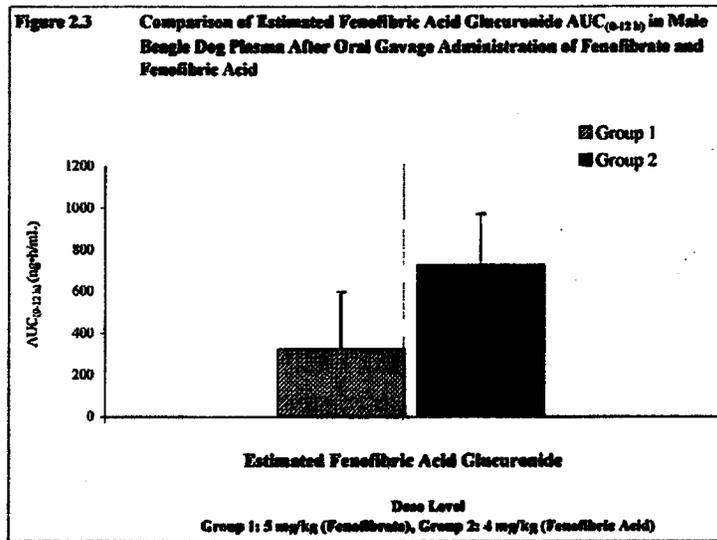
(Sponsor)

Table 5.1 Group Comparison of Systemic Exposure Parameters of Fenofibric Acid and its Metabolites in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

Analysis	C _{max} (ng/mL)		R	AUC _(0-12h) (ng·h/mL)		R	AUC _(0-12h) (ng·h/mL)		R
	Group 1 (5 mg/kg)	Group 2 (4 mg/kg)		Group 1 (5 mg/kg)	Group 2 (4 mg/kg)		Group 1 (5 mg/kg)	Group 2 (4 mg/kg)	
	Fenofibric Acid	1254	3676	0.34	8826	16350	0.54	-	-
Reduced Fenofibric Acid	3035	5156	0.59	35738	55157	0.65	-	-	-
Estimated Fenofibric Acid Glucuronide	58.2	182	0.32	593	992	0.60	321	722	0.45
Estimated Reduced Fenofibric Acid Glucuronide	626	894	0.70	4474	6504	0.69	-	-	-

- Not calculated.

(Sponsor)



(Sponsor)

Table 5.2 Ratio (R) of C_{max} and AUC_(0-24h) of Various Analytes in Male Beagle Dog Plasma After Oral Gavage Administration of Fenofibrate and Fenofibric Acid

Dose Level Group (mg/kg)	Reduced Fenofibric Acid	Fenofibric Acid	R	Estimated Fenofibric Acid Glucuronide	Fenofibric Acid	R	Estimated Reduced Fenofibric Acid Glucuronide	Reduced Fenofibric Acid	R
1 5 C _{max} (ng/mL)	3035	1254	2.42	58.2	1254	0.05	626	3035	0.21
AUC _(0-24h) (ng·h/mL)	35738	8826	4.05	599	3826	0.07	4474	35738	0.13
2 4 C _{max} (ng/mL)	5156	3676	1.40	182	3676	0.05	894	5156	0.17
AUC _(0-24h) (ng·h/mL)	55157	16350	3.37	992	16350	0.06	6504	55157	0.12

(Sponsor)

Summary: In order to rely upon the FDA's prior judgment of safety and efficacy for the approved reference drug Tricor[®], the sponsor demonstrated comparability between pharmacokinetic profiles of fenofibrate and fenofibric acid. The sponsor administered 5 mg/kg of fenofibrate and 4 mg/kg of fenofibric acid to adult male Beagle dogs (represents 10% greater fenofibric acid than fenofibrate by molarity).

Mean pharmacokinetic exposure parameters for fenofibric acid and major metabolites after administration of fenofibric acid were greater than those observed after administration of fenofibrate. These differences likely occurred due to poorer bioavailability of fenofibrate (compared to fenofibric acid) in the dog. Poorer bioavailability likely led to the high animal-to-animal, intragroup variability in absorption after fenofibrate administration.

Absorption of fenofibric acid was far more predictable and the mean pharmacokinetic parameters were uniformly higher. However, the exposure profiles observed after administration of fenofibric acid were within the range of those profiles observed after fenofibrate administration, albeit higher on average.

MPC-028-08-0001 – Toxicokinetics of Fenofibric Acid in the Male Mouse Following Dietary Administration of Fenofibrate for up to 4 Weeks

Key study findings: A comparator arm with Tricor[®] has not been included and the fenofibrate used is Mutual's at doses tested in Tricor[®] reproductive toxicology, genetic toxicology, and carcinogenicity studies. These studies do not provide a useful bridge to Tricor[®].

Summary: Toxicokinetic studies were carried out with the same concentrations of fenofibrate (Mutual) as those described in labeling for the reference listed drug (Tricor[®]) for the 2-year mouse carcinogenicity study.

Volume #, and page #: M4, MPC-028-08-0001-final-report

Conducting laboratory and location: _____

b(4)

Date of study initiation: March 14, 2008.

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity:

Identity:	Fenofibrate
Description:	White crystalline powder
Lot number:	RD060190
Chemical purity:	99.5%
Retest date:	07 February 2009
Storage conditions:	Room temperature
Supplier:	_____ via URL/Mutual Pharmaceutical Company

b(4)

(Sponsor)

Methods:

Doses:

Group Number	Strain	Dose Level (mg/kg)	Necropsy Day	Animal Numbers
				Males
1	CD-1	10	2, 28	1001-1048 1104, 1117, 1119-1121 ^a
2	CD-1	45	2, 28	2001-2048 2101, 2103, 2106, 2108, 2109, 2115, 2122, 2123 ^a
3	CD-1	200	2, 28	3001-3048 3104, 3106, 3122-3124 ^a

^a Replacement animal numbers. Animals were replaced for Day 2, where yields of plasma from the original animals were only half, or less than half, of the required volume. Replacements were made from spare animals, obtained from the same shipment and maintained under the same environmental conditions.

(Sponsor)

Species/strain: CD-1 mice

Number/sex/group or time point (main study): 48 males/group

Route, formulation, volume, and infusion rate: Dietary, PMI Certified Rodent

Meal 5002: PMI Nutrition International, ad libitum, 28 days

Satellite groups used for toxicokinetics or recovery:

Age: 6-8 weeks

Weight: Average 28.6 g (24.6 – 31.9 g)

Sampling times: Day 2 and Day 28

Unique study design or methodology (if any): Study was carried out primarily for bridging of TK data from fenofibric acid studies to TK studies conducted with the reference listed drug (Tricor[®]) in the mouse.

Observations and times:

Mortality and clinical signs: Animals were examined twice daily throughout the study.

Body weights: Body weights were collected weekly, but were reported as individual animal data for Day 2 and Day 28 only.

Pharmacokinetic blood sampling times: On Days 2 and 28, samples were collected at 0, 1, 2, 4, 6, 8, 12, and 24 hours (n=3 animals/time-point) post-light.

Results:

Mortality: No mortality was observed in this study.

Clinical signs: No dose-related clinical signs were reported for this study.

Body weights: There were no significant differences between the body weight gains between the three dose groups of fenofibrate.

Toxicokinetics:

Table 3 Pharmacokinetic Parameters of Fenofibric Acid in Male CD-1 Mice Plasma Following Oral Dietary Administration of Fenofibrate									
Day 2									
Group No.	Dose Level (mg/kg)	Tmax (h)	Tlast (h)	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-12h) (ng·h/mL)	C _{max} /Dose	AUC _(0-12h) /Dose	
1	10	24	24	448	7949	3451	44.8	345	
2	45	24	24	4107	55798	20720	91.3	460	
3	200	12	12	20367	176751	176751	102	884	
Day 28									
Group No.	Dose Level (mg/kg)	Tmax (h)	Tlast (h)	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-12h) (ng·h/mL)	C _{max} /Dose	AUC _(0-12h) /Dose	
1	10	24	24	532	9512	4196	53.2	420	
2	45	0	24	5739	62898	28576	83.1	635	
3	200	24	24	34333	544088	256280	172	1281	

(Sponsor)

Table 4 Dose Proportionality of Fenofibric Acid C_{max} and AUC_{0-12h} in Male CD-1 Mice Plasma Relative to Ascending Dose Level of Fenofibrate Delivered by Oral Dietary Administration

Day 2

Group No.	Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	AUC_{0-12h} (ng ² /mL)	Fold Increase
1	10	1.00	448	1.00	3451	1.00
2	45	4.50	4107	9.17	20720	6.00
3	200	4.44	20367	4.96	176751	8.53

Day 28

Group No.	Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	AUC_{0-12h} (ng ² /mL)	Fold Increase
1	10	1.00	532	1.00	4196	1.00
2	45	4.50	3739	7.03	28576	6.81
3	200	4.44	34335	9.18	256280	8.97

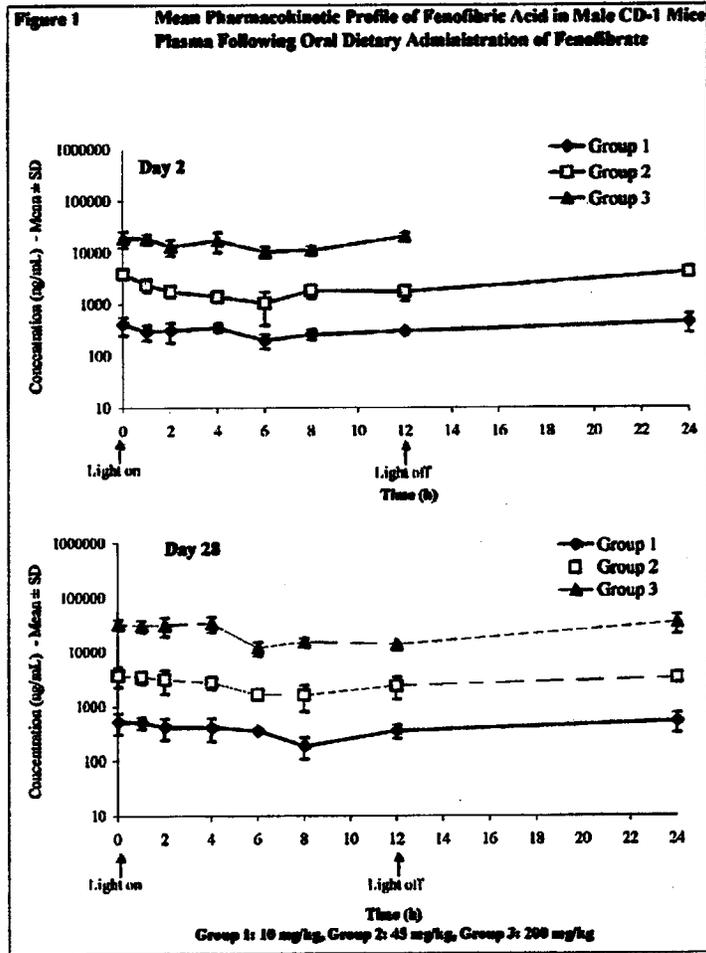
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Table 5 Accumulation Ratio (R) of Fenofibric Acid in Male CD-1 Mice Plasma Following Oral Dietary Administration of Fenofibrate

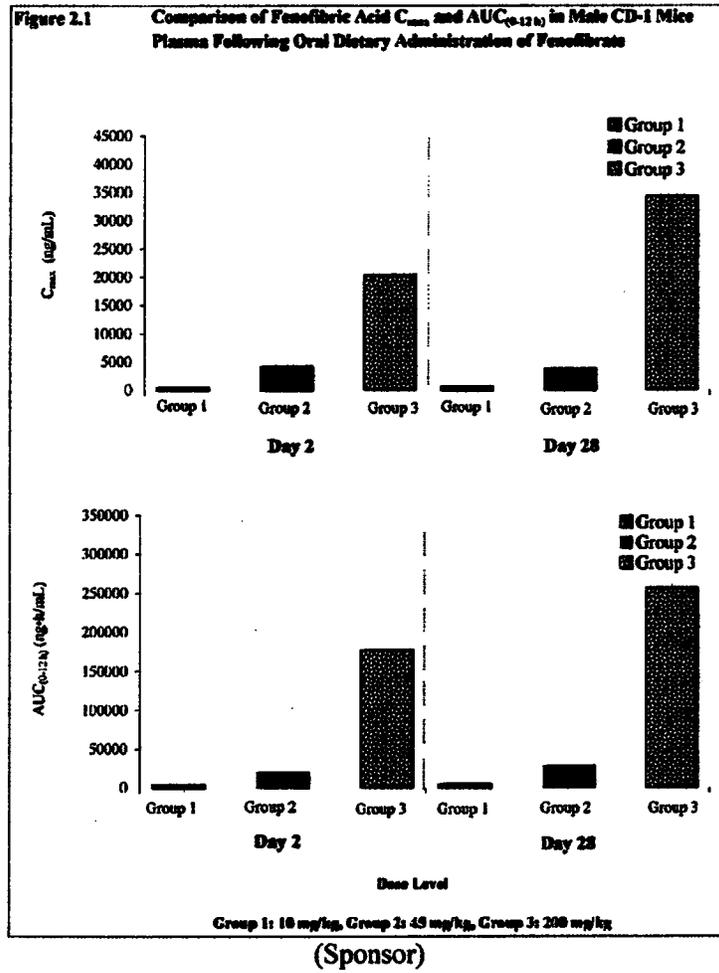
Group No.	Dose Level (mg/kg)	C_{max} (ng/mL)		R
		Day 2	Day 28	
1	10	448	532	1.19
2	45	4107	3739	0.91
3	200	20367	34335	1.69

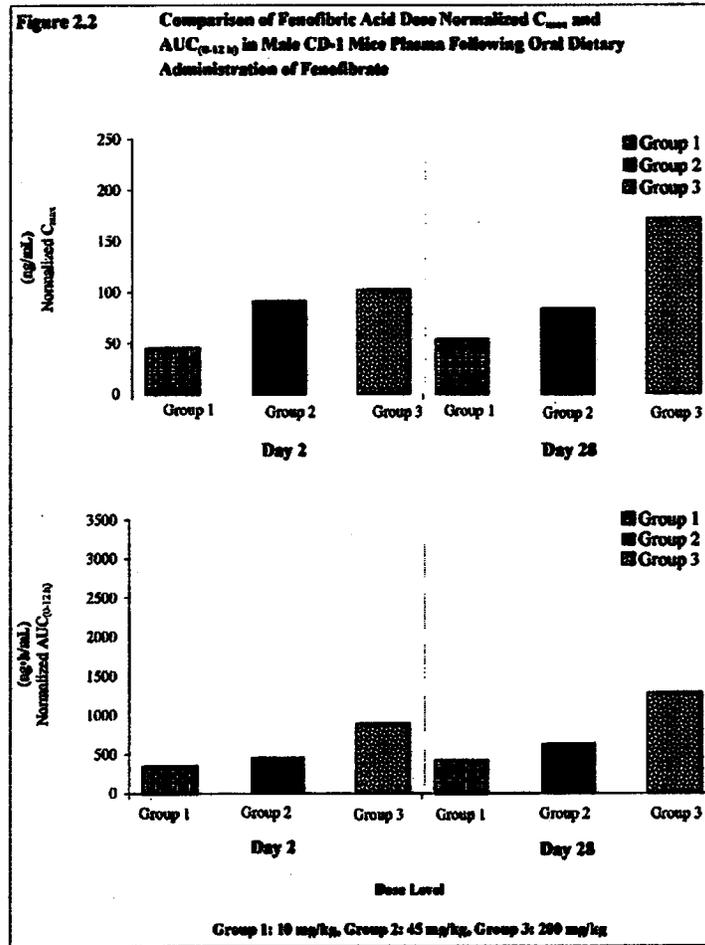
Group No.	Dose Level (mg/kg)	AUC_{0-12h} (ng ² /mL)		R
		Day 2	Day 28	
1	10	3451	4196	1.22
2	45	20720	28576	1.38
3	200	176751	256280	1.45

(Sponsor)

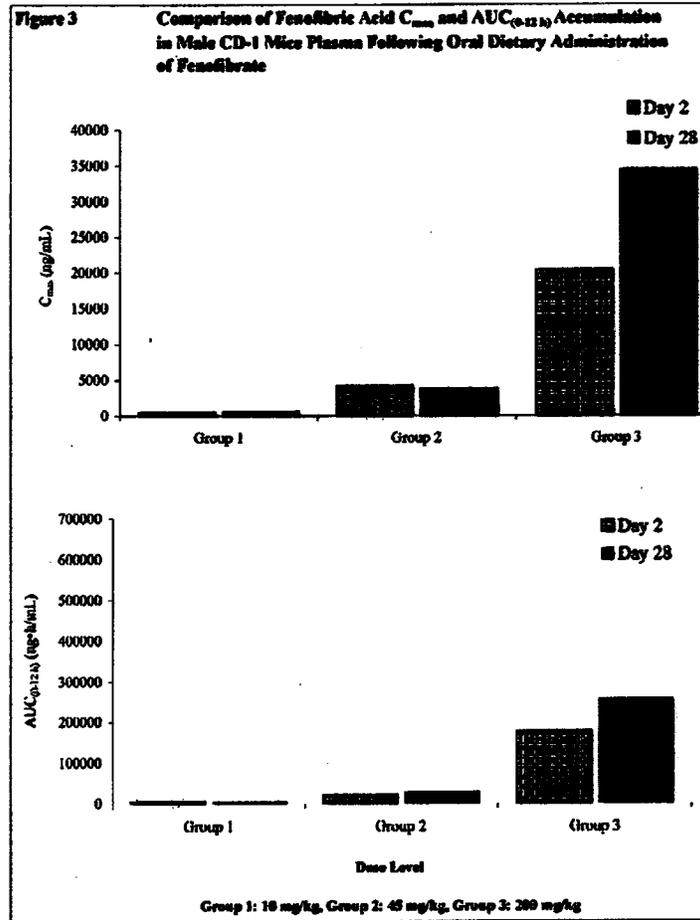


(Sponsor)





(Sponsor)



(Sponsor)

MPC-028-08-0002 – Toxicokinetics of Fenofibric Acid in Two Strains of Male Rat Following Dietary Administration of Fenofibrate for up to 4 Weeks

Key study findings: A comparator arm with Tricor[®] has not been included and the fenofibrate used is Mutual's at doses tested in Tricor[®] carcinogenicity as well as developmental and reproductive toxicology studies. These studies do not provide a useful bridge to Tricor[®].

Summary: Toxicokinetic studies in male rats were performed with fenofibrate at doses described for the pivotal 2-year rat carcinogenicity, as well as developmental and reproductive toxicology studies, in labeling for the reference listed drug (Tricor[®]).

Volume #, and page #: M4, MPC-028-08-0002-final-report

Conducting laboratory and location: _____

b(4)

Date of study initiation: March 28, 2008

GLP compliance: Yes
 QA report: yes (X) no ()
 Drug, lot #, and % purity:

Identity	Fenofibrate
Description	White crystal powder
Lot Number	RD060190
Chemical Purity	99.5%
Retest date	February 07, 2009
Storage Conditions	Store at room temperature with adequate ventilation
Supplier	_____ via URL/Mutual Pharmaceutical Company

b(4)

(Sponsor)

Methods:**Doses:**

- 1) Targeted at 10, 15, 60, 127, 300, and 361 mg/kg/day for male Sprague-Dawley rats administered fenofibrate.
- 2) Targeted at 10, 45, and 200 mg/kg/day for Wistar Han rats administered fenofibrate.

Species/strain: Adult, male Sprague-Dawley and Wistar Han rats

Number/sex/group or time point: 12 males/group (9 groups for a total of 108 test animals)

Route, formulation, volume, and infusion rate: Administered in the diet, Certified Rodent Meal 5002: PMI Nutrition International Inc.

Age: 6-8 weeks old

Weight: 249 to 288 g (SD) and 172 to 207 (Wistar Han)

Sampling times: Day 1 and Day 28

Observations and times:

Mortality: Twice daily.

Clinical signs: Twice daily.

Body weights: Weekly.

Food consumption: Weekly pre-dosing, daily during dosing.

Gross pathology: Early decedents only.

Pharmacokinetic blood sampling times: On Days 2 and 28, samples were collected at 0, 1, 2, 4, 6, 8, 12, and 24 hours (n=3 animals/time-point) post-light.

Results:

Mortality: One Sprague-Dawley rat in the highest dose, 361 mg/kg/day group was found dead on Day 28. Two Wistar Han rats died: one in the mid-dose and one in the high-dose on Day 2. Deaths occurred shortly after the blood collection procedure (jugular vein), and thus were probably related to this procedure.

Clinical signs: Dose-related clinical signs were observed in the 300 and 361 mg/kg/day groups in SD rats. These observations included prominent backbone, thin, cold to touch,

and dry/blackened skin, which probably relate to signs of dehydration and body weight decreases. It is not clear if this is related to palatability of the test compound or to toxicity.

Body weights:

Body Weight Decrements, Sprague Dawley				
Dose	Day	Body wt (g)	Delta	Decrement (%)
10	2	297	144	-
	28	441		
15	2	299	150	+4
	28	449		
60	2	293	121	-16
	28	414		
127	2	295	100	-31
	28	395		
300	2	275	37	-74
	28	312		
361	2	273	-9	-106
	28	267		

Body Weight Decrements, Wistar Han				
Dose	Day	Body wt (g)	Delta	Decrement (%)
10	2	199	80	-
	28	279		
45	2	204	78	-3
	28	282		
200	2	196	43	-46
	28	239		

Food consumption: Food consumption was generally lower with increased dose. For SD rats up to 127 mg/kg/day on Day 28, food consumption ranged from 19.7 to 24.4 g. At 300 mg/kg/day, food consumption was 15.0 g. Food consumption was 13.2 g at 361 mg/kg/day.

For Wistar Han rats, food consumption was 16.8, 18.3, and 14.4 g at 10, 45, and 200 mg/kg/day on Day 28.

Gross pathology: No cause of deaths could be determined from autopsy in the three early decedents.

Toxicokinetics:

Table 3 Pharmacokinetic Parameters of Fenofibric Acid in Male Sprague-Dawley and Wistar Han Rat Plasma Following Oral Dietary Administration of Fenofibrate

Day 2								
Group No.	Strain	Dose Level (mg/kg)	Target		C _{max} (ng/mL)	AUC _(0-24h) ^a (ng·h/mL)	C _{min} /Dose	AUC _(0-24h) /Dose
			Tmax (h)	Tlast (h)				
1	Sprague-Dawley	10	24	24	8498	136784	850	13678
2	Sprague-Dawley	15	24	24	10983	187692	732	12513
3	Sprague-Dawley	60	24	24	80074	1345931	1335	22432
4	Sprague-Dawley	127	24	24	263871	4933764	2078	38849
5	Sprague-Dawley	300	24	24	372632	7417566	1242	24725
6	Sprague-Dawley	361	24	24	413813	7149030	1146	19803
7 ^b	Wistar Han	10	4	24	7916	161151	792	16115
8 ^b	Wistar Han	45	24	24	70894	1218570	1575	27079
9 ^b	Wistar Han	200	0	24	354712	6117636	1774	30588

Day 28								
Group No.	Strain	Dose Level (mg/kg)	Target		C _{max} (ng/mL)	AUC _(0-24h) ^a (ng·h/mL)	C _{min} /Dose	AUC _(0-24h) /Dose
			Tmax (h)	Tlast (h)				
1	Sprague-Dawley	10	6	24	13983	238084	1398	23808
2	Sprague-Dawley	15	1	24	19136	402591	1276	26839
3	Sprague-Dawley	60	0	24	162797	3303210	2713	55054
4	Sprague-Dawley	127	1	24	450782	8211691	3549	64659
5	Sprague-Dawley	300	0	24	503795	10028589	1679	33429
6	Sprague-Dawley	361	0	24	462237	9658564	1280	26755
7 ^c	Wistar Han	10	2	24	7853	142023	785	14202
8 ^c	Wistar Han	45	2	24	101626	1838224	2258	40849
9 ^c	Wistar Han	200	0	24	433749	8482971	2169	42415

^a K_e could not be determined, thus, all parameters relying on it were not reported.

^b Day 2 study samples stored for up to 44 days at -80°C. Long-term matrix stability has been demonstrated for up to 11 days at -80°C. Long-term matrix stability assessments for 50 and 63 days at -80°C failed to meet acceptance criteria. No long-term matrix stability to support the result data, thus, presented for information purpose only.

^c Day 28 study samples stored for up to 18 days at -80°C. Long-term matrix stability has been demonstrated for up to 11 days at -80°C. Long-term matrix stability for 18 days at -80°C is on-going. Plasma concentration data of Day 28 samples is pending the result of the stability, thus, presented for information purpose only.

(Sponsor)

Table 4.1 Dose Proportionality of Fenofibric Acid C_{max} and $AUC_{(0-24h)}$ in Male Sprague-Dawley Rat Plasma Relative to Ascending Dose Level of Fenofibrate Delivered by Oral Dietary Administration

Day 2

Group No.	Target Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$AUC_{(0-24h)}$ (ng·h/mL)	Fold Increase
1	10	1.00	8498	1.00	136784	1.00
2	15	1.50	10983	1.29	187692	1.37
3	60	4.00	80074	7.29	1345931	7.17
4	127	2.12	263871	3.30	4933764	3.67
5	300	2.36	372632	1.41	7417566	1.50
6	361	1.20	413813	1.11	7149030	0.96

Day 28

Group No.	Target Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$AUC_{(0-24h)}$ (ng·h/mL)	Fold Increase
1	10	1.00	13983	1.00	238084	1.00
2	15	1.50	19136	1.37	402391	1.69
3	60	4.00	162797	8.51	3303210	8.20
4	127	2.12	450782	2.77	8211691	2.49
5	300	2.36	503795	1.12	10028589	1.22
6	361	1.20	462237	0.92	9658364	0.96

(Sponsor)

Table 4.2 Dose Proportionality of Fenofibric Acid C_{max} and $AUC_{(0-24h)}$ in Male Wistar Han Rat Plasma Relative to Ascending Dose Level of Fenofibrate Delivered by Oral Dietary Administration

Day 2

Group No.	Target Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$AUC_{(0-24h)}$ (ng·h/mL)	Fold Increase
7 ^a	10	1.00	7916	1.00	161151	1.00
8 ^a	45	4.50	70894	8.96	1218570	7.56
9 ^a	200	4.44	354712	5.00	6117656	5.02

Day 28

Group No.	Target Dose Level (mg/kg)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$AUC_{(0-24h)}$ (ng·h/mL)	Fold Increase
7 ^b	10	1.00	7853	1.00	142023	1.00
8 ^b	45	4.50	101626	12.9	1838224	12.9
9 ^b	200	4.44	433749	4.27	8482971	4.61

^a = Day 2 study samples stored for up to 44 days at -80°C. Long-term matrix stability has been demonstrated for up to 11 days at -80°C. Long-term matrix stability assessments for 50 and 65 days at -80°C failed to meet acceptance criteria. No long-term matrix stability to support the result data, thus, presented for information purpose only

^b = Day 28 study samples stored for up to 18 days at -80°C. Long-term matrix stability has been demonstrated for up to 11 days at -80°C. Long-term matrix stability for 18 days at -80°C is on-going. Plasma concentration data of Day 28 samples is pending the result of the stability, thus, presented for information purpose only

(Sponsor)

Table 5.1 Accumulation Ratio (R) of Fenofibric Acid in Male Sprague-Dawley Rat Plasma Following Oral Dietary Administration of Fenofibrate

Group No.	Target Dose Level (mg/kg)	C _{max} (ng/mL)		R
		Day 2	Day 28	
		1	10	
2	15	10983	19136	1.74
3	60	80074	162797	2.03
4	127	263871	450782	1.71
5	300	372632	503795	1.35
6	361	413813	462237	1.12

Group No.	Target Dose Level (mg/kg)	AUC _(0-24h) (ng·h/mL)		R
		Day 2	Day 28	
		1	10	
2	15	187692	402591	2.14
3	60	1345931	3303210	2.45
4	127	4933764	8211691	1.66
5	300	7417566	10028589	1.35
6	361	7149030	9658564	1.35

(Sponsor)

Table 5.2 Accumulation Ratio (R) of Fenofibric Acid in Male Wistar Han Rat Plasma Following Oral Dietary Administration of Fenofibrate

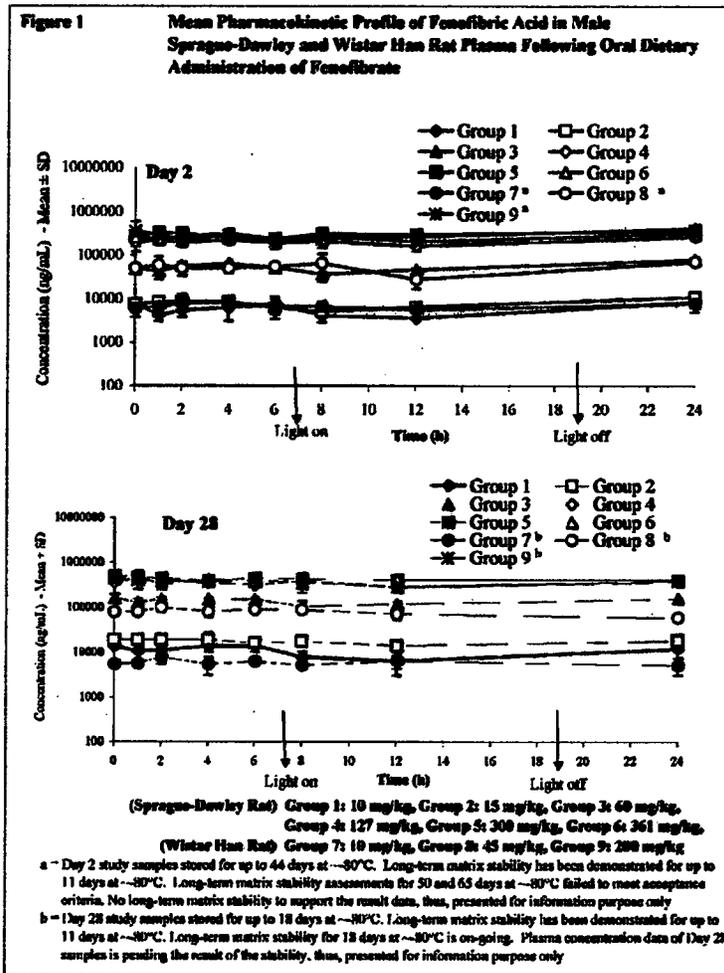
Group No.	Target Dose Level (mg/kg)	C _{max} (ng/mL)		R
		Day 2	Day 28	
7 ^a	10	7916	7833	0.99
8 ^a	45	70894	101626	1.43
9 ^a	200	354712	433749	1.22

Group No.	Target Dose Level (mg/kg)	AUC _(0-t_{last}) (ng·h/mL)		R
		Day 2	Day 28	
7 ^b	10	161151	142023	0.88
8 ^b	45	1218570	1838224	1.51
9 ^b	200	6117656	8482971	1.39

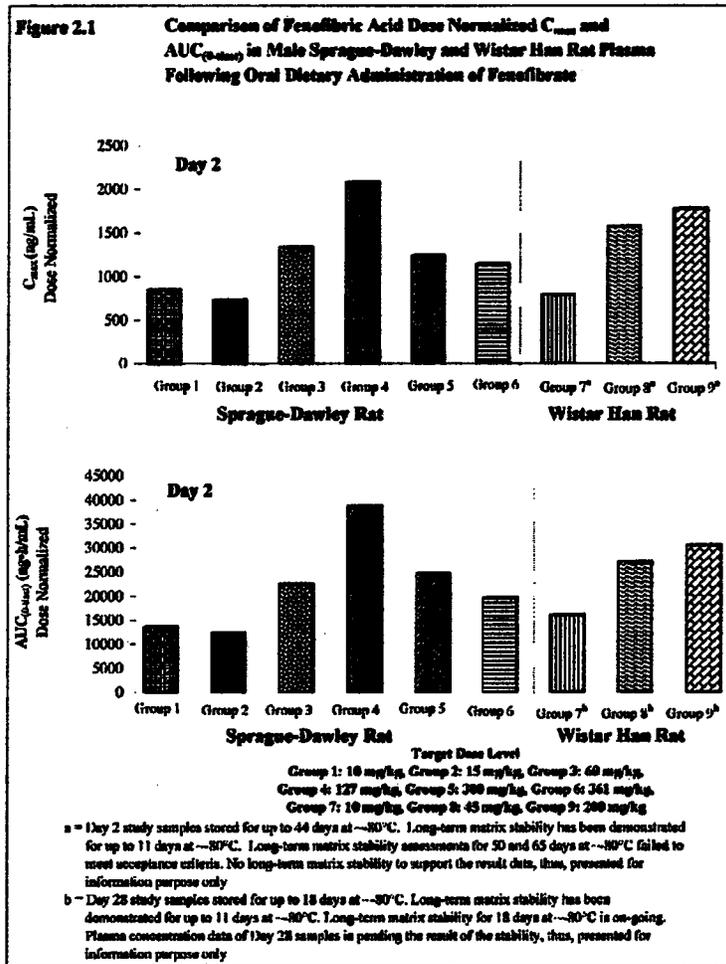
^a = Day 2 study samples stored for up to 44 days at ~-80°C. Long-term matrix stability has been demonstrated for up to 11 days at ~-80°C. Long-term matrix stability assessments for 50 and 65 days at ~-80°C failed to meet acceptance criteria. No long-term matrix stability to support the result data, thus, presented for information purpose only

^b = Day 28 study samples stored for up to 18 days at ~-80°C. Long-term matrix stability has been demonstrated for up to 11 days at ~-80°C. Long-term matrix stability for 18 days at ~-80°C is on-going. Plasma concentration data of Day 28 samples is pending the result of the stability, thus, presented for information purpose only

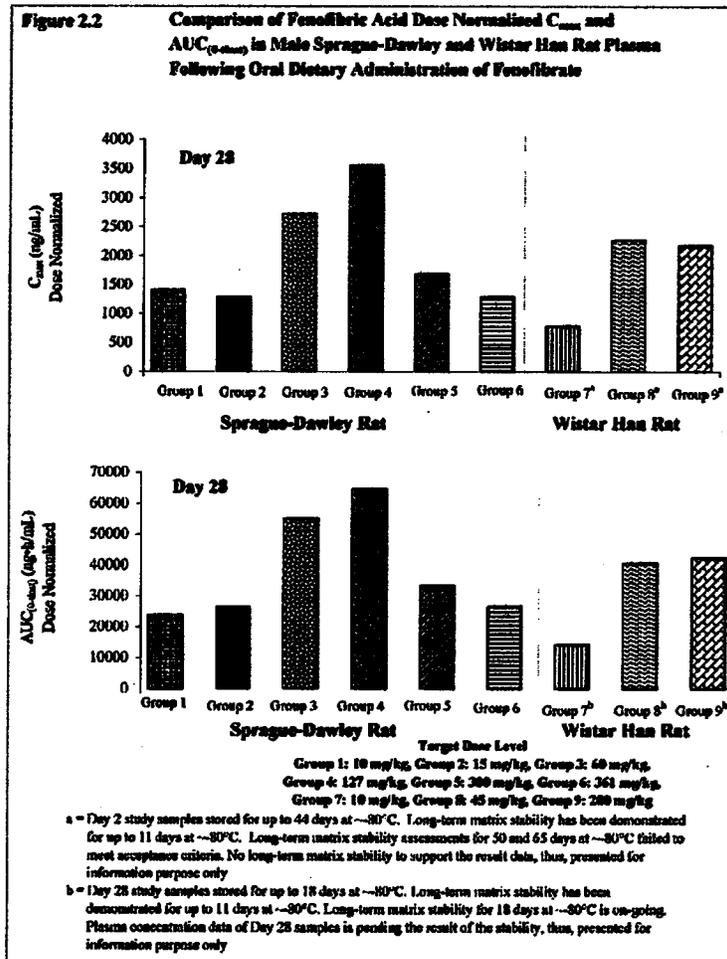
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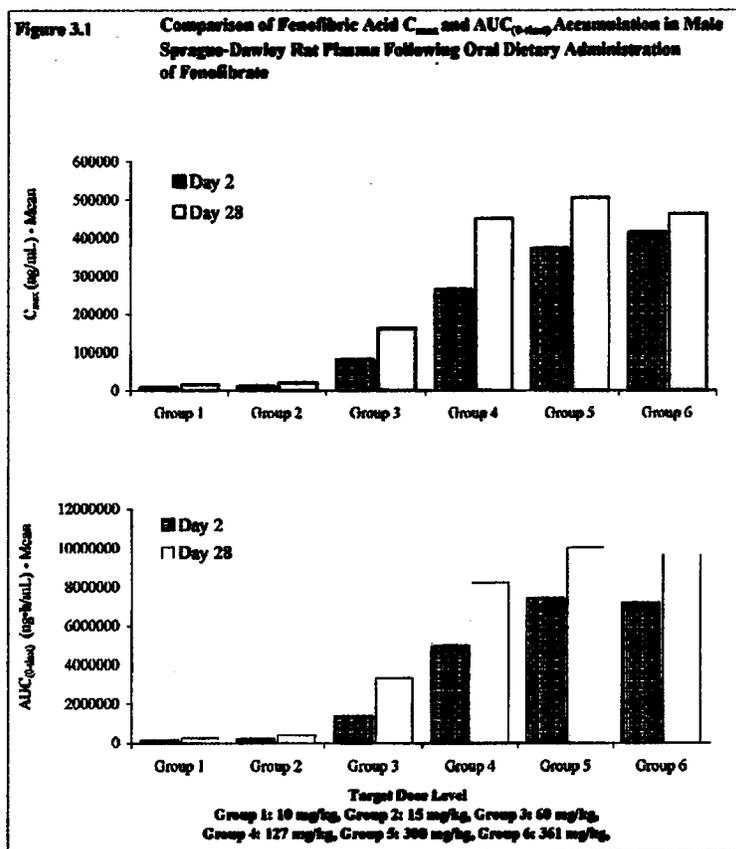
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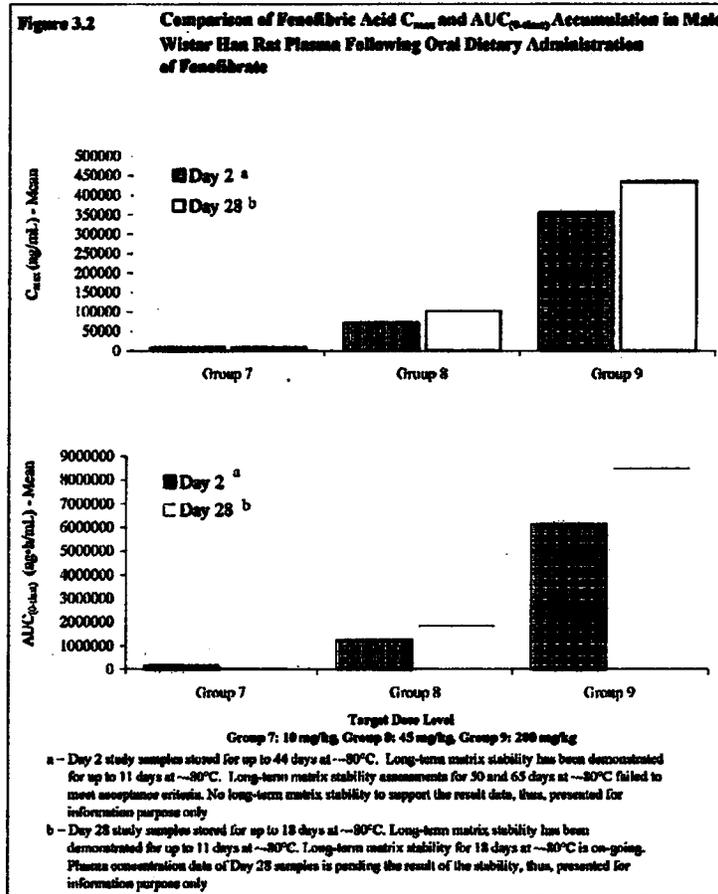
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(Sponsor)



(Sponsor)

MPC-028-08-0003 - Toxicokinetics of Fenofibric Acid in the Male Rabbit Following Oral Gavage Administration of Fenofibrate for 4 Weeks

Key study findings: This study used Mutual's fenofibrate in male Dutch Belted rabbits (different strain from Tricor[®]) to estimate exposure in pregnant NZW rabbits at doses identified in the Tricor[®] label. This study does not provide a bridge.

Summary: Toxicokinetic studies were performed in male Dutch Belted rabbits using the same doses of fenofibrate (Mutual) that were utilized in reproductive toxicology studies with the reference listed drug (Tricor[®]).

Volume #, and page #: M4, MPC-028-08-0003-final-report
Conducting laboratory and location: _____

b(4)

Date of study initiation: March 19, 2008
GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity:

Identity:	Fenofibrate
Description:	White crystalline powder
Lot number:	RD060190
Chemical purity:	99.5%
Retest date:	07 February 2009
Storage conditions:	Room temperature
Supplier:	via URL/Mutual Pharmaceutical Company

b(4)

(Sponsor)

Methods:

Group No.	Dose Level (mg/kg/day)	Concentration (mg/mL)	Animal Numbers
			Males
1	15	3	101-103
2	150	30	201-203
3	300	60	301-303

(Sponsor)

Species/strain: Dutch Belted rabbits

Number/sex/group or time point (main study): 3 males/group

Route, formulation, volume, and infusion rate: Oral gavage, 3% aqueous suspension of 3% (w/v) Gum Arabic, 5 mL/kg, daily, 28 days

Satellite groups used for toxicokinetics or recovery: All animals (9) used for TK

Age: 5 months

Weight: Average 1.9 kg (1.7 – 2.0 kg)

Sampling times: Day 1 and Day 28

Unique study design or methodology (if any): Study was carried out primarily for bridging of TK data from fenofibric acid studies to TK studies conducted with the fenofibrate comparator (Tricor) in the rabbit.

Observations and times:Mortality: Twice daily, except once on day of arrival and once on day of euthanasia.Clinical signs: Twice daily, except once on day of arrival and once on day of euthanasia.Body weights: Once during acclimatization, on Day 1, and once weekly thereafter.Pharmacokinetic blood sampling: Fenofibric acid levels in plasma on Days 1 and 28, post-dose time 0, 1, 2, 3, 4, 6, 8, and 24 hours.**Results:**Mortality: One animal in the high dose, 300 mg/kg/day group was found dead and one was found moribund and euthanized. No deaths or instances of moribundity occurred in the 15 and 150 mg/kg/day dose groups.

Clinical signs: Dose-related clinical signs were reduced appetite (1/3, 3/3), thin (1/2, 2/3), and feces output decreased (1/3, 2/3) in the 150 and 300 mg/kg/day dose groups, respectively. Clinical signs that showed increased incidence in the high-dose, 300 mg/kg/day group only were muscle tone decreased (1/3), feces absent (2/3), urine absent (2/3), weak (1/3), and discharge from the right (1/3) and left (1/3) eyes in the high-dose group. Dehydration (1/3, 1/3) and cold to touch (1/3, 1/3), were observed at the same incidence in the mid- and high-dose, 150 and 300 mg/kg/day groups, respectively.

It is unknown whether the clinical signs observed were due to poor palatability of the drug substance, because food consumption was not estimated. However, it appears that body weight was not decreased in the mid-dose, 150 mg/kg/day group, even though there were reported clinical signs (e.g. reduced appetite, decreased feces, thin, dehydration suspected, etc.) in that group. Therefore, adverse clinical signs are likely drug-related toxicities.

Body weights: Body weight decrements were higher in the mid-dose, 150 mg/kg/day group (↑40%) and decreased in the high-dose, 300 mg/kg/day group (↓230%) on Day 28.

Toxicokinetics:

Table 3.1 Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1							
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2α} (h)	K _{el} (1/h)	R ²	T% (h)
1	15	101	6	24	b	1.00	b
		102	4	24	0.07	1.00	9.70
		103	6	24	b	1.00	b
		Mean ^a	6	24	-	-	-
		SD	-	-	-	-	-
Day 28							
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2α} (h)	K _{el} (1/h)	R ²	T% (h)
1	15	101	4	24	b	1.00	b
		102	1	24	b	1.00	b
		103	4	24	b	1.00	b
		Mean ^a	4	24	-	-	-
		SD	-	-	-	-	-

^a Median value reported for T_{max} and T_{1/2α}.
^b Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 3.2 Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1								
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2} (h)	K _{e1} (1/h)	R ²	T _{1/2} (h)	
2	150	201	4	24	b	1.00	b	
		202	8	24	0.08	0.98	9.25	
		203	6	24	0.08	1.00	8.31	
		Mean ^a	6	24	0.08		8.78	
		SD						-

Day 28								
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2} (h)	K _{e1} (1/h)	R ²	T _{1/2} (h)	
2	150	201	6	24	0.08	1.00	9.15	
		202	6	24	b	1.00	b	
		203	6	24	0.08	1.00	8.40	
		Mean ^a	6	24	0.08		8.78	
		SD						-

^a Median value reported for T_{max} and T_{1/2}.
 b Values are not reported because the AUC₍₀₋₂₄₎ was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 3.3 Pharmacokinetic Observed and Secondary Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1								
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2} (h)	K _{e1} (1/h)	R ²	T _{1/2} (h)	
3	300	301	6	24	b	1.00	b	
		302	6	24	b	1.00	b	
		303	6	24	b	1.00	b	
		Mean ^a	6	24	-		-	
		SD						-

Day 28								
Group No.	Dose Level (mg/kg/day)	Animal No.	T _{max} (h)	T _{1/2} (h)	K _{e1} (1/h)	R ²	T _{1/2} (h)	
3	300	302	4	24	b	0.02	b	
		303	8	24	b	0.97	b	
		Mean ^a	6	24	-		-	
		SD						-

^a Median values reported for T_{max} and T_{1/2}.
 b Values are not reported because the AUC₍₀₋₂₄₎ was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 4.1 Pharmacokinetic Exposure Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-24h) /Dose
1	15	101	77435	1166139	a	24.9	5162	77743
		102	88393	1229645	1525000	19.4	5893	81976
		103	78585	1327768	a	30.9	5239	88518
		Mean	81471	1241184	-	25.1	5431	82746
		SD	6022	81430	-	5.78	401	5429

Day 28								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-24h) /Dose
1	15	101	83540	1235059	a	21.1	5569	82337
		102	122147	1621920	a	20.8	8143	108128
		103	95516	1488458	a	22.5	6368	99231
		Mean	100401	1448479	-	21.5	6693	96565
		SD	19762	196505	-	0.92	1317	13100

a Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 4.2 Pharmacokinetic Exposure Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-24h) /Dose
2	150	201	282362	4083083	a	21.2	1882	27221
		202	315718	5094237	6228571	18.2	2105	33962
		203	274669	4138369	4872454	15.1	1831	27589
		Mean	290916	4438563	5550512	18.2	1939	29590
		SD	21820	568503	-	3.08	145	3790

Day 28								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-24h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-24h) /Dose
2	150	201	310716	4842314	5899370	17.9	2071	32282
		202	211622	3516041	a	20.2	1411	23440
		203	256692	4034528	4767982	15.4	1711	26897
		Mean	259677	4130961	5333676	17.8	1731	27540
		SD	49614	668375	-	2.42	331	4456

a Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 4.3 Pharmacokinetic Exposure Parameters of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate

Day 1								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-12h) /Dose
3	300	301	350261	5707258	a	25.5	1168	19024
		302	351817	5551784	a	25.4	1173	18506
		303	399339	6246938	a	24.0	1331	20823
		Mean	367139	5835326	-	25.0	1224	19451
		SD	27897	364844	-	0.81	93.0	1216

Day 28								
Group No.	Dose Level (mg/kg/day)	Animal No.	C _{max} (ng/mL)	AUC _(0-12h) (ng·h/mL)	AUC _(0-∞) (ng·h/mL)	AUC% (last-∞)	C _{max} /Dose	AUC _(0-12h) /Dose
3	300	302	374539	8053042	a	97.5	1248	26843
		303	440946	7198847	a	23.4	1470	23996
		Mean	407743	7625944	-	60.5	1359	25420
		SD	-	-	-	-	-	-

a Values are not reported because the AUC_(0-∞) was extrapolated by more than 20% or R² is <0.8.
 - Not calculated.

(Sponsor)

Table 5 Dose Proportionality of Fenofibric Acid C_{max} and AUC_(0-12h) in Male Dutch Belted Rabbit Plasma Relative to Ascending Dose Level of Fenofibrate Delivered by Oral Gavage Administration

Day 1							
Gender	Group No.	Dose Level (mg/kg/day)	Fold Increase	C _{max} (ng/mL)	Fold Increase	AUC _(0-12h) (ng·h/mL)	Fold Increase
Males	1	15	1.00	81471	1.00	1241184	1.00
	2	150	10.0	290916	3.57	4438563	3.58
	3	300	2.00	367139	1.26	5835326	1.31

Day 28							
Gender	Group No.	Dose Level (mg/kg/day)	Fold Increase	C _{max} (ng/mL)	Fold Increase	AUC _(0-12h) (ng·h/mL)	Fold Increase
Males	1	15	1.00	100401	1.00	1448479	1.00
	2	150	10.0	239677	2.39	4130961	2.85
	3	300	2.00	407743	1.57	7625944	1.85

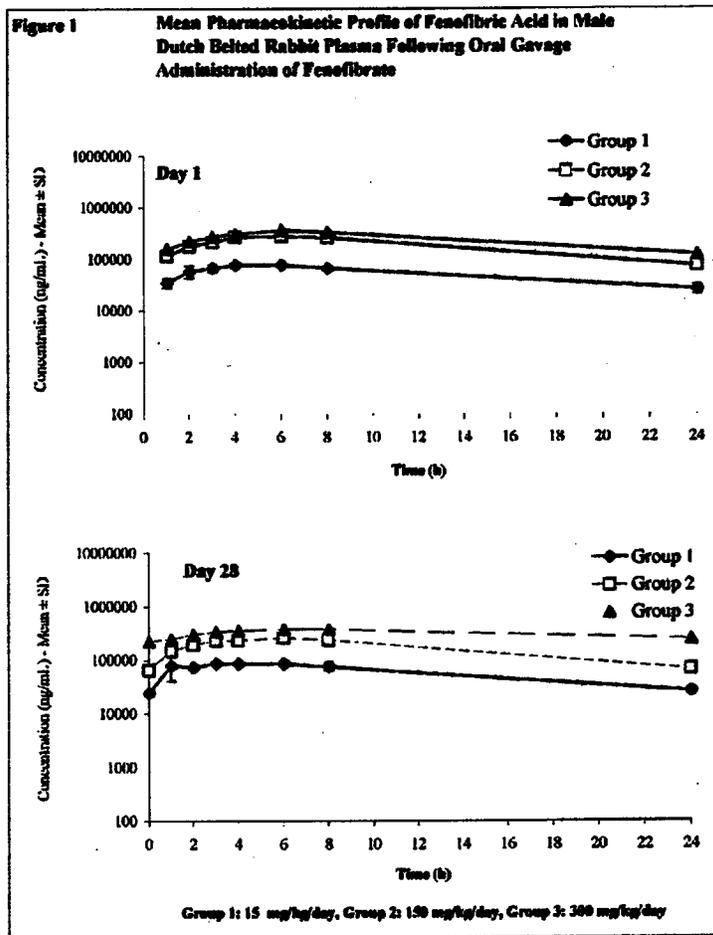
(Sponsor)

Table 6 **Accumulation Ratio (R) of Fenofibric Acid in Male Dutch Belted Rabbit Plasma Following Oral Gavage Administration of Fenofibrate**

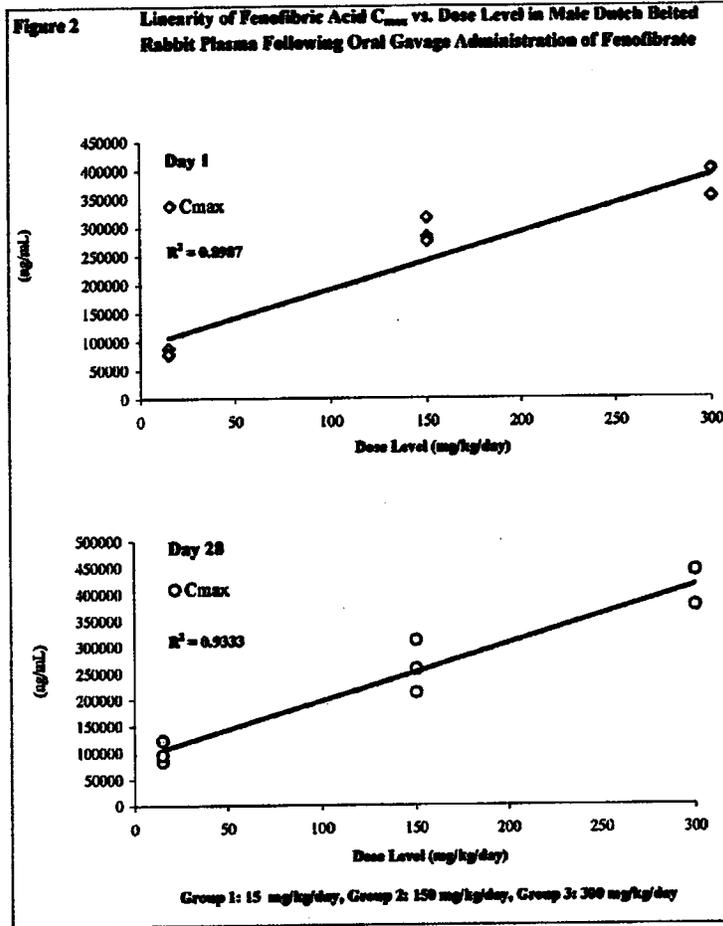
Gender	Group No.	Dose Level (mg/kg/day)	C _{max} (ng/mL)		R
			Day 1	Day 28	
			Males	1	
	2	150	290916	259677	0.89
	3	300	367139	407743	1.11

Gender	Group No.	Dose Level (mg/kg/day)	AUC _(0-24h) (ng·h/mL)		R
			Day 1	Day 28	
			Males	1	
	2	150	4438563	4130961	0.93
	3	300	5833326	7625944	1.31

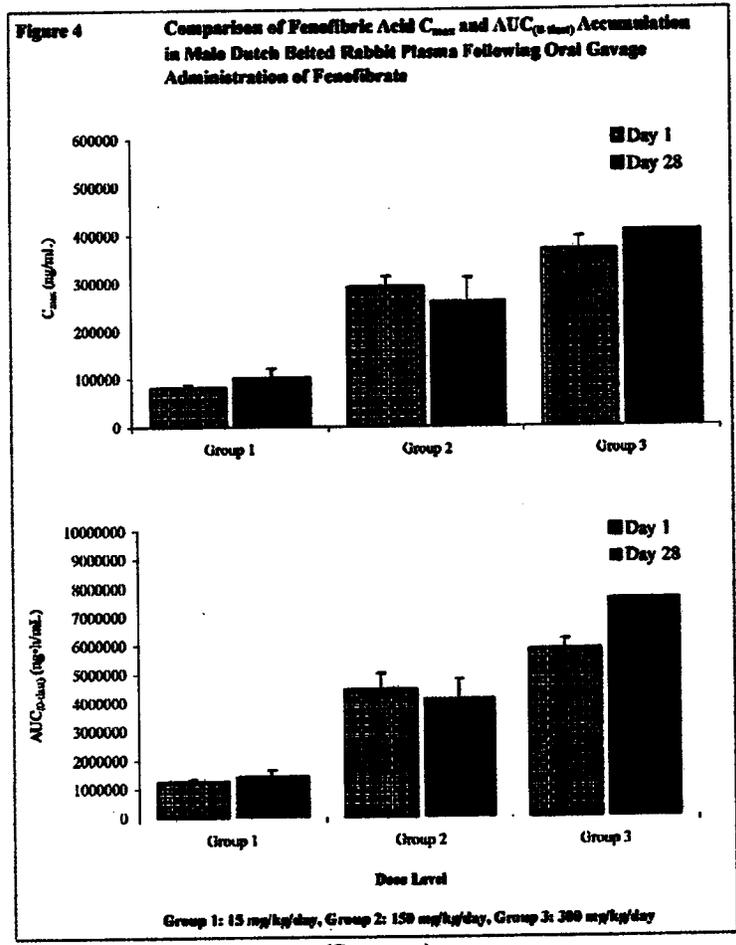
(Sponsor)



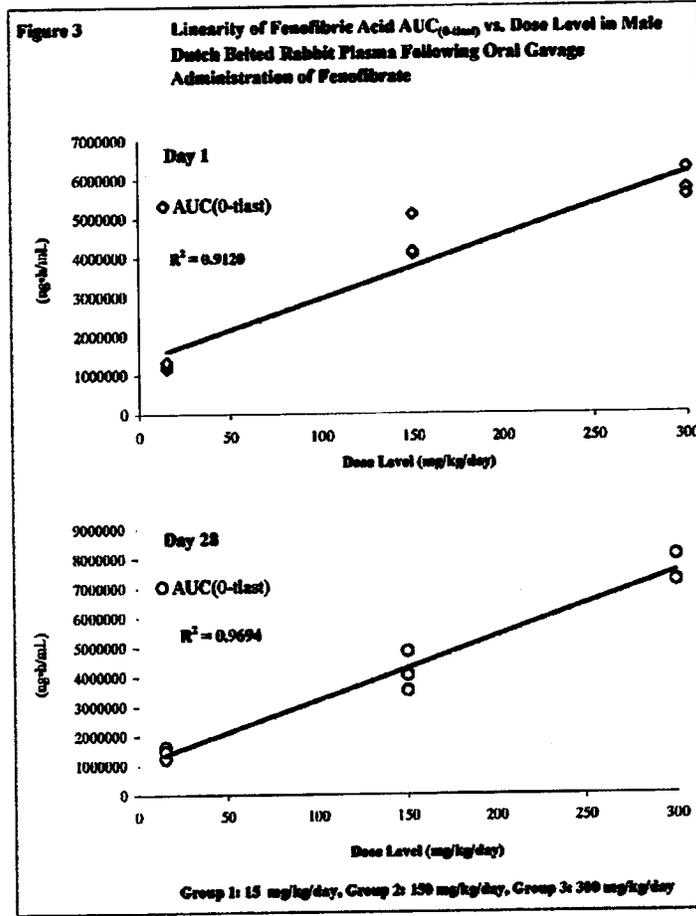
(Sponsor)



(Sponsor)



(Sponsor)



(Sponsor)

2.6.4.10 Tables and figures to include comparative TK summary

No comparative TK studies were performed.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Table 2.4.3:1

Comparison of Mean Pharmacokinetic Parameters of Fenofibric Acid Following a Single Oral Dose of Fenofibrate or Fenofibric Acid (Rats, Dogs) or Fenofibric Acid (Humans) Obtained in Mutual Sponsored Studies (Extracted from Table 2.6.4:3).

Species (n)	Drug Dosed	Dose	Human Equiv. Dose ² (mg/kg)	FA C _{max} (µg/mL)	FA T _{max} (hr)	FA AUC _{0-∞} (µg-hr/mL)	FA T _{1/2elim} (hr)
Rat ¹ (3)	FEN	14 mg/kg	2.3	26.5 (1.9)	4	234.7	6.5
Rat ¹ (3)	FA	12 mg/kg	1.9	24.9 (5.8)	3	219.3	7.4
Dog ² (3)	FEN	5 mg/kg	2.8	1.3 (1.5)	1	8.8 (7.0) ⁴	8.8
Dog ² (3)	FA	4 mg/kg	2.2	3.7 (1.1)	1	16.3 (2.4) ⁴	9.6
Human ³ (34)	FA	105 mg ⁵	2.1	9.9 (2.0)	3.5 (1.5-5.1)	134.9 (50.3) ⁶	17.3 (5.5)

¹MPC-028-08-0004; ²MPC-028-08-0005; ³Study MPC-028-08-1009; 105-mg dose, standard meal; ⁴based on T_{max} of 48 hours, when adjusted for body surface area; 50-kg person; ⁵oral tablet; maximum proposed human dose; ⁶oral suspension in 3% gum arabic; ⁷based on T_{max} of 72 hours;

FEN=fenofibrate; FA=fenofibric acid

(Sponsor, M2.4, Non-clinical overview, p5)

Table 2.4.4:2

Comparisons of Exposure Levels of Fenofibric Acid in Male Animals Receiving Daily Doses of Fenofibrate for 28 Days versus Man Receiving One MRHD Dose of Fenofibric Acid

Species/strain	FEN Dose level (mg/kg/day)	Day-28 AUC ₀₋₂₄ of FA (µg-hr/mL)	Ratio compared to human MRHD	Study Number
CD-1 Mouse				MPC-028-08-0001
	10	9.50	0.05	
	45	62.9	0.3	
	200	544	2.7	
Sprague-Dawley rat				MPC-028-08-0002
	10	238	1.2	
	60	3303	16.5	
Human*				MPC-028-07-1009
	2.1 mg/kg FA	200	N.A.	

FEN=fenofibrate; FA=fenofibric acid

* Estimated steady state AUC derived from Study MPC-028-07-1009; 105 mg dose of FA, standard meal. The AUC_{0-∞} (134.9 µg-hr/mL) was multiplied by 1.44 to estimate accumulation at steady state.

(Sponsor, M2.4, Non-clinical overview, p11)

Table 2.4.4:4
Comparison of Exposure Levels of Fenofibric Acid in SD Rats and Dutch Belted Rabbits Receiving Daily Doses of Fenofibrate for 28 Days versus Man Receiving One MRHD Dose of Fenofibric Acid

Species/strain	FEN Dose level (mg/kg/day)	Day-28 AUC ₀₋₂₄ of FA (µg·hr/mL)	Ratio compared to human MRHD	Study Number
Sprague-Dawley rat				MPC-028-08-0002
	15	403	2.0	
	127	8212	41	
	300	10029	50	
	361	9639	48	
Dutch Belted Rabbit				MPC-028-08-0003
	15	1449	7.2	
	150	4131	20	
	300	7626	38	
Human*				MPC-028-07-1009
	2.1 mg/kg FA	200	N.A.	

FEN=fenofibrate; FA=fenofibric acid

* Estimated steady state AUC derived from Study MPC-028-08-1009; 105 mg dose of FA, standard meal. The AUC₀₋₂₄ (134.9 µg·hr/mL) was multiplied by 1.44 to account for accumulation.

(Sponsor, M2.4, Non-clinical overview, p13)

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new general toxicology studies were conducted for this 505(b)(2) submission.

Genetic toxicology: No new genetic toxicology studies were conducted for this 505(b)(2) submission.

Carcinogenicity: No new carcinogenicity studies were conducted for this 505(b)(2) submission.

Reproductive toxicology: No new reproductive toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.2 Single-dose toxicity

No new single-dose toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.3 Repeat-dose toxicity

No new repeat-dose toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.4 Genetic toxicology

No new genetic toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.5 Carcinogenicity

No new carcinogenicity studies were conducted for this 505(b)(2) submission.

2.6.6.6 Reproductive and developmental toxicology

No new reproductive toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.7 Local tolerance

2.6.6.8 Special toxicology studies

No new special toxicology studies were conducted for this 505(b)(2) submission.

2.6.6.9 Discussion and Conclusions

No new toxicology studies were conducted for this 505(b)(2) submission.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No new toxicology studies were conducted for this 505(b)(2) submission.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

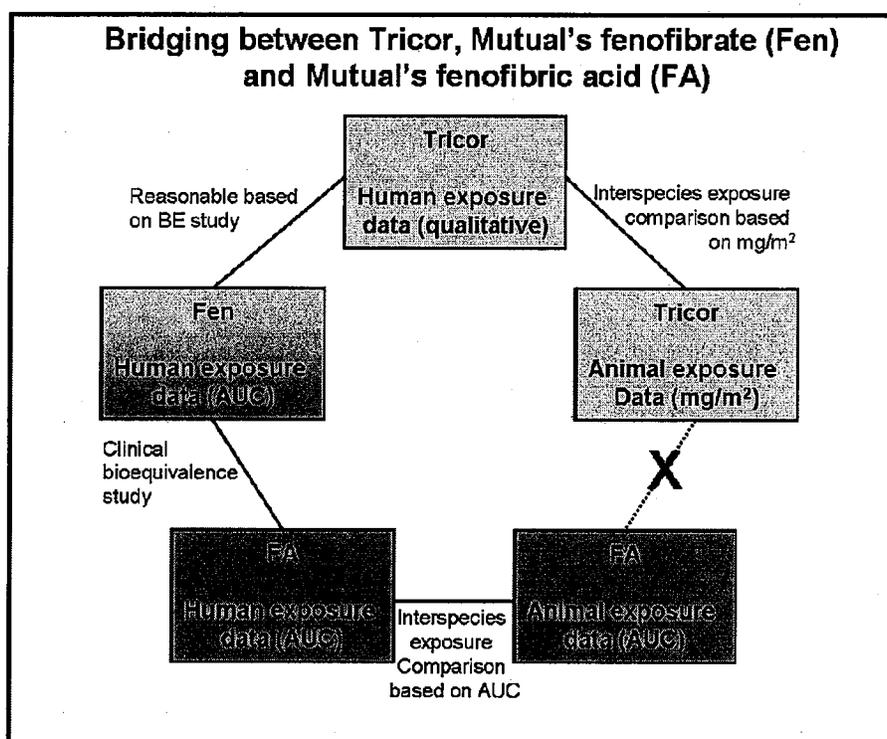
The sponsor conducted five non-clinical studies in support of this 505(b)(2) new drug application.

Two comparative pharmacokinetic studies were carried out in rats and dogs to measure exposures to fenofibric acid after administration of equimolar fenofibric acid (Mutual) or the prodrug fenofibrate (Mutual). Pharmacokinetic studies with rats showed that mean exposures to fenofibric acid and its major metabolites were highly similar in that model. In dogs, administration of fenofibric acid produced mean exposures for fenofibric acid that were greater (~90%) than that measured after administration of equimolar fenofibrate in dogs (AUC_{0-last}). When AUC in dogs was extrapolated to infinity, exposures were more similar. Bioavailability for fenofibrate is lower in dogs (~19%) than in rats (~64%).

Three toxicokinetic studies were performed in mouse, rat and rabbit after administration of fenofibrate (Mutual) at doses of fenofibrate that were administered to non-clinical species in the pivotal carcinogenicity and reproductive toxicology studies conducted for marketing of the reference listed drug (Tricor[®]) for up 28 days. Comparative

toxicokinetic studies between Mutual's to-be-marketed fenofibric acid drug substance and Mutual's fenofibrate and/or the reference listed product (Tricor[®]) were not provided.

However, a bridge is provided through the clinical data, which supports bioequivalence of 105 mg (2.1 mg/kg) fenofibric acid to Tricor[®] (fenofibrate, Abbott) 145 mg, in combination with the limited non-clinical data. Comparative pharmacokinetics from single-dose rat and dog studies with fenofibric acid (12 mg/kg rat and 4 mg/kg dog) and equimolar fenofibrate (14 mg/kg rat and 5 mg/kg dog) show that the two are bioequivalent in animals. The 12 mg/kg rat fenofibric acid dose is 2.2 mg/kg human equivalent dose (HED), the 4 mg/kg dog fenofibric acid dose is 2.2 mg/kg HED, and the maximum recommended human dose represents 2.1 mg/kg in humans (50 kg human body weight).



Unresolved toxicology issues (if any): Mutual's toxicokinetic studies were performed in mice, rats, and rabbits with Mutual's not-for-marketing fenofibrate drug substance only, and did not utilize Mutual's to-be-marketed fenofibric acid drug substance or the reference listed Tricor[®] product. Mutual requested altered labeling to reflect new (increased) safety margins based on actual exposure (AUC), whereas the safety margins described in labeling for Tricor[®] were based on body surface area calculations, not actual exposure. Since no direct comparison was made, no direct bridge was established between non-clinical exposures for Mutual's drug substance and exposures that supported labeling for the reference listed drug (Tricor[®]). Therefore, Mutual's labeling should be identical to that of the reference listed drug (Tricor[®]).

Recommendations: Approval provided the labeling for Mutual's fenofibric acid product is identical to that of the reference listed product (Tricor®).

Suggested labeling: Nonclinical labeling *must be identical* to that of the reference listed drug (Tricor®, NDA 21-656, NDA 21-203, and NDA 19-304).

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this page is the manifestation of the electronic signature.**

/s/

Calvin Elmore
4/30/2009 07:19:35 AM
PHARMACOLOGIST

Karen Davis-Bruno
4/30/2009 08:10:40 AM
PHARMACOLOGIST

10/14/08

**45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

Submission date: August 15, 2008
Application number: NDA 22-418
Drug: Fenofibric acid tablets
Application type: 505(b)(2), relies upon safety and efficacy in approved NDA 19-304 and NDA 21-656.
Sponsor: Mutual Pharmaceutical Company, Inc.

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		All files have been submitted electronically in eCTD format.
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		All files have been submitted electronically in eCTD format.
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		<p>No new toxicology data have been provided. Sponsor refers to two previously marketed fenofibrate NDAs: NDA 19-304, NDA 21-656.</p> <p>Sponsor provided two new bridging PK studies and three new bridging TK studies (see below).</p> <p>These studies are presented in an appropriate manner.</p>
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA. (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		<p>The sponsor has filed a 505b2 application and the safety will be based on the finding of safety and efficacy for approved NDA 19-304 and NDA 21-656 and published scientific literature.</p> <p>The following studies were performed where data were not already publicly available:</p> <p>Two PK studies were performed to bridge between the exposure to fenofibric acid (active metabolite) after administration of fenofibrate (active ingredient and prodrug) to that occurring after administration of fenofibric acid directly.</p> <p>Three TK studies were performed to bridge the exposure to fenofibric acid after administration of fenofibrate to that established after exposure to fenofibrate during carcinogenicity and reproductive toxicology studies. These studies were described in publicly available reviews of NDA 19-304 and NDA _____</p>

b(4)

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		The five PK/TK studies were adequately designed. There were no new toxicology studies submitted for this 505b2 application. The sponsor references the Agency's finding of safety and efficacy for approved NDA 19-304 and NDA _____
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		The formulation to be marketed utilizes excipients that are found in other approved NDAs. For bridging TK studies, the drug was blended into chow for dietary administration, which was the route of exposure for carcinogenicity and reproductive toxicology studies performed in support of NDA 19-304 and NDA _____
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		The route of administration used in bridging PK studies was the same as that intended for human exposure (oral). The route of administration used in bridging TK studies was also oral, but was drug was added to chow. This was necessary for bridging to data obtained after dietary exposure in carcinogenicity and reproductive toxicology studies.
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m ² or comparative serum/plasma AUC levels?	X		Labeling is similar to the approved referenced product approved under NDA 19-304 and NDA _____. Information is present to express human dose multiples in mg/m ² .

b(4)

b(4)

b(4)

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Reviewing Pharmacologist: C. Lee Elmore
Supervisory Pharmacologist: Karen Davis-Bruno

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

/s/

Calvin Elmore

10/14/2008 03:22:02 PM

PHARMACOLOGIST

From the Pharm/Tox point of view, this NDA is fileable.
This NDA is fileable.

Karen Davis-Bruno

10/14/2008 03:38:21 PM

PHARMACOLOGIST