

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-612

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

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-612	Submission Date(s): July 4, 2005
Brand Name	CIP-FENOFIBRATE
Generic Name	Fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Cipher Pharmaceuticals Limited
Relevant IND(s)	62,780
Submission Type	Amendment
Formulation; Strength(s)	Oral capsules; 50, 100, and 150 mg
Indication	Type IV and V hypercholesterolemia

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1 Executive Summary

To respond to the Agency's tentative approval letter dated July 15, 2004, Cipher Pharmaceuticals Limited submitted an amendment on November 30, 2004. The current amendment submitted on July 4, 2005 was to replace the one submitted on November 30, 2004 due to the fact that _____

~~In this amendment, the sponsor proposed three strengths including 50 mg, 100 mg, and 150 mg capsules. Two comparative bioavailability studies (FENPK.04.01 and FENPK.04.02)~~

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were conducted comparing the 150 mg strength of CIP-FENOFIBRATE capsules and 160 mg strength of Tricor® tablets.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-612 submitted on July 4, 2005 and finds it acceptable providing a satisfactory agreement on labeling was reached between the Agency and the sponsor. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability of CIP-Fenofibrate Capsule 150 mg Compared to Tricor® 160 mg Tablet:

Relative bioavailability of CIP-fenofibrate capsule 150 mg was compared to Tricor® fenofibrate tablet 160 mg under low-fat and high-fat fed conditions. The rate and extent of absorption of CIP-fenofibrate capsule 150 mg were bioequivalent to that of Tricor® fenofibrate tablet 160 mg.

Under low-fat fed condition, ratios (CIP-fenofibrate capsule 150 mg / Tricor® fenofibrate tablet 160 mg) of least-square means for AUC_{inf} and C_{max} of fenofibric acid were 93.09 and 89.99%, respectively. Since the 90% confidence intervals of AUC_{inf} and C_{max} ratios were within the 80% - 125% range, it was concluded that the rate and extent of absorption of CIP-fenofibrate capsule 150 mg and Tricor® fenofibrate tablet 160 mg were bioequivalent when administered following a low-fat meal.

Under high-fat fed condition, ratios (CIP-fenofibrate capsule 150 mg / Tricor® fenofibrate tablet 160 mg) of least-square means for AUC_{inf} and C_{max} of fenofibric acid were 97.11 and 92.33%, respectively. Since the 90% confidence intervals of AUC_{inf} and C_{max} ratios were within the 80% - 125% range, it was concluded that the rate and extent of absorption of CIP-fenofibrate capsule 150 mg and Tricor® fenofibrate tablet 160 mg were bioequivalent when administered following a high-fat meal.

2 Question Based Review

2.1 General Attributes

Not available.

2.2 General Clinical Pharmacology

Not available.

2.3 Intrinsic Factors

Not available.

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2.4 Extrinsic Factors

Not available.

2.5 General Biopharmaceutics

Q. What is the bioavailability of CIP-Fenofibrate 150 mg capsules compared to Tricor® 160 mg tablets under low-fat and high-fat fed conditions?

CIP-fenofibrate capsules 150 mg were found to be bioequivalent to Tricor® 160 mg tablets under low-fat and high-fat fed conditions.

Low-Fat Fed: The bioavailability of a single dose CIP-fenofibrate capsule 150 mg was compared to a single dose of Tricor® tablet 160 mg in healthy subjects under low-fat fed condition in study No. 2004-814 (FENPK.04.02). This was a single-dose, randomized, two-sequence, two-period, crossover study. Thirty subjects were recruited and all subjects completed the study. The 90% confidence intervals of ratios of geometric means (CIP-fenofibrate: Tricor®) for plasma fenofibric acid AUC and Cmax were within the 80-125% acceptance range (**Table 1**). The bioequivalence between CIP-fenofibrate capsules and Tricor® tablets was established.

Table 1. Plasma Fenofibric Acid Pharmacokinetic Data for a Single-Dose, Low-fat Bioavailability Study of CIP-Fenofibrate 150 mg Capsules and Tricor® 160 mg Tablets (N=30) in Study No. 2004-814 (FENPK.04.02)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geom. Means (%)	90% Confidence Interval (%)
	CIP-Fenofibrate 150 mg Capsule	Tricor® 160 mg Tablet		
AUCt (µg/mL.hr)	122.25 127.88 (30)	133.08 138.89(30)	91.86	87.97-95.94
AUCinf (µg/mL.hr)	133.08 141.18 (36)	142.96 150.76 (34)	93.09	87.97-95.94
Cmax (µg/mL)	7.73 7.89 (20)	8.59 8.73 (18)	89.99	84.68-95.64
Tmax* (hr)	4.50 (3.00, 5.50)	4.50 (2.00, 5.50)	--	--

* Median (min, max)

High-Fat Fed: The bioavailability of a single dose CIP-fenofibrate capsule 150 mg was compared to a single dose of Tricor® tablet 160 mg in healthy subjects under high-fat fed condition in study No. 2004-813 (FENPK.04.01). This was a single-dose, randomized, two-sequence, two-period, crossover study. Thirty subjects were recruited and 28 subjects completed the study. The 90% confidence intervals of ratios of geometric means (CIP-fenofibrate: Tricor®) for plasma fenofibric acid AUC and Cmax were within the 80-125% acceptance range (**Table 2**). The bioequivalence between CIP-fenofibrate capsules and Tricor® tablets was established.

Table 2. Plasma Fenofibric Acid Pharmacokinetic Data for a Single-Dose, High-fat Bioavailability Study of CIP-Fenofibrate 150 mg Capsules and Tricor® 160 mg Tablets (N=30) in Study No. 2004-813 (FENPK.04.01)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geom. Means (%)	90% Confidence Interval (%)
	CIP-Fenofibrate 150 mg Capsule	Tricor® 160 mg Tablet		
AUCt (µg/mL.hr)	152.58 158.22 (29)	157.60 162.31 (24)	96.81	93.30-100.45

AUCinf (µg/mL.hr)	162.12	166.95	97.11	93.38-100.98
	169.52 (34)	173.15 (28)		
Cmax (µg/mL)	10.32	11.18	92.33	87.24-97.72
	10.52 (20)	11.41 (20)		
Tmax* (hr)	4.50 (2.50, 7.00)	3.50 (1.50, 7.00)	--	--

* Median (min, max)

2.6 Analytical Section

Q. Was the analytical method adequately validated?

The liquid chromatographic tandem mass spectrometric (LC/MS/MS) analytical method for fenofibric acid was adequately validated and shown to be specific, sensitive, precise and accurate.

The lower limit of quantitation was 0.05 µg/mL and the calibration range was _____ µg/mL for fenofibric acid. The between-batch precision (% CV) and accuracy (% Norminal) of the QCs of fenofibric acid ranged from _____ respectively.

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3 Detailed Labeling Recommendations

Pharmacokinetics/Metabolism

The extent and rate of absorption of fenofibric acid after administration of 150 mg CIP-FENOFIBRATE capsules are equivalent under low-fat and high-fat fed conditions to 160 mg Tricor® tablets.

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 radiolabeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces.

The absorption of fenofibrate is increased when administered with food.

With CIP-FENOFIBRATE, the extent of absorption is increased by approximately 58% and 25% under high-fat fed and low-fat fed conditions as compared to fasting conditions, respectively.

In a single dose and multiple dose bioavailability study with CIP-FENOFIBRATE capsules 200 mg, the extent of absorption (AUC) of fenofibric acid, the principal metabolite of fenofibrate, was 42% larger at steady state compared to single-dose administration. The rate of absorption (C_{max}) of fenofibric acid was 73% greater after multiple-dose than after single-dose administration.

The extent of absorption of CIP-FENOFIBRATE in terms of AUC value of fenofibric acid increased in a less than proportional manner while the rate of absorption in terms of C_{max} value of fenofibric acid increased proportionally related to dose.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved after 5 days of once a day dosing and demonstrated a mean 2.4-fold accumulation following multiple dose administration. Steady-state plasma levels of fenofibrate demonstrated no accumulation. 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; unchanged fenofibrate is detected at low concentrations in plasma compared to fenofibric acid over most of the single dose and multiple dosing periods.

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

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant degree.

Excretion

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

Fenofibric acid is eliminated with a half-life between 10 and 35 hours (mean approximately 20 hours) allowing once daily administration in a clinical setting.

4 Appendix

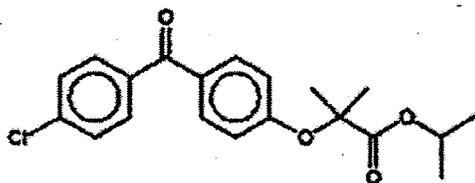
4.1 proposed labeling

CIP-FENOFIBRATE **(fenofibrate capsules)**

Rx only

DESCRIPTION

CIP-FENOFIBRATE (fenofibrate capsules), is a lipid regulating agent available as hard gelatin capsules for oral administration. Each hard gelatin capsule contains 50, 100 or 150 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW

NDA: 21-612	Submission Date(s): March 30, 2004
Brand Name	Luxacor
Generic Name	Fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Cipher Pharmaceuticals Limited
Relevant IND(s)	62,780
Submission Type	B2
Formulation; Strength(s)	Oral capsules; 50, 100, 150, <u> </u> mg
Indication	Type IV and V hypercholesterolemia

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1 Executive Summary

To respond to the Agency's approvable letter dated December 18, 2003, Cipher Pharmaceuticals Limited submitted a response on March 30, 2004. The OCPB related issue was the dissolution method and specification. The sponsor accepted the Agency's recommendation of the dissolution method, which is paddle speed of 75 rpm and medium of 2% Tween 80 and 0.1% Pancreatin at pH 6.8. In terms of dissolution specification, the sponsor proposed the Q = after 120 minutes.

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Originally the Agency recommended ~~_____~~ With more available data, the specification of not less than ~~_____~~ is recommended.

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Although the bioequivalence study No. 2003-647 (FENPK.03.01) submitted on November 7, 2003 was not part of the response, the results were incorporated in the labeling. The bioequivalence study No. 2003-647 showed that the rate and extent of absorption of ~~_____~~ fenofibrate capsules and Tricor[®] tablets were bioequivalent when administered following a low-fat meal.

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1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-612 submitted on November 7, 2003, March 30, 2004 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

Based on the dissolution profiles in different conditions, the dissolution specification of not less than ~~_____~~ is recommended.

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1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability of Luxacor Fenofibrate Capsule Compared to Tricor[®] Tablet:

Relative bioavailability of Luxacor fenofibrate capsule 160 mg was compared to Tricor[®] micronized fenofibrate tablet 160 mg under low-fat fed condition. The rate and extent of absorption of Luxacor fenofibrate capsule 160 mg was bioequivalent to that of Tricor[®] micronized fenofibrate tablet 160 mg.

Ratios (Luxacor fenofibrate capsule 160 mg / Tricor[®] micronized fenofibrate tablet 160 mg) of least-square means for AUC_{inf} and C_{max} of fenofibric acid were 97.80 and 98.53%, respectively. Since the 90% confidence intervals of AUC_{inf} and C_{max} ratios were within the 80% - 125% range, it was concluded that the rate and extent of absorption of Luxacor fenofibrate capsule 160 mg and Tricor[®] micronized fenofibrate tablet 160 mg were bioequivalent when administered following a low-fat meal.

2 Question Based Review

2.1 General Attributes

Not available.

2.2 General Clinical Pharmacology

Not available.

2.3 Intrinsic Factors

Not available.

2.4 Extrinsic Factors

Not available.

2.5 General Biopharmaceutics

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

Luxacor fenofibrate capsules 160 mg were found to be bioequivalent to Tricor® 160 mg tablets under low-fat fed conditions.

The bioavailability of a single dose Luxacor fenofibrate capsule 160 mg was compared to a single dose of Tricor® tablet 160 mg in healthy subjects under low-fat fed condition in study No. 2003-647 (FENPK.03.01). This was an open-label, single-dose, randomized, two-sequence, two-period, crossover study. Thirty subjects were recruited and 28 subjects completed the study. The 90% confidence intervals of ratios of geometric means (Luxacor: Tricor®) for plasma fenofibric acid AUC and Cmax were within the 80-125% acceptance range (**Table 1**). The bioequivalence between Luxacor capsules and Tricor® tablets was established.

Table 1. Plasma Fenofibric Acid Pharmacokinetic Data for a Single-Dose, Low-fat Bioavailability Study of Luxacor Fenofibrate 160 mg Capsules and Tricor® 160 mg Tablets (N=28) in Study No. 2003-647 (FENPK.03.01)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geom. Means (%)	90% Confidence Interval (%)
	Luxacor Fenofibrate 160 mg Capsule	Tricor® 160 mg Tablet		
AUCt (µg/mL.hr)	124.14 131.52 (34)	130.61 135.92 (30)	95.04	90.96-99.30
AUCinf (µg/mL.hr)	137.80 147.48 (36)	140.90 148.31 (34)	97.80	94.07-101.68
Cmax (µg/mL)	7.08 7.37 (29)	7.18 7.39 (25)	98.53	92.33-105.15

The batch size of Luxacor fenofibrate capsules 160 mg used in this study was ~~_____~~. The clinical and analytical sites have been inspected by DSI (7/22-7/24/03) for studies FENPK.02.01 and FENPK.01.07. (See Appendix)

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Q. Was the dissolution method and specification adequately justified?

In the original NDA review, the Agency recommended the following dissolution method that is accepted by the sponsor:

Apparatus Type: USP apparatus 2 (Paddles)
Rotation Speed: 75 rpm
Medium: 2% Tween 80 and 0.1% pancreatin at pH 6.8, 37°C

With regard to the dissolution specification, the Agency recommended not less than ~~_____~~. Instead, the sponsor proposed a dissolution specification of not less than ~~_____~~ (Q) in 120 minutes, which was inadequately justified. With additional data available, the Agency recommends a specification of not less than ~~_____~~.

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To select an appropriate dissolution specification for product quality control purpose, the sponsor analyzed the dissolution data by counting the number of failures at level S1, S2, and S3 for specifications such as ~~_____~~ minutes. The sponsor proposed the

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condition of acceptance of the specification being the number of S1 failures requiring S2 level testing of not more than . The dissolution data from two studies are shown in Tables 2 and 3. The calculated percent of dissolution tests failures at levels S1, S2, and S3 for and Q= after t = 120, minutes are shown in Table 4.

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Table 2. Fenofibrate dissolved (%) from dissolution data of the report of October 2003

Strength [mg]	Lot #	After 105 min							After 120 min							After 135 min						
		1	2	3	4	5	6	mean	1	2	3	4	5	6	mean	1	2	3	4	5	6	mean
200	11D01	80	82	75	75	88	93	82	88	88	83	82	95	98	89	95	94	89	89	98	101	94
	16D01	76	77	75	72	82	75	76	83	84	82	79	88	82	83	87	89	87	85	92	86	88
	16D012	84	82	69	79	80	86	80	89	87	77	85	86	91	86	93	91	83	90	90	94	90
160	24E01	97	94	92	92	94	97	94	102	99	97	98	99	102	100	104	102	101	102	102	105	102
	18D012	94	93	75	91	93	87	89	98	98	79	96	97	95	94	100	101	81	100	100	100	97
150	5E01	101	100	94	97	84	93	95	104	102	100	101	91	100	100	105	103	104	103	97	103	102
	4E01	103	102	102	108	102	105	104	104	105	102	108	102	105	104	104	105	103	109	102	105	105
50	4E012	104	101	106	105	103	100	103	105	104	106	105	105	101	105	106	105	107	105	104	101	105
	4E013	107	107	107	110	111	106	108	108	107	108	110	112	109	109	108	107	108	110	111	109	109

Table 3. Fenofibrate dissolved (%) from comparative study of February 2004

Strength [mg]	Lot #	After 105 min							After 120 min							After 135 min						
		1	2	3	4	5	6	mean	1	2	3	4	5	6	mean	1	2	3	4	5	6	mean
200	11D01	84	68	78	67	75	78	75	90	75	85	75	83	85	82	93	81	90	81	88	90	87
	16D01	80	79	81	85	81	70	79	87	86	86	91	87	77	86	93	91	91	95	92	83	91
	16D012	80	84	84	81	84	85	83	87	90	89	88	90	90	89	91	94	93	92	94	93	93
	2E01	79	77	83	79	72	85	79	86	83	89	85	80	91	86	90	88	93	90	85	95	90
	3E01	84	85	83	88	80	85	84	91	90	89	93	86	90	90	95	94	93	95	90	95	94
	3E012	83	76	80	81	83	77	80	89	82	86	86	89	82	86	92	87	91	90	93	87	90
	24E01	95	94	82	88	95	94	91	98	98	90	95	99	98	96	99	101	96	98	101	100	99
150	18D012	80	95	94	88	81	89	88	87	99	98	94	88	96	94	92	101	100	98	94	99	97
	7E012	89	86	90	86	90	96	89	95	93	95	92	96	101	95	98	96	97	97	99	103	98
100	5E01	100	94	97	102	91	100	97	101	99	98	103	97	102	100	102	101	99	103	99	103	101
	7E01	98	97	96	95	99	95	97	99	99	99	99	100	98	99	99	99	100	99	100	99	99
50	4E01	102	104	100	103	103	103	102	102	104	100	104	103	103	102	102	104	100	104	103	103	102
	17D01	107	102	94	103	104	103	102	108	102	94	104	104	103	102	108	102	94	104	104	103	102
	4E012	99	99	99	89	98	100	97	99	100	99	97	99	101	99	99	100	99	99	98	101	99
	17D012	99	99	99	101	96	102	99	99	99	99	101	99	102	100	99	99	99	101	99	102	100
	4E013	95	103	98	97	99	100	99	94	102	97	97	98	100	98	93	102	96	96	97	99	97
	18D01	96	97	99	102	105	102	100	97	99	99	103	105	102	101	98	99	99	104	105	102	101

Table 4. Percent of dissolution tests failures at levels S1, S2, and S3 for and Q= after 120, minutes.

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Study Origin	Level	<u> </u>			Q= <u> </u>		
		105min	120min	135min	105min	120min	135min
Oct 2003 n= 9	S1	44	44	22	44	33	0
	S2	11	0	0	0	0	0
	S3	0	0	0	0	0	0
Feb 2004 n= 17	S1	47	24	12	24	12	0
	S2	18	0	0	0	0	0
	S3	0	0	0	0	0	0
All Data n= 26	S1	46	31	15	36	19	0
	S2	15	0	0	0	0	0
	S3	0	0	0	0	0	0

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The data from lots of capsules with lots 200 mg strength, lot 160 mg strength, lots 150 mg, lots 100 mg strength, and lots 50 mg strength were included for calculation. The

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rational for including the 200 mg strength was based upon the study results of a pharmacokinetic study where the lowest 50 mg and the highest 200 mg strengths were demonstrated to be bioequivalent.

For Q= [redacted] the amount of S1 failures was [redacted], 19% after 120 min [redacted]

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Reviewer's comments:

1. The dissolution specifications of not less than [redacted] (Q) in 120 minutes or [redacted] were selected based on the analysis of lots for strengths 50 mg, 100 mg, 150 mg, 160 mg and 200 mg. Since [redacted] and the specification is going to be applied for other lower strengths, the data from 200 mg strengths should not be included. Excluding the 200 mg strength, the percentage failure at S1 values was calculated (Table 5).

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Table 5. Percent of dissolution tests failures at S1 level for [redacted], and [redacted] after [redacted] 120, [redacted] minutes excluding 200 mg strength.

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Study Origin	Level	Q= [redacted]			Q= [redacted]		
		105 min	120 min	135 min	105 min	120 min	135 min
Oct 2003 n=6	S1	33%	17%	17%	17%	17%	0%
Feb 2004 n=11	S1	18%	0%	0%	0%	0%	0%
All data n=17	S1	24%	6%	6%	6%	6%	0%

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For Q= [redacted] the percent of S1 failure was 6% [redacted] 120 minutes [redacted]

2. S2 and S3 calculation was not appropriate since only [redacted] capsules were tested. In order to have S2 calculation another set of [redacted] capsules of each lot should be evaluated. For S3 calculation, additional [redacted] capsules of each lot should be examined.

2.6 Analytical Section

Q. Was the analytical method adequately validated?

The liquid chromatographic tandem mass spectrometric (LC/MS/MS) analytical methods for fenofibric acid and fenofibrate were adequately validated and shown to be specific, sensitive, precise and accurate.

The lower limit of quantitation was 0.05 µg/mL and the calibration range was [redacted] µg/mL for fenofibric acid. The between-batch precision (% CV) and accuracy (% Nominal) of the QCs of fenofibric acid ranged from [redacted] and [redacted] respectively.

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3 Detailed Labeling Recommendations

Pharmacokinetics/Metabolism

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2 Individual Study Reviews

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Study Report, Fenofibrate, 160 mg Capsules – Single-dose, Fed
Protocol No. FENPK.03.01 Version 1
PMRI Study No. 2003-647

4.0 Synopsis

Title: An Open-Label, Single-Dose, Randomized, Two-Way Crossover Comparative Bioavailability Study of Two 160 mg Fenofibrate Formulations in Healthy Subjects under Fed Conditions

Sponsor: Cipher Canada Inc., 6560 Kennedy Road, Mississauga, Ontario, Canada L5T 2X4

Protocol Number: FENPK.03.01 Version 1

Objective: The objective of this study is to evaluate the comparative bioavailability between Fenofibrate 160 mg capsules (Cipher Pharmaceuticals Ltd., Barbados) and TRICOR® 160 mg tablets (Abbott Laboratories, USA), in healthy male and female volunteers, when administered after a low fat meal.

Treatment A: (Test) FENOFIBRATE 160 mg Capsules; (GALEPHAR P.R. Inc. for Cipher Pharmaceuticals Ltd., Barbados); Lot No.: 24E01
One 160 mg capsule was administered after the complete ingestion of a standardized low fat breakfast, which followed an overnight fast of at least 10 hours.

Treatment B: (Reference) TRICOR® 160 mg Tablets; (Abbott Laboratories, USA); Lot No.: 040472E21
One 160 mg tablet was administered after the complete ingestion of a standardized low fat breakfast, which followed an overnight fast of at least 10 hours.

The contents of the low fat breakfast were as follows:

Item	Weight (g)	Fat (g)	Energy (kcal)
2 Slice of white toast	44	1.76	128.92
1/2 Patty Butter	2.5	4.06	35.85
10oz Corn flakes	35	0.28	126.35
250 ml of 2% Milk	244	4.81	122.00
180 ml Orange Juice	178.6	0.36	80.00
Total		11.27	493.12

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Study Report, Fenofibrate, 160 mg Capsules – Single-dose, Fed
Protocol No. FENPK.03.01 Version 1
PMRI Study No. 2003-647

Number of Subjects: Thirty (30) male and female subjects were dosed in Period 1, and 28 subjects completed the entire study.

Study Dosing Dates: Period 1: August 7, 2003
Period 2: August 14, 2003

Sampling Schedule: Blood samples were obtained pre-dose (0.0 hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 24, 48 and 72 hours following drug administration.

Adverse Events: There was only one adverse event reported during the study.

Analytical Requirements: Analyte: Fenofibric Acid
Assay: LC-MS/MS
Calibration Range: _____ µg/ml

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Study Report, Fenofibrate, 160 mg Capsules – Single-dose, Fed
 Protocol No. FENPK.03.01 Version 1
 PMRI Study No. 2003-647

**Summary of Results for Plasma Fenofibric Acid
 (N = 28)**

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC _t (µg*h/ml)	124.1374 131.5251 (34)	130.6141 135.9226 (30)	95.04	90.96 - 99.30	10
AUC _i (µg*h/ml)	137.8044 147.4797 (36)	140.9045 148.3142 (34)	97.80	94.07 - 101.68	9
C _{max} (µg/ml)	7.0787 7.3675 (29)	7.1844 7.3918 (25)	98.53	92.33 - 105.15	14
T _{max} ^a (h)	4.50 (16)	4.06 (19)	-	-	-
K _{el} ^a (h ⁻¹)	0.0368 (24)	0.0396 (21)	-	-	-
T _{half} ^a (h)	20.05 (27)	18.53 (28)	-	-	-

^a Presented as arithmetic mean (CV%) only.

Treatment A: FENOFIBRATE 160 mg Capsules (GALEPHAR P.R. Inc. for Cipher Pharmaceuticals Ltd., Barbados); Lot No.: 24E01
 1 x 160 mg capsule was administered after the complete ingestion of a standardized low fat breakfast, which followed an overnight fast of at least 10 hours.

Treatment B: TRICOR® 160 mg Tablets (Abbott Laboratories, USA) ; Lot No.: 040472E21
 1 x 160 mg tablet was administered after the complete ingestion of a standardized low fat breakfast, which followed an overnight fast of at least 10 hours.

Study Conclusions

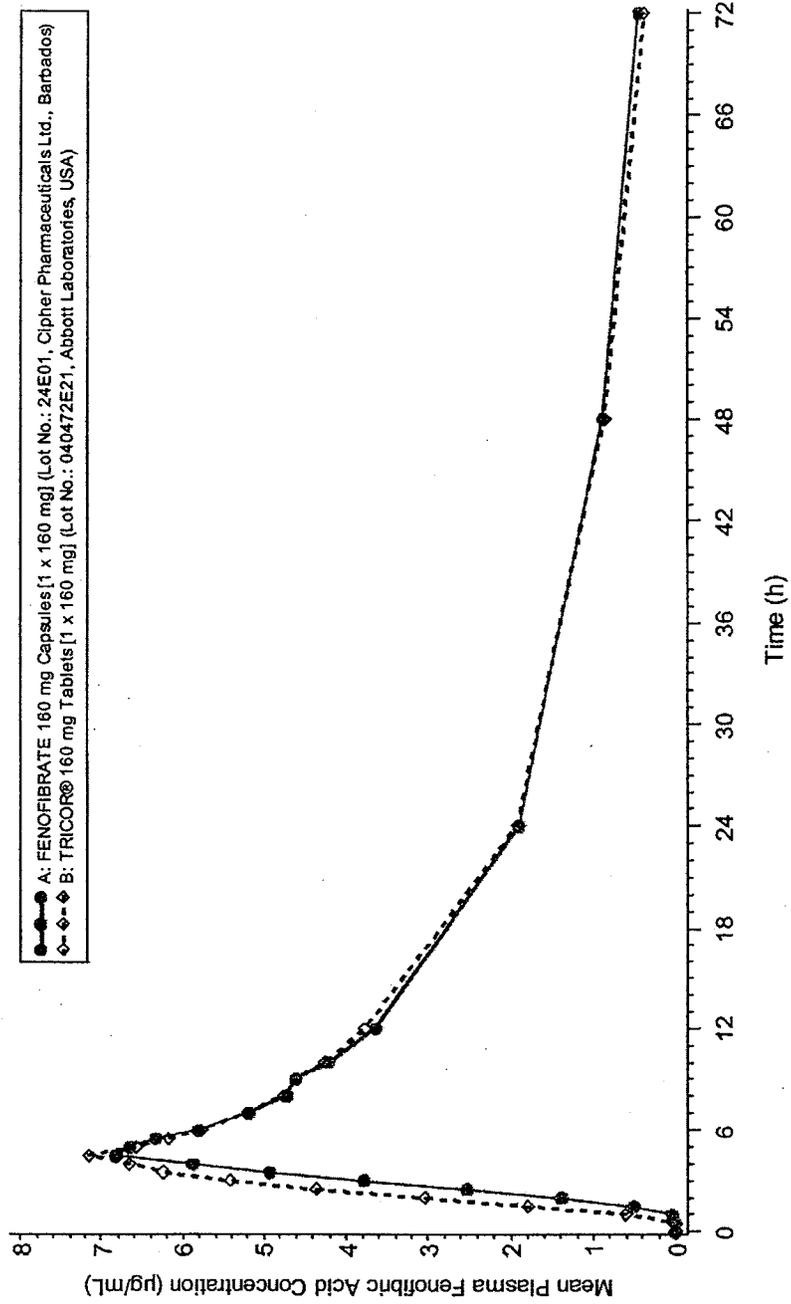
The 90% confidence intervals for the ratios of geometric means of the test to reference products for AUC_t, AUC_i and C_{max} were within the 80%-125% range.

Therefore, Fenofibrate 160 mg capsules (Cipher Pharmaceuticals Ltd., Barbados) exhibited equivalent rate and extent of absorption to TRICOR® 160 mg tablets (Abbott Laboratories, USA) in healthy volunteers when administered as a single dose, after a low fat breakfast. The two drug products are, therefore, bioequivalent.

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Study Report, Fenofibrate, 160 mg Capsules -- Single-dose, Fed
Protocol No. FENPK.03.01 Version 1
PMRI Study No. 2003-647

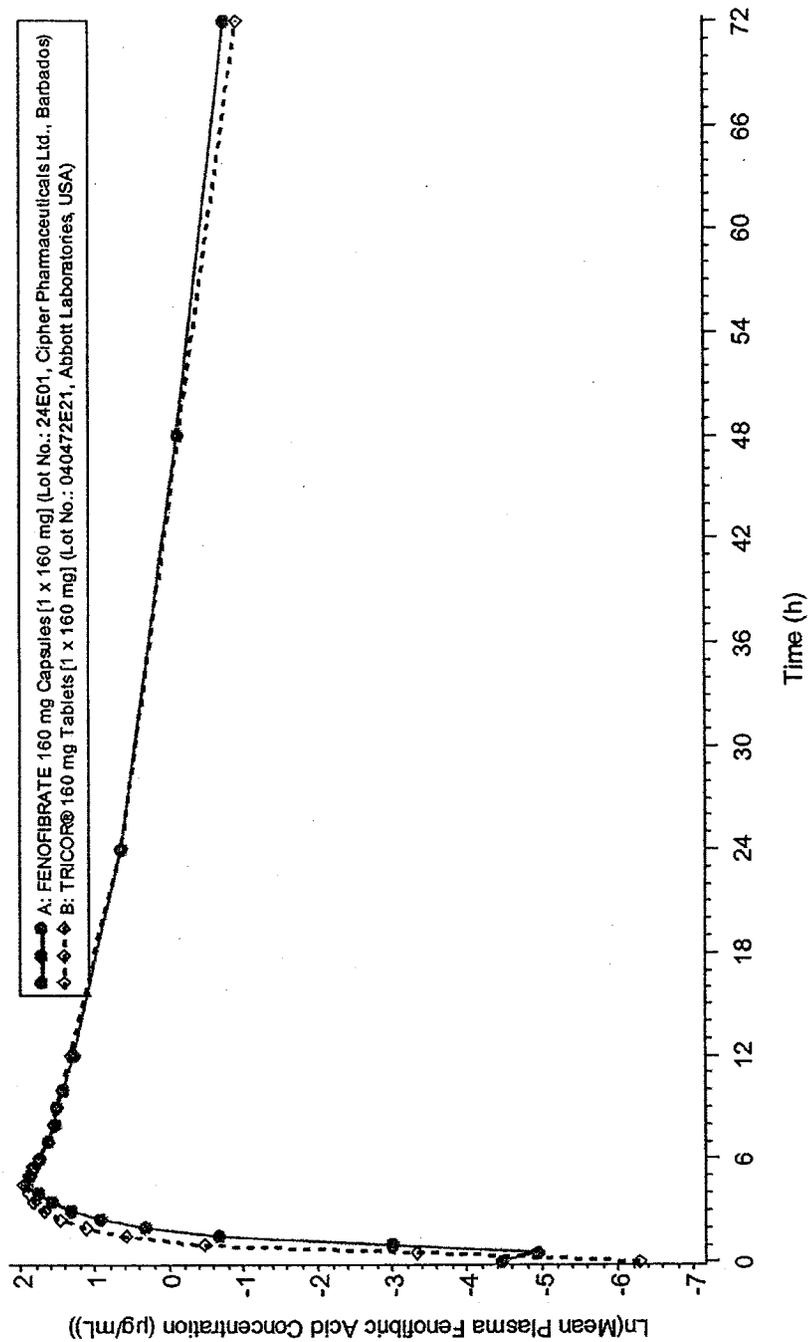
STUDY No.: 2003-647
MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES
N=28



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Study Report, Fenofibrate, 160 mg Capsules - Single-dose, Fed
Protocol No. FENPK.03.01 Version 1
PMRJ Study No. 2003-647

STUDY No.: 2003-647
LOG MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES
N=28



4.3 Cover Sheet and OCPB Filing/Review Form

Not available.

4.4 DSI Inspection Memo

MEMORANDUM

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

DATE: October 20, 2003

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *CTV 10/20/03*
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-612, CIP-Fenofibrate™
(Fenofibrate Capsules)
Sponsored by Cipher Pharmaceuticals

TO: David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
HFD-510)

At the request of HFD-510, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Protocol FENPK.02.01: Relative Bioavailability Study
Comparing Single Dose of
CIP-Fenofibrate 160 mg Capsules and
Tricor 160 mg Tablets Under Fasting
Conditions

Protocol FENPK.01.07: Bioequivalence Study Comparing Single
Dose of CIP-Fenofibrate 160 mg Capsules
and Tricor 160 mg Tablets Under
High-Fat Fed Conditions

The clinical and analytical portions of both studies were conducted at _____ in _____, and

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Following the inspection (7/22-7/24/03) at _____ in _____ Form FDA-483 was issued. The objectionable finding and our evaluation are as follows:

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Study 02-494, Protocol FENPK.01.07

1. Failure to retain a sufficient quantity of reserve samples of the test and reference products that were representative of the products used for dosing study subjects, and that were maintained in the originally provided container. Instead, for Tricor (fenofibrate Lot No. 671502E21/02-833 R1) received on 11/8/01, _____ unused ("spare") tablets were stored in dispensing vials. For Galephar fenofibrate capsules (Lot No. 24E01 received on 9/6/01), only _____ capsules were retained as reserves in the original container and seven unused ("spare") capsules were stored in dispensing vials.

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For the "fed" study, the sponsor had asked _____ to substitute tablets and capsules from separate shipments as the reserve samples. Thus, the separate shipments were not representative of the products used for dosing study subjects. However, _____ saved a few tablets and capsules from the original shipments, including some tablets and capsules that were dispensed but not administered to subjects. While these quantities are less than the "5x" quantity specified by the regulation, and not all were stored in their original containers, they serve the limited purpose of confirming the identity of the dosed products. For the subsequent "fasted" study, _____ retained sufficient quantities of reserve samples according to the regulation.

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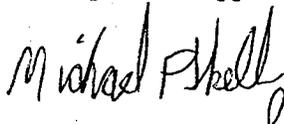
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Conclusion:

Following our review of the bioequivalence study audit from the clinical and analytical site, the Division of Scientific Investigations recommends that the data obtained from Protocols #FENPK.02.01 and FENPK.01.07 be accepted for Agency review.

After you have reviewed this memo, please append it to the original NDA submission.



Michael F. Skelly, Ph.D.

Final Classification:

✓

NAI
- NAI

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CC:

HFA-224

HFD-45/rf

ACH

HFD-48/Skelly/Himaya/cf

HFD-510/Jimenez/NDA 21-612

HFD-870/Qiu

HFR-PA2535/Hall

Draft: MFS 10/20/03

Edit: MKJ 10/20/03

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FACTS # 424210

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/s/

Wei Qiu
5/13/04 11:52:49 AM
BIOPHARMACEUTICS

Hae-Young Ahn
5/13/04 11:57:14 AM
BIOPHARMACEUTICS

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11/12/03

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW

NDA: 21-612	Submission Date(s): Dec. 24, 2002, Jan 10, 2003
Brand Name	CIP-Fenofibrate
Generic Name	Fenofibrate
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Cipher Pharmaceuticals Limited
Relevant IND(s)	62,780
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Oral capsules; 50, 100, 150, _____ mg
Indication	Type IV and V hypercholesterolemia

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1 Executive Summary

Cipher Pharmaceuticals Limited submitted a 505(b)(2) application under NDA 21-612 for CIP-Fenofibrate capsules to treat Type IV and V hypercholesterolemia.

Fenofibrate is a lipid-lowering agent, which acts primarily by increasing the activity of lipoprotein lipase.

CIP-Fenofibrate utilizes a _____ where fenofibrate _____ in a _____. The current U.S.-approved fenofibrate products include Lipidil® non-micronized capsule 100 mg, Tricor® micronized capsule 67 mg, 134 mg, and 200 mg and Tricor® micronized tablet 54 mg and 160 mg. The Reference Listed Drug (RLD) is Tricor® tablet 160 mg, under NDA 21-203. All these products exhibit food effect. Tricor® capsules and tablets have increased bioavailability compared to Lipidil®. With micronized fenofibrate (Tricor® micronized capsule and tablet), the absorption is increased by approximately 35% under fed condition compared to fasting conditions. Therefore, for both Tricor® capsule and tablet, it is recommended to be given with meals.

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The Human Pharmacokinetic (PK) and BA study report/data and full chemistry data for CIP-fenofibrate were submitted in this NDA as well as summaries of clinical and nonclinical information from the marketed product and literature. No Phase III clinical trial was conducted with this product.

Clinical pharmacology section included the following studies:

- No. 01-399 (FENPK.01.03)---Dose proportionality study
- No. 01-400 (FENPK.01.02)---Food effect on CIP-Fenofibrate capsules
- No. 01-401 (FENPK.01.01)---Single dose and multiple dose study
- No. 02-481 (FENPK.01.06)---Food effect on Tricor® tablets

- No. 02-494 (FENPK.01.07)---Bioequivalence study under high-fat fed condition
- No. 02-557 (FENPK.02.01)---Bioequivalence study under fasting condition
- No. 02-558 (FENPK.02.02)---Dosage form equivalence study

Historically, due to the low exposure to the parent drug, fenofibrate, sensitive analytical method for the determination of plasma fenofibrate concentrations was not available. Therefore, the bioavailability of fenofibrate products refers to the extent and rate of absorption of the active metabolite, fenofibric acid. To maintain the consistency, this review will continue to use the extent and rate of absorption of fenofibric acid as the bioavailability of fenofibrate products. In this NDA submission, only fenofibric acid was measured in all studies except study 01-401 (FENPK.01.01) where fenofibrate concentration was measured as well.

The study results showed that the extent and rate of absorption of CIP-Fenofibrate capsules was significantly increased by food. The rate and extent of absorption of CIP-Fenofibrate capsules and Tricor® tablets were bioequivalent when administered following a high-fat meal. Under fasting condition, the extent of absorption of CIP-Fenofibrate capsules and Tricor® tablets were bioequivalent but not the rate of absorption. The mean Cmax value of fenofibric acid with CIP-Fenofibrate capsules was 35% lower than that of Tricor® tablets under fasting conditions. It is reasonable to believe that under low-fat fed conditions CIP-Fenofibrate capsules would be bioequivalent to Tricor® tablets in terms of extent of absorption. However, the Cmax of fenofibric acid with CIP-Fenofibrate capsules may be lower than that of Tricor® tablets under low-fat fed conditions.

Dosage form equivalence between four 50 mg capsules and one 200 mg capsule was established.

After single dose administration, plasma concentrations of fenofibric acid were similar between women and men. However, plasma concentrations of the parent compound, fenofibrate, were approximately 30% lower in women than in men. At steady state in the same subjects, plasma concentrations of fenofibric acid were slightly lower (< 20%) in women than in men while plasma concentrations of fenofibrate were approximately 40% lower in women than in men.

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1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed _____ submitted on 24 Dec 2002 and Jan 10, 2003 and finds it acceptable. Recommendation, comments, and labeling comments should be conveyed to the sponsor as appropriate.

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1.2 Phase IV Commitments

None.

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3 Summary of CPB Findings

Food Effects:

The bioavailability of CIP-Fenofibrate capsule 200 mg was examined under fasting, low-fat fed, and high-fat fed conditions. Ratios (low-fat fed/fasting) of least-square means for AUCinf and Cmax of fenofibric acid were 125.14% and 226.16%, respectively. Ratios (high-fat fed/fasting) of least-square means for AUCinf and Cmax of fenofibric acid were 158.47% and 364.95%, respectively. Ratios (high-fat fed/low-fat fed) of least-square means for AUCinf and Cmax of fenofibric acid were 126.64% and 161.37%, respectively.

Since the 90% confidence intervals of AUCinf and Cmax ratios were not within the 80% - 125% range, it was concluded that the extent and rate of absorption of CIP-Fenofibrate capsule 200 mg was affected by food. Additionally, the extent and rate of absorption of CIP-Fenofibrate capsules were positively related to fat content.

The bioavailability of Tricor® tablet 160 mg was examined under fasting, low-fat fed, and high-fat fed conditions. Ratios (low-fat fed/fasting) of least-square means for AUCinf and Cmax of fenofibric acid were 110.38% and 177.10%, respectively. Ratios (high-fat fed/fasting) of least-square means for AUCinf and Cmax of fenofibric acid were 126.28% and 248.59%, respectively. Ratios (high-fat fed/low-fat fed) of least-square means for AUCinf and Cmax of fenofibric acid were 114.40% and 140.36%, respectively.

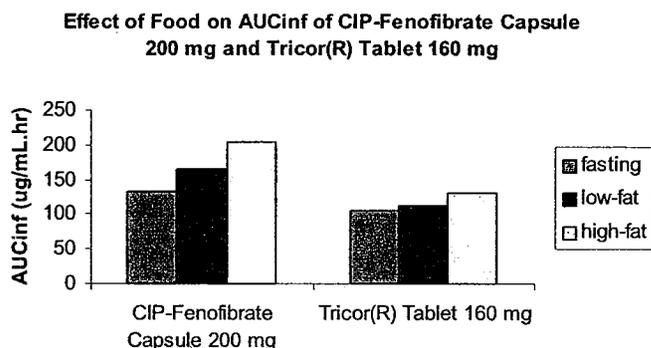


Figure 1. Effect of High-Fat and Low-Fat Meals on AUC of Fenofibric Acid for CIP-Fenofibrate Capsules 200 mg and Tricor® Tablets 160 mg

**Effect of Food on Cmax of CIP-Fenofibrate Capsule
200 mg and Tricor(R) Tablet 160 mg**

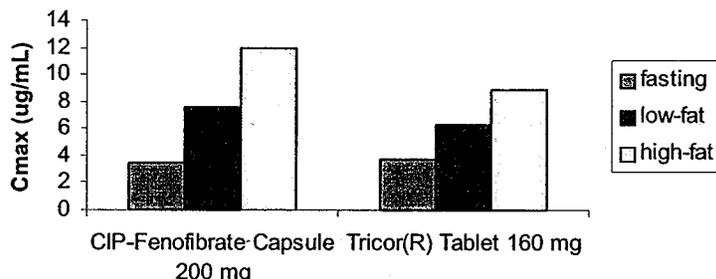


Figure 2. Effect of High-Fat and Low-Fat Meals on Cmax of Fenofibric Acid for CIP-Fenofibrate Capsules 200 mg and Tricor® Tablets 160 mg

Relative Bioavailability Compared to Tricor® Tablet:

Relative bioavailability of CIP-Fenofibrate capsule 160 mg compared with Tricor® micronized fenofibrate tablet 160 mg was examined under both high-fat fed and fasting conditions. The bioavailability of CIP-Fenofibrate capsule 160 mg was bioequivalent to that of Tricor® micronized fenofibrate tablet 160 mg under high-fat fed conditions. Under fasting conditions, the extent of bioavailability of CIP-Fenofibrate capsule 160 mg was equivalent to that of Tricor® micronized fenofibrate tablet 160 mg, however, CIP-Fenofibrate 160 mg capsules exhibited lower Cmax of fenofibric acid, 65% on average when compared to Tricor®.

Under high-fat fed conditions, ratios (CIP-Fenofibrate capsule 160 mg / Tricor® micronized fenofibrate tablet 160 mg) of least-square means for AUCinf and Cmax of fenofibric acid were 102.21% and 94.73%, respectively. Since the 90% confidence intervals of AUCinf and Cmax ratios were within the 80% - 125% range, it was concluded that the rate and extent of absorption of CIP-Fenofibrate capsule 160 mg and Tricor® micronized fenofibrate tablet 160 mg were bioequivalent when administered following a high-fat meal.

Under fasting condition, ratios (CIP-Fenofibrate capsule 160 mg / Tricor® micronized fenofibrate tablet 160 mg) of least-square means for AUCinf and Cmax of fenofibric acid were 95.28% and 65.43%, respectively. The CIP-Fenofibrate capsule 160 mg demonstrated a similar extent but a lower rate of absorption compared to Tricor® micronized fenofibrate tablet 160 mg.

Dosage Form Equivalence:

The bioavailabilities of four CIP-Fenofibrate 50 mg capsules versus one CIP-Fenofibrate 200 mg capsule were compared under low-fat fed conditions. Ratios (four 50 mg capsules/one 200 mg capsule) of least-square means for AUCinf and Cmax of fenofibric acid were 103.37% and 106.16%, respectively. Because the 90% confidence intervals of AUCinf and Cmax ratios were within the 80% - 125% range, it was concluded that the extent and rate of absorption of CIP-Fenofibrate capsules were comparable when administered as 1x200 mg capsule or as 4x50 mg capsules under low-fat fed conditions. Therefore, dosage form equivalence between the two strengths was established.

Table 1. Composition of CIP-Fenofibrate 50, 100, 150, _____ mg

Ingredient (and Test Standard)	Amount/Capsule (mg)		
	50 mg Capsule	100 mg Capsule	150 mg Capsule
Fenofibrate (EP)	50	100	150
Lauroyl Macrogol Glycerides Type 1500 (Gelucire 44/14)			
Polyethylene Glycol 20,000			
Polyethylene Glycol 8,000 (NF)			
Hydroxypropylcellulose (NF)			
Sodium Starch Glycolate (NF)			
Total Fill Weight			

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Fenofibrate is a lipid-regulating agent that reduces plasma levels of TC and triglycerides (TG) in healthy subjects and in patients with hyperlipidemia. The mechanism of action of fenofibrate is complex and not completely understood. The major effect of fenofibrate is to increase the activity of lipoprotein lipase (LPL), which promotes the lipolysis of very low density lipoprotein (VLDL) and consequently lowers plasma TG levels. Fenofibrate also inhibits hepatic synthesis of fatty acids and triglycerides and inhibits the release of fatty acids from adipose tissue. These actions lead to decreased VLDL synthesis and production of smaller VLDL particles, which in turn favors the formation of more rapidly catabolized low-density lipoprotein (LDL). The mechanism of action of fenofibrate at the molecular level has recently been elucidated and involves the nuclear peroxisome proliferator-activated receptors alpha (PPAR α). PPAR α belongs to the nuclear steroid hormone receptor gene superfamily and has the potential to control the expression of genes involved in intracellular and extracellular lipid metabolism.

The proposed indication of CIP-Fenofibrate capsules is for the treatment of hypertriglyceridemia (type IV and V).

The proposed dosage and route of administration is _____ strength (50, 100, 150, _____ mg) capsule given orally.

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4.2 General Clinical Pharmacology

Q. Does the pharmacokinetics of fenofibrate change after multiple dosing? How much do the fenofibrate and fenofibric acid accumulate at steady state?

On average, the fenofibric acid AUC value was 42% larger at steady-state compared to the single dose under high-fat fed conditions. It appears that the bioavailability of plasma fenofibric acid increases after multiple-dose administration. However, the fenofibrate AUC value was comparable between steady-state and single dose administration.

The fenofibric acid levels increased with multiple-dose administration and reached steady-state after at least 6 doses of CIP-Fenofibrate capsules 200 mg. The degree of accumulation using a commonly employed method based on AUC values (AUC_{ss}/AUC(1, τ)) is 2.35 ranging from 1.22 to 4.24. However, no accumulation was observed for fenofibrate.

The single dose and multiple-dose pharmacokinetic profiles of CIP-fenofibrate 200 mg capsules were determined in healthy males and females under high-fat fed condition. The study 01-401 (FENPK.01.01) was designed as a single-period study with a single-dose phase (3 days), followed by a multiple-dose phase (8 days). There was no washout between the single-dose and multiple-dose phases. Twenty-six (26) subjects were enrolled and twenty-five subjects completed the study. The mean (%CV) single dose and steady-state pharmacokinetics of fenofibric acid are summarized in **Table 2**.

Table 2. Plasma Fenofibric Acid Pharmacokinetic Data for a Single- and Multiple-Dose Study of CIP-Fenofibrate 200 mg (N=25) (FENPK.01.01)

PK Parameter	Arithmetic Mean (%CV)		Ratio % *(Steady-state vs. single dose)	90% Confidence Interval *
	Phase 1 (single dose)	Phase 2 (steady-state)		
AUC _{0-t} (ug/mL.hr)	189.17 (29)	289.47 (33)		
AUC _{inf} (ug/mL.hr)	203.50 (35)	—	142.47**	135.28-150.05
C _{max} (ug/mL)	12.15 (20)	21.34 (27)	173.37	154.98-193.95
T _{max} (hr)	4.73 (19)	4.81 (21)		
Kel (1/hr)	0.0439 (22)	—		
T _{1/2} (hr)	16.76 (30)	—		

* Estimated through paired t-test on log-transformed individual values

** Contrast between the AUC_t at steady state and AUC_{inf} after single-dose administration.

In contrast, the fenofibrate AUC values were similar at steady-state compared to the single dose. There was no accumulation of fenofibrate when administered as a 200 mg capsule every 24 hours. The mean (%CV) single dose and steady-state pharmacokinetics of fenofibrate are summarized in **Table 3**. Fenofibrate data exhibited more variability compared to fenofibric acid. It may be partially attributed to the low exposure in plasma.

Table 3. Plasma Fenofibrate Pharmacokinetic Data for a Single- and Multiple-Dose Study of CIP-Fenofibrate 200 mg (N=25) (FENPK.01.01)

PK Parameter	Arithmetic Mean (%CV)		Ratio % *(Steady-state vs. single dose)	90% Confidence Interval *
	Phase 1 (single dose)	Phase 2 (steady-state)		
AUC _{0-t} (ng/mL.hr)	41.42 (42)	39.05 (54)		
AUC _{inf} (ng/mL.hr)	39.80 (37)	—	98.13**	80.79-119.18
C _{max} (ng/mL)	22.48 (49)	19.53 (60)	81.63	65.79-101.30
T _{max} (hr)	3.71 (28)	3.67 (32)		
Kel (1/hr)	1.3528 (52)	—		
T _{1/2} (hr)	0.91 (113)	—		

* Estimated through paired t-test on log-transformed individual values

** Contrast between the AUC_t at steady state and AUC_{inf} after single-dose administration.

4.3 Intrinsic Factors

Q. How does gender influence the pharmacokinetics of fenofibrate?

The gender effect was evaluated in study 01-401 (FENPK.01.01) where a single dose and multiple-dose of CIP-fenofibrate 200 mg capsules were given to healthy males and females under high-fat fed condition. Results (**Table 4**) showed that after a single dose administration the ratios (female/male) were 91.84% and 92.24% for AUC_{inf} and C_{max} of fenofibric acid, respectively. After multiple dose administration, the ratios (female/male) were 83.24% and 85.35% for AUC_t and C_{max} of fenofibric acid, respectively. Results (**Table 5**) showed that after a single dose administration the ratios (female/male) were 69.08% and 66.86% for AUC_{inf} and C_{max} of fenofibrate, respectively. After multiple dose administration, the ratios (female/male) were 62.17% and 52.07% for AUC_t and C_{max} of fenofibrate, respectively.

Table 4. Summary of Gender Effect Analysis Based on Fenofibric Acid Plasma Levels (FENPK.01.01)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio, % (Female/Male)	90% Confidence Interval
	Female (N=13)	Male (N=12)		
	Phase 1 (Single-Dose)			
Weight (kg)	64.8 (15)	75.6 (10)	85.68	77.56-93.81
AUC _{inf} (ug/mL.hr)	64.53	70.26	91.84	72.21-116.81
	67.93 (35)	75.56 (47)		
C _{max} (ug/mL)	3.97	4.30	92.24	81.18-104.80
	4.08 (26)	4.33 (10)		
T _{max} (hr)	5.05 (15)	4.38 (21)	115.08	101.79-128.38

T1/2 (hr)	15.17 (17)	18.48 (35)	82.09	63.97-100.22
		Phase 2 (Steady-State)		
AUC _τ (ug/mL.hr)	87.70	105.35	83.24	66.23-104.63
	91.48 (31)	113.26 (48)		
C _{max} (ug/mL)	6.63	7.77	85.35	70.22-103.73
	6.77 (22)	8.23 (38)		
T _{max} (hr)	4.85 (18)	4.76 (25)	101.81	86.98-116.65
C _{min} (ug/mL)	1.86	2.40	77.78	57.44-105.33
	2.01 (41)	2.73 (68)		

Table 5. Summary of Gender Effect Analysis Based on Fenofibrate Plasma Levels (FENPK.01.01)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio, % (Female/Male)	90% Confidence Interval
	Female (N=13)	Male (N=12)		
Weight (kg)	64.8 (15)	75.6 (10)	85.68	77.56-93.81
		Phase 1 (Single-Dose)		
AUC _{inf} (ug/mL.hr)	10.56	15.29	69.08	47.54-100.37
	11.19 (37)	16.52 (33)		
C _{max} (ug/mL)	5.56	9.47	66.85	45.84-97.49
	6.19 (46)	8.31 (46)		
T _{max} (hr)	3.73 (21)	3.68 (35)	101.48	81.91-121.04
T1/2 (hr)	1.18 (120)	0.71 (91)	165.46	40.90-290.02
		Phase 2 (Steady-State)		
AUC _τ (ug/mL.hr)	9.29	14.95	62.17	41.84-92.39
	10.69 (56)	17.18 (48)		
C _{max} (ug/mL)	4.02	7.73	52.07	32.79-82.70
	4.94 (65)	9.08 (50)		
T _{max} (hr)	3.50 (34)	3.84 (30)	91.04	70.04-112.05

4.4 Extrinsic Factors

Not available.

4.5 General Biopharmaceutics

Q1. Is the proposed product bioequivalent to Tricor?

CIP-Fenofibrate 160 mg capsules were found to be bioequivalent to Tricor® 160 mg tablets under high-fat fed conditions. Under fasting condition, the extent of absorption for the two drugs was equivalent, but not the rate of absorption. The CIP-Fenofibrate 160 mg capsules exhibited 35% lower fenofibric acid C_{max} when compared to Tricor® 160 mg tablets.

The bioavailability of single dose Cipher Fenofibrate capsules was compared to single dose of Tricor® tablets 160 mg in healthy subjects under high-fat fed condition in study 02-494 (FENPK.01.07). This was an open-label, single-dose, randomized, two-sequence, two-period, crossover study. Twenty-four subjects were recruited and 23 subjects completed the study. The 90% confidence intervals of ratios of geometric means (CIP-Fenofibrate:Tricor®) for plasma fenofibric acid AUC and C_{max} were within the 80-125% acceptance range (Table 6). The bioequivalence between CIP-fenofibrate capsules and Tricor® tablets was established.

Table 6. Plasma Fenofibric Acid Pharmacokinetic Data for a Single-Dose, High-Fat Fed Bioequivalence Study of CIP-Fenofibrate 160 mg Capsules and Tricor® 160 mg Tablets (N=23) (FENPK.01.07)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geom. Means (%)	90% Confidence Interval (%)
	CIP-Fenofibrate 160 mg Capsule	Tricor® 160 mg Tablet		
	AUCt (ug/mL.hr)	153.35 161.29 (32)		
AUCinf (ug/mL.hr)	162.14 172.04 (35)	158.64 164.48 (26)	102.21	96.93-107.77
Cmax (ug/mL)	10.44 10.81 (30)	11.02 11.30 (22)	94.73	88.24-101.70

The bioavailability of a single dose CIP-Fenofibrate capsule 160 mg was also compared to single dose of Tricor® tablets 160 mg in healthy subjects under fasting condition in study 02-557 (FENPK.02.01). This was an open-label, single-dose, two-way crossover, relative bioavailability study in 36 healthy subjects. Based on ln-transformed fenofibric acid data, the 90% confidence intervals of the ratios of geometric means (CIP-Fenofibrate:Tricor®) for AUC were within the 80-125% range. However, the 90% confidence intervals of ratios of geometric means (CIP-Fenofibrate:Tricor®) for Cmax was not within the 80-125% range. The CIP-Fenofibrate 160 mg capsules exhibited 35% lower Cmax when compared to Tricor® (Table 7). Since five subjects had pre-dose plasma concentrations greater than 5% of their respective Cmax values, these five subjects were removed from the statistical analysis for bioequivalence evaluation.

Table 7. Plasma Fenofibric Acid Pharmacokinetic Data for a Single-Dose, Fasting Bioavailability Study of CIP-Fenofibrate 160 mg Capsules and Tricor® 160 mg Tablets (N=30) (FENPK.02.01)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geom. Means (%)	90% Confidence Interval (%)
	CIP-Fenofibrate 160 mg Capsule	Tricor® 160 mg Tablet		
	AUCt (ug/mL.hr)	84.87 91.49 (39)		
AUCinf (ug/mL.hr)	104.70 114.04 (51)	109.89 117.26 (40)	95.28	86.45-105.01
Cmax (ug/mL)	2.69 3.03 (45)	4.11 4.42 (41)	65.43	57.09-74.99

Q2. How does food affect the bioavailability of CIP-Fenofibrate capsules and Tricor® tablets?

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Food increased CIP-Fenofibrate absorption significantly and the extent of increase was positively related to the fat and calorie content of the meal. High-fat and low-fat meals increased AUCinf of fenofibric acid by 58% and 25%, respectively, compared to fasting condition. Meanwhile, high-fat and low-fat meals increased Cmax of fenofibric acid by 265% and 126%, respectively, compared to fasting state.

In contrast, high-fat and low-fat meals increased Tricor® AUCinf values of fenofibric acid by 26% and 10%, respectively, compared to fasting condition. The Cmax values of fenofibric acid was increased by 148% and 77%, respectively, compared to fasting state.

It appears that CIP-Fenofibrate capsules exhibited more food effect than Tricor® tablets. However, BA/BE studies (No. 02-494 and No. 02-557) showed that under both fasting and high-fat fed conditions, these two products were bioequivalent in terms of AUCinf of fenofibric acid.

Study 01-400 (FENPK.01.02) was conducted to evaluate food effect on the absorption of CIP-Fenofibrate capsule. This was a single-dose, randomized, three-treatment, three-period, six-sequence, crossover study involving 17 healthy male volunteers. A single dose of CIP-

Fenofibrate 1 x 200 mg capsule was administered after a high-fat breakfast, a low-fat breakfast, or under fasting conditions. Based on ln-transformed fenofibric acid data, high-fat and low-fat meals increased fenofibric acid AUCinf values 58% and 25%, respectively (Table 8).

Table 8. Plasma Fenofibric Acid Pharmacokinetic Data for a CIP-Fenofibrate 200 mg Food Effect Study (N=17) (FENPK.01.02)

PK parameter	Geometric Mean Arithmetic Mean (%CV)			Ratio of Geometric Means (%) 90% Confidence Interval (%)		
	High-Fat (A)	Low-Fat (B)	Fasting (C)	A vs. C	B vs. C	A vs. B
AUCinf (ug/mL.hr)	195.69 205.26 (34)	154.53 164.79 (39)	123.49 133.72 (47)	158.47 (139.44-180.09)	125.14 (110.11-142.21)	126.64 (111.75-143.51)
Cmax (ug/mL)	11.88 11.93 (18)	7.36 7.52 (24)	3.25 3.45 (37)	364.95 (315.32-422.40)	226.16 (195.41-261.76)	161.37 (139.42-186.77)

Study 02-481 (FENPK.01.06) was conducted to evaluate the food effect on bioavailability of Tricor® 160 mg. This was a randomized, crossover, 3-period, 6-sequence study. A single dose of Tricor® 1x160 mg tablet was administered to 12 healthy male volunteers after a high-fat breakfast, low-fat breakfast, or under fasting conditions. The high-fat meal increased AUCinf and Cmax of fenofibric acid by 26% and 148%, respectively. The low-fat meal increased AUC and Cmax of fenofibric acid by 10% and 77%, respectively (Table 9).

Table 9. Plasma Fenofibric Acid Pharmacokinetic Data for Tricor® tablet 160 mg Food Effect Study (N=12) (FENPK.01.06)

PK parameter	Geometric Mean Arithmetic Mean (%CV)			Ratio of Geometric Means (%) 90% Confidence Interval (%)		
	High-Fat (A)	Low-Fat (B)	Fasting (C)	A vs. C	B vs. C	A vs. B
AUCinf (ug/mL.hr)	125.57 129.93 (26)	109.76 113.39 (27)	99.43 105.48 (37)	126.28 (115.91-137.58)	110.38 (101.32-120.26)	114.40 (105.01-124.64)
Cmax (ug/mL)	8.69 8.88 (23)	6.19 6.24 (12)	3.50 3.67 (32)	248.59 (217.24-284.46)	177.10 (154.77-202.66)	140.36 (122.66-160.62)

Q3. Does the dose proportionality exist?

Dose proportionality was not established within the range of 50, 100, and 200 mg.

Study 01-399 (FENPK.01.03) was conducted to evaluate dose proportionality of CIP-Fenofibrate capsules 50, 100, and 200 mg. This was a single-dose, randomized, three-way crossover study conducted in healthy subjects under high-fat fed conditions. Nineteen subjects were dosed in the first period and 17 subjects completed at least two periods of the study. A bioequivalence approach was conducted to evaluate dose proportionality (Table 10). Random coefficients model approach was used to evaluate the intercept and slope (Table 11). Since the y-intercept for AUCinf was statistically significant different from zero, it was concluded that dose proportionality was not established for fenofibric acid AUCinf within the range of 50 to 200 mg.

Table 10. Plasma Fenofibric Acid Pharmacokinetic Data for a ~~50, 100, 200 mg~~ Dose Proportionality Study (N=17) (FENPK.01.03)

Parameter	Treatment	Dose (mg)	Mean		Contrast	Ratio of Geometric Mean	90% CI
			Arithmetic	Geometric*			
AUCinf	A	50	64.42	1.226	A vs. B	118.89	111.68 - 126.55
	B	100	106.80	1.031	B vs. C	112.12	105.30 - 119.38
	C	200	191.11	0.919	A vs. C	133.29	125.40 - 141.69
Cmax	A	50	3.24	0.0652	A vs. B	107.82	98.43 - 118.10
	B	100	6.12	0.0605	B vs. C	97.71	89.17 - 107.06
	C	200	12.29	0.0619	A vs. C	105.35	96.38 - 115.15

* geometric means of dose-normalized AUCinf and Cmax values.

b(4)

Table 11. Dose Proportionality Analysis

PK parameter	Coefficients	Estimate	Std. Error	Prob.*
AUCinf	y-intercept	22.37	4.15	<0.0001
	Slope	0.84	0.06	<0.0001
Cmax	y-intercept	0.16	0.21	0.4713
	Slope	0.06	0.002	<0.0001

* Significance for the coefficient estimate to be different from zero.

Q4. Was the dosage form equivalence established?

Dosage form equivalence of 4 x 50 mg and 1 x 200 mg was established because the 90% confidence intervals of geometric mean ratios for AUC and Cmax of fenofibric acid fell within the range of 80-125%.

Bioavailability of CIP-Fenofibrate 4 x 50 mg capsules and CIP-Fenofibrate 1 x 200 mg capsules were compared under low-fat fed conditions in study 02-558 (FENPK.02.02). This was an open-label, single-dose, two-way crossover, comparative bioavailability study in 18 healthy subjects. Based on log-transformed fenofibric acid data, the 90% confidence intervals of geometric mean ratios (4 x 50 mg: 1 x 200 mg) for AUCinf and Cmax were within the 80-125% range (Table 12).

Table 12. Plasma Fenofibric Acid Pharmacokinetic Data for a CIP-Fenofibrate 50 and 200 mg Dose Proportionality Study (N=18) (FENPK.02.02)

PK Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratios of Geom. Means (%)	90% Confidence Interval (%)
	CIP-Fenofibrate 4x50 mg Capsule	CIP-Fenofibrate 1x200 mg Capsule		
AUCinf (ug/mL.hr)	210.09 217.40 (28)	203.25 212.08 (31)	103.37	98.52-108.45
Cmax (ug/mL)	12.09 12.43 (24)	11.39 11.52 (16)	106.16	95.25-118.32

Q5. Was the dissolution method and specification adequately justified? Can biowaiver for the lower strengths be granted based on dissolution similarity?

The sponsor proposed the following dissolution method and specification:

Medium: _____

Apparatus: USP Apparatus 2 (paddles)

Speed: _____

Specification: not less than _____ (Q) of the labeled amount is dissolved in _____

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The sponsor evaluated baskets and paddles between 50 and 150 rpm in three media.

Medium 1: _____

Medium 2: 2% Tween 80 and 0.1% pancreatin at pH 6.8

Medium 3: _____

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The dissolution profiles by using USP Apparatus 2 (paddles) at 75 rpm with Medium 2 exhibited the least variability among strengths. _____

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Using the proposed dissolution method / _____ the following dissolution profiles for all strengths were obtained (Figure 4). The f2 values for all strengths compared to the strength 160 mg were between 31.5 and 49.8. All f2 values are less than 50, indicating that the dissolution profiles of strengths 50, 100, and 150 mg are not similar to that of the 160 mg strength. All 50 mg strength capsules dissolved faster than the 160 mg strength which dissolved faster than the 100 mg, 150 mg and 200 mg strengths.

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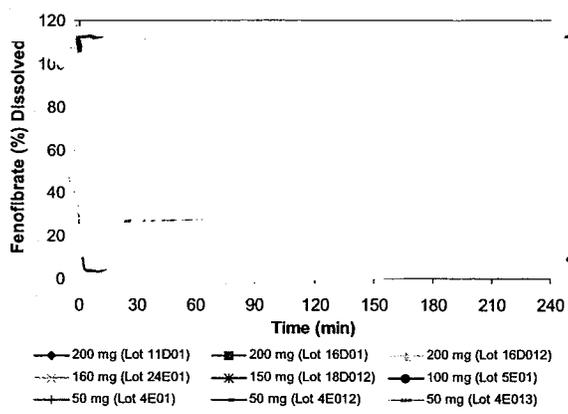


Figure 4. Comparison of Dissolution Profiles in

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As indicated earlier, Medium 2 appears to exhibit least variability among strengths, the dissolution data using paddles at 75 rpm in Media 2 is shown in Table 13 and Figure 5. The 100 mg and 150 mg strengths are similar to the 160 mg strengths with f2 values of 64.63 and 77.88, respectively. The 50 mg strengths dissolved faster than other strengths. F2 values of the 50 mg is smaller than 50.

Table 13. Dissolution Profiles using USP Apparatus 2 (Paddles) at 75 rpm in Media 2

Time (min)	Mean (N=6) Fenofibrate Percent Dissolved (range)								
	200 mg		160 mg	150 mg	100 mg	50 mg			
	11D01	16D01	16D012	24E01	18D012	5E01	4E01	4E012	4E013
0	0	0	-1	0	0	0	0	1	3
15	2	1	0	2	2	4	7	7	10
30	13	9	11	15	13	19	33	30	39
45	30	26	28	37	32	41	62	56	70
60	47	42	46	57	51	59	83	76	89
75	61	56	61	74	67	74	95	91	101
90	73	67	72	86	80	86	101	99	106
105	82	76	80	(83-90)	(67-85)	(73-94)	(96-105)	(91-103)	(99-110)
				94	89	95	104	103	108
				(92-97)	(87-94)*	(84-101)	(96-105)	(100-106)	(106-110)
120	89	83	86	100	94	100	104	105	109
135	94	88	90	102	97	102	105	105	109
150	98	91	93	104	98	103	105	105	109
165	100	94	95	105	99	104	104	105	109
180	102	96	96	106	99	104	105	104	109
195	102	98	98	106	99	104	105	104	109
210	103	99	98	107	100	104	105	103	109
225	104	100	99	107	100	104	105	102	109
240	104	101	99	107	100	104	105	103	110
F2	50.50	41.97	47.72	-	64.63	77.88	35.31	40.52	29.71

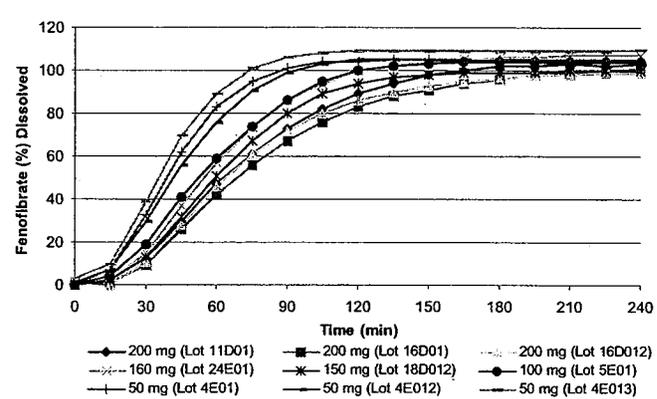


Figure 5. Comparison of Dissolution Profiles in Medium 2 using Paddles at 75 rpm

Reviewer's Comments:

1. For quality control purpose, based on the dissolution profiles in different conditions, the most appropriate method would be USP Apparatus 2 (Paddles) at 75 rpm in Media 2 consisting 2% Tween 80 and 0.1% of pancreatin at pH of 6.8. b(4)
2. Biowaiver for lower strengths: Formulation for all strengths was proportional. Bioequivalence was established between CIP-fenofibrate capsule 160 mg and Tricor® tablet 160 mg. Biowaiver can be granted to strengths 100 and 150 mg based on similarity of dissolution profiles.
3. The dissolution profiles of the 50 mg are different from the other strengths, using the sponsor's proposed dissolution condition as well as the Agency's recommended method. Nevertheless, dosage form equivalence was established between 4 x 50 mg and 1 x 200 mg. It was realized that the lots used in the dosage form equivalence study were not included in the dissolution study. Although the dosage form equivalence was not established between the 160 mg and the 50 mg, biowaiver for the 50 mg can be granted since the 50 mg dissolves faster than the other strengths. Meanwhile, it was noted that b(4)

This reviewer consulted with Dr. Mary Parks, Deputy Director of DMEDP regarding the efficacy issue of the 50 mg strength. Dr. Parks indicated that the b(4)
is not expected to cause efficacy concern because the efficacy endpoint, serum triglyceride level, can be monitored.

4.6 Analytical

Q. Is the analytical method adequately validated?

The liquid chromatographic tandem mass spectrometric (LC/MS/MS) analytical methods for fenofibric acid and fenofibrate were adequately validated and shown to be specific, sensitive, precise and accurate.

The calibration range was _____ ng/mL for fenofibrate and _____ µg/mL for fenofibric acid. The between-batch precision (CV%) and accuracy (% Nominal) of the QC samples of fenofibrate ranged from _____ respectively. The between-batch precision and accuracy of the QCs of fenofibric acid ranged from _____ and _____ respectively. b(4)

5 Comments

Based on the dissolution profiles in different conditions, the following dissolution method and specification are recommended:

Dissolution Method: Apparatus Type: USP apparatus 2 (Paddles)
Rotation Speed: 75 rpm
Medium: 2% Tween 80 and 0.1% pancreatin at pH 6.8, 37°C

Dissolution specifications: _____ b(4)

6 Labeling

CLINICAL PHARMACOLOGY

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

7.2 Individual Study Reviews

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Study Report, Fenofibrate Capsules, 50, 100, and 200 mg – Dose Proportionality
Protocol No. 01-399 (FENPK.01.03) Version 2.00

May 2002

**A Single-Dose, Randomized, Three-Way Crossover Dose Proportionality Study of a
Formulation of Fenofibrate 50, 100, and 200 mg Capsules in Healthy Subjects,
Under Fed Conditions**

Sponsor: Cipher Pharmaceuticals Ltd.,
11A High Park, St. James
Barbados, W.I.

Test Product: Fenofibrate Capsules, 50, 100, and 200 mg (Cipher
Pharmaceuticals Ltd.; Manufactured by Galepher P.R.
Inc.). Lot No. 4E013, 7E01, and 16D01, respectively

Number of Subjects: Nineteen (19) subjects were dosed in the first period, and
17 subjects completed at least two periods of the study.

Study Dates: Period I: September 30, 2001
Period II: October 7, 2001
Period III: October 14, 2001
Period III-A: October 21, 2001 (Subject 19 only)

Blood Sampling Times: Pre-dose and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10,
12, 24, 48, and 72 hours post-dose.

Adverse Events: Eight (8) different adverse events involving six subjects
were reported. All adverse events were mild and were
resolved without medication.

No serious adverse events were reported during the study.

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Analytical:

Analyte: Fenofibric acid
Assay: LC MS/MS
Calibration Range: _____ ug/mL

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Plasma samples from the 17 subjects who completed the study were assayed.

Study Conclusions:

The plasma fenofibric acid exhibited linear pharmacokinetics with respect to dose within the 50 mg to 200 mg dose-range measured.

The parameters characterizing the apparent elimination of fenofibric acid (Kel and Thalf) were not significantly different from one dose to the other. Similarly, there was no statistically significant difference in the Tmax parameter between dose.

The Cmax parameter proved bioequivalence over the dose-range, when the dose-normalized values were analyzed.

The AUCt and AUCinf parameters exhibited similar linear relationships to the dose. However, the conclusion of bioequivalence for the dose-normalized values was reached only after the adjustment for a significant difference from zero in the y-intercept. As a consequence, the increase in AUCs with the dose can be described through a linear equation, but the dose-proportionality, in the strict sense, was not fully respected.

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Study No. 01-399 (FENPK.01.03)

Treatment (A): Fenofibrate Capsules 1 x 50 mg (Cipher Pharmaceuticals Ltd., Canada)
 Treatment (B): Fenofibrate Capsules 1 x 100 mg (Cipher Pharmaceuticals Ltd., Canada)
 Treatment (C): Fenofibrate Capsules 1 x 200 mg (Cipher Pharmaceuticals Ltd., Canada)

Summary of Study Results
 (Parameters Estimated Based on Plasma Fenofibric Acid Levels)
 (N = 17)

Parameter	Treatment	Dose	Means		Contrast	Ratio	90% CI		Prob.**
			Arithmetic	Geometric*			Lower	Upper	
AUC _t	A	50	58.44	1.126	A vs. B	117.57	110.66 - 124.91	0.0002	
	B	100	98.04	0.958	B vs. C	110.81	104.27 - 117.75	0.0230	
	C	200	178.21	0.864	A vs. C	130.27	122.79 - 138.21	< 0.0001	
AUC _{inf}	A	50	64.42	1.226	A vs. B	118.89	111.68 - 126.55	0.0001	
	B	100	106.80	1.031	B vs. C	112.12	105.30 - 119.38	0.0130	
	C	200	191.11	0.919	A vs. C	133.29	125.40 - 141.69	< 0.0001	
C _{max}	A	50	3.24	0.0652	A vs. B	107.82	98.43 - 118.10	0.4973	
	B	100	6.12	0.0605	B vs. C	97.71	89.17 - 107.06	> 0.9999	
	C	200	12.29	0.0619	A vs. C	105.35	96.38 - 115.15	0.9731	
T _{max} ***	A	50	4.50		A vs. B			0.3414	
	B	100	4.50		B vs. C			> 0.9999	
	C	200	4.50		A vs. C			0.3477	
K _{el}	A	50	0.0415		A vs. B			0.5552	
	B	100	0.0396		B vs. C			0.3025	
	C	200	0.0421		A vs. C			> 0.9999	
T _{half}	A	50	18.23		A vs. B			> 0.9999	
	B	100	18.28		B vs. C			0.6428	
	C	200	17.30		A vs. C			0.7756	

* Geometric Means were estimated from dose-normalized AUCs and C_{max} parameters.

** Significance of the difference between treatments.

*** For T_{max} parameter median values are presented instead of the arithmetic means.

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**Summary of Study Results for AUCs Parameters Adjusted for the y-intercept
(Parameters Estimated Based on Plasma Fenofibric Acid Levels)**

Parameter	Treatment	Dose	Means		Contrast	Ratio	90% CI		Prob.**
			Arithmetic	Geometric*			Lower	Upper	
AUCt	A	50	39.98	0.7304	A vs. B	95.13	86.07 - 105.14	> 0.9999	
	B	100	79.59	0.7678	B vs. C	99.81	90.28 - 110.35	> 0.9999	
	C	200	159.75	0.7692	A vs. C	94.95	86.11 - 104.70	> 0.9999	
AUCinf	A	50	42.05	0.7354	A vs. B	92.13	82.07 - 103.43	0.6990	
	B	100	84.43	0.7981	B vs. C	99.41	88.51 - 111.64	> 0.9999	
	C	200	168.74	0.8029	A vs. C	91.59	81.80 - 102.54	0.5800	

* Geometric Means were estimated from dose-normalized AUCs parameters.
** Significance of the difference between treatments.

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**Random Coefficients Model Approach
(Parameters Estimated Based on Plasma Fenofibric Acid Levels)**

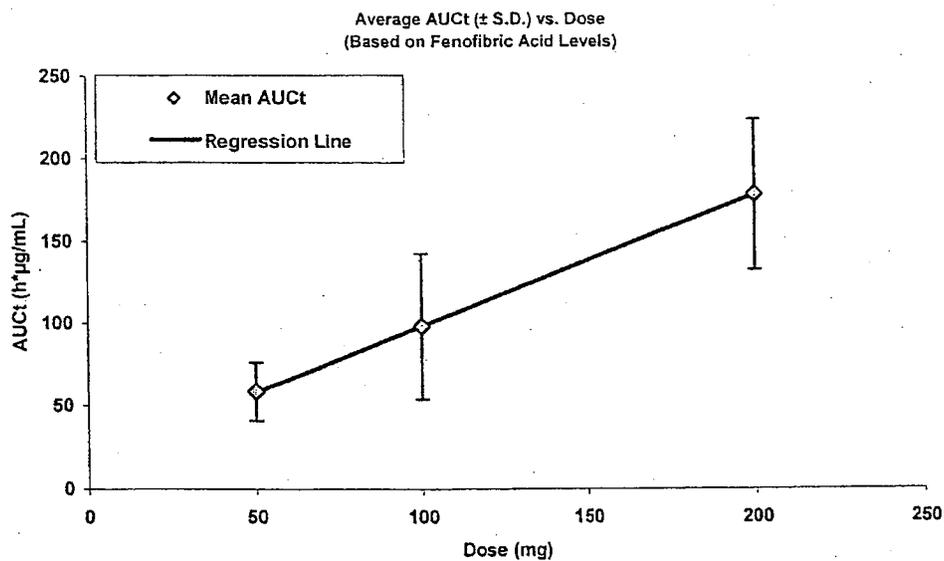
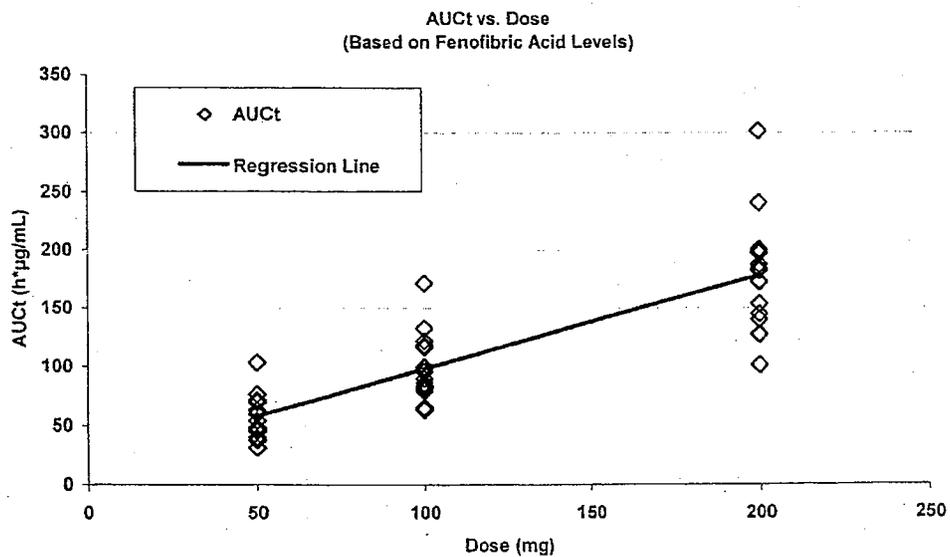
Parameter	Significance of the Model*		Coefficients	Estimate	Std. Error	Prob.**
	Chi-square	Pr > ChiSq				
AUCt	73.63	< 0.0001	y-intercept	18.4588	3.2622	< 0.0001
			Slope	0.7986	0.05299	< 0.0001
AUCinf	78.75	< 0.0001	y-intercept	22.3728	4.1471	< 0.0001
			Slope	0.8441	0.06174	< 0.0001
Cmax	19.63	< 0.0001	y-intercept	0.1556	0.2109	0.4713
			Slope	0.0605	0.002576	< 0.0001

* Null Model Likelihood Ratio Test in the PROC MIXED in SAS®
** Significance for the coefficient estimate to be different from zero.

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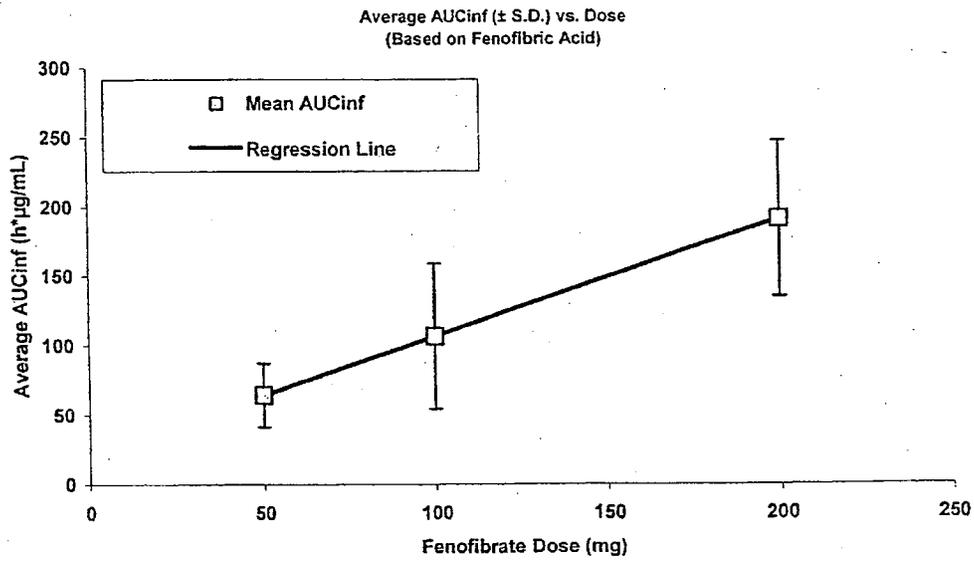
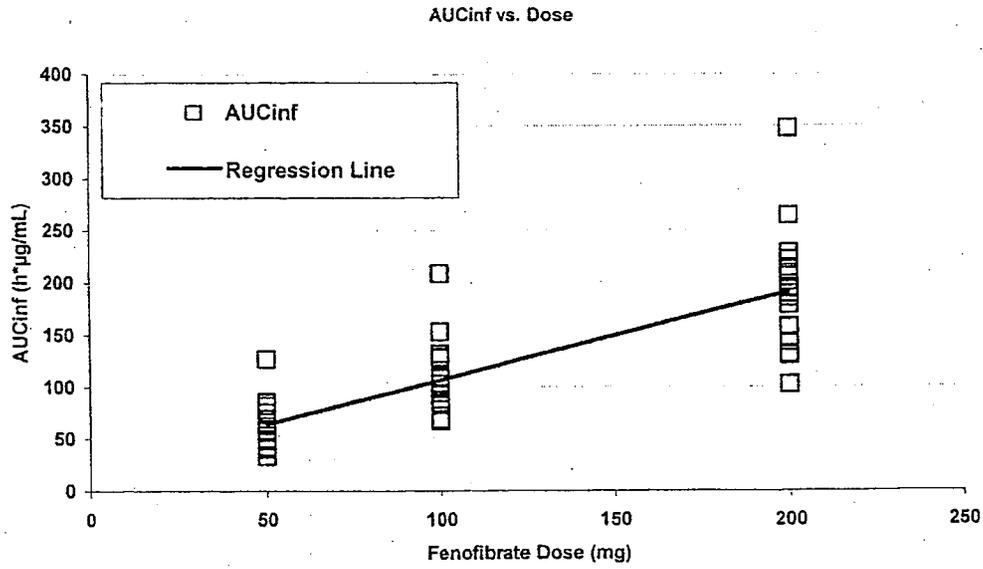
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Dose Proportionality Analysis: Unadjusted AUCt Parameter



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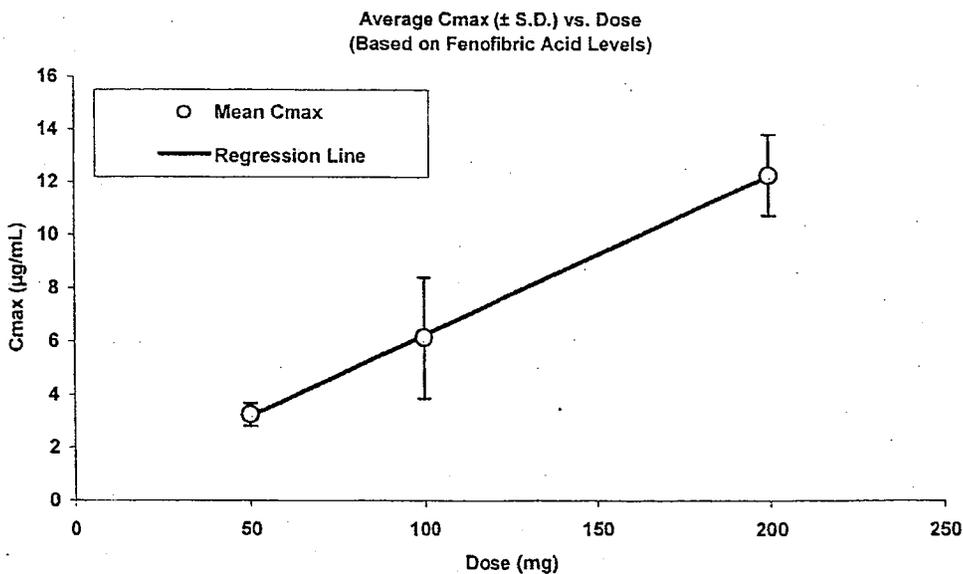
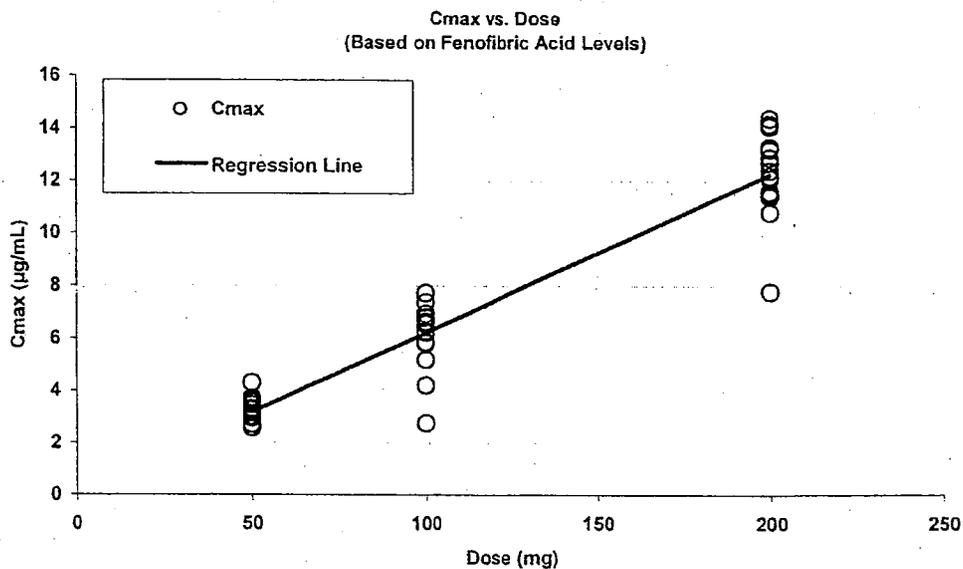
Dose Proportionality Analysis: Unadjusted AUCinf Parameter



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Dose Proportionality Analysis: Unadjusted Cmax Parameter



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A Single-Dose, Randomized, Three-Way Crossover Food Effect Study of Fenofibrate Capsules 200 mg in Healthy Subjects

Sponsor: Cipher Pharmaceuticals Ltd.
11A High Park, St. James
Barbados, W.I.

Test Product: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd., Canada; Manufactured by Galephar P.R. Inc.). Lot No. 16D01; Manufacturing Date: Mar/01.

Number of Subjects: Eighteen (18) subjects were dosed in Period I and 17 subjects completed the study.

Study (Dosing) Dates: Period I: August 28, 2001
Period II: September 4, 2001
Period III: September 11, 2001

Blood Sampling Times: Pre-dose (0 hour), and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24, 48, and 72 hours post-dose.

Adverse Events: Eight (8) adverse events involving five subjects were reported. All adverse events were mild and were resolved without medication.

No serious adverse events were reported during the study.

Analytical: Analyte: Fenofibric Acid
Assay: LC/MS/MS
Calibration Range: _____ µg/mL

Plasma samples from the 17 subjects who completed the study were assayed.

b(4)

Study Conclusions:

Based on ln-transformed fenofibric acid data, the ratios of geometric means (high fat breakfast vs. fasting, low fat breakfast vs. fasting, and high fat breakfast vs. low fat breakfast) for AUC(0-72), AUC(0-inf), and C_{max} are greater than 125%.

This demonstrates that when Cipher's Fenofibrate 200 mg Capsules are given with food, fenofibrate's absorption is significantly increased. The extent of increase is positively related to the fat and calorie content of meals.

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**Summary of Study Results
 (N = 17)**

Analyte: Fenofibric Acid

Test Product: Fenofibrate Capsules, 200 mg (Lot No. 16D01, Cipher Pharmaceuticals Ltd.)

A single dose of the test product (1 x 200mg) was administered under the following conditions:

- A: after a high fat breakfast, served 30 minutes prior to drug administration, following an overnight fast of at least 10 hours.
- B: after a low fat breakfast, served 30 minutes prior to drug administration, following an overnight fast of at least 10 hours.
- C: following an overnight fast of at least 10.5 hours.

Parameter	Geometric Mean Arithmetic Mean (CV, %)			Ratio of Geometric Means (%) 90% Confidence Interval (%)			Intra-Subject CV (%)
	High Fat (A)	Low Fat (B)	Fasting (C)	A vs. C	B vs. C	A vs. B	
AUC(0-72) (µg·h/mL)	183.70 189.55 (30)	137.16 142.92 (31)	97.57 103.53 (35)	188.29 169.48 - 209.19	140.58 126.54 - 156.18	133.94 120.55 - 148.80	18
AUC(0-inf) (µg·h/mL)	195.69 205.26 (34)	154.53 164.79 (39)	123.49 133.72 (47)	158.47 139.44 - 180.09	125.14 110.11 - 142.21	126.64 111.75 - 143.51	22
C _{max} (µg/mL)	11.88 11.93 (18)	7.36 7.52 (24)	3.25 3.45 (37)	364.95 315.32 - 422.40	226.16 195.41 - 261.76	161.37 139.42 - 186.77	25
T _{max} (h)	5.00 (3-6)	4.50 (3.5-7)	4.50 (3-12)	-	-	-	-
K _{el} (h ⁻¹)	0.0425 (25)	0.0345 (34)	0.0248 (41)	-	-	-	-
T _{1/2} (h)	17.31 (25)	22.06 (30)	33.22 (47)	-	-	-	-

*T_{max} is expressed as median (range).

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The information in this study report is legally privileged and confidential. Any disclosure, copying or distribution of the information contained within is strictly prohibited without written consent from the sponsor.

**A Single- and Multiple-Dose Study of Fenofibrate Capsules 200 mg
in Healthy Subjects, Under Fed Conditions**

Sponsor: Cipher Pharmaceuticals Ltd.,
11A High Park, St. James
Barbados, W.I.

Test Product: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals
Ltd., Canada; Manufactured by Galepher P.R. Inc.), Lot
No.: 16D01, Manufacturing Date: Mar/01 (as specified on
C. of A.)

Number of Subjects: Twenty-six (26) subjects were dosed on Day 1, in the
single-dose phase. Twenty-five (25) subjects were dosed on
Days 4 to 10, and completed the multiple-dose phase.

Study Dates: **Single-Dose Phase:**
Day 1 Dosing: October 16, 2001

Multiple-Dose Phase:
Days 4 to 10 Dosing: October 19 to 25, 2001

Blood Sampling Times: **Single-Dose Phase:** pre-dose on Day 1, and 1, 2, 3, 3.5, 4,
4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24, 48, and 72 hours post-
dose.

Multiple-Dose Phase: pre-dose on Days 7 to 10, and on
Day 10, blood collections continued at 1, 2, 3, 3.5, 4, 4.5, 5,
5.5, 6, 7, 8, 10, 12, and 24 hours post-dose.

Adverse Events: **Single-Dose Phase:** Three (3) different adverse events
involving 4 subjects were reported. All of the adverse
events were mild and were resolved without medication.

Multiple-Dose Phase: Sixteen (16) different adverse
events involving 11 subjects were reported. Fifteen (15) of
the adverse events were mild and one was moderate. All
adverse events were resolved without medication.

No serious adverse events were reported during the study.

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b(4)

Study Report, Fenofibrate Capsules 200 mg – Single and Multiple Dose
 Protocol No. 01-401 (FENPK.01.01) Version 2.00

May 2002

Study No: 01-401 (FENPK.01.01)
 Test: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd.)
 Lot No.: 16D01
 Phase 1: Single-Dose Administration
 Phase 2: Multiple-Dose Administration for Steady-State

*Summary of Study Results
 Based on Fenofibric Acid Plasma Levels
 (N = 25)*

Pharmacokinetic Parameter	Arithmetic Mean (%CV)		Ratio %* (Steady-State vs. Single-Dose)	90% Confidence interval*
	Phase 1 (Single-Dose)	Phase 2 (Steady-State)		
AUCT (h·µg/ml)	189.17 (29)	289.47 (33)		
AUCI (h·µg/ml)	203.50 (35)	-	142.47 **	135.28 – 150.05
Cmax (µg/ml)	12.15 (20)	21.34 (27)	173.37	154.98 - 193.95
Tmax (h)	4.73 (19)	4.81 (21)		
Kel (1/h)	0.0439 (22)	-		
Half-life (h)	16.76 (30)	-		
Cmin (µg/ml)	-	6.62 (49)		
Cav (µg/ml)	-	12.06 (33)		
DF (%)	-	129.29 (31)		

* Estimated through paired t-test on log-transformed individual values.

** Contrast between the AUC_t at steady-state and AUCI after single-dose administration.

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b(4)

Study No: 01-401 (FENPK.01.01)

Test: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd.)
 Lot No.: 16D01

Phase 1: Single-Dose Administration

Phase 2: Multiple-Dose Administration for Steady-State

*Summary of Study Results
 Based on Fenofibrate Plasma Levels
 (N = 25)*

Pharmacokinetic Parameter	Arithmetic Mean (%CV)		Ratio %* (Steady-State vs. Single-Dose)	90% Confidence interval*
	Phase 1 (Single-Dose)	Phase 2 (Steady-State)		
AUC (h·ng/ml)	41.42 (42)	39.05 (54)		
AUCI (h·ng/ml)	39.80 (37)	-	98.13 **	80.79 – 119.18
Cmax (ng/ml)	22.48 (49)	19.53 (60)	81.63	65.79 – 101.30
Tmax (h)	3.71 (28)	3.67 (32)		
Kel (1/h)	1.3528 (52)	-		
Half-life (h)	0.91 (113)	-		
Cmin (ng/ml)	-	0.00 (-)		
Cav (ng/ml)	-	1.63 (54)		
DF (%)	-	1165.7 (25)		

* Estimated through paired t-test on log-transformed individual values.

** Contrast between the AUC at steady-state and AUCI after single-dose administration.

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b(4)

Study No: 01-401 (FENPK.01.01)

Test : Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd.)
 Lot No.: 16D01

Phase 1: Single-Dose Administration

Phase 2: Multiple-Dose Administration for Steady-State

Summary of Study Results
Repeated Measure Analyses for Fenofibric Acid Pre-Dose Concentrations
Day 8, 9, 10, and 11

Least Squares Means						
Effect	day	Estimate	Standard Error	DF	t Value	Pr > t
day	8	6.0692	0.6327	24	9.59	<.0001
day	9	7.2460	0.7457	24	9.72	<.0001
day	10	7.2356	0.6887	24	10.51	<.0001
day	11	7.1468	0.7514	24	9.51	<.0001

Differences of Least Squares Means							
Effect	day	_day	Estimate	Standard Error	DF	t Value	Pr > t
day	8	9	-1.1768	0.2009	24	-5.86	<.0001
day	8	10	-1.1664	0.1991	24	-5.86	<.0001
day	8	11	-1.0776	0.1759	24	-6.13	<.0001
day	9	10	0.01040	0.1689	24	0.06	0.9514
day	9	11	0.09920	0.1858	24	0.53	0.5984
day	10	11	0.08880	0.1911	24	0.46	0.6463

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Study No: 01-401 (FENPK.01.01)

Test: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd.)
 Lot No.: 16D01

Phase 1: Single-Dose Administration

Phase 2: Multiple-Dose Administration for Steady-State

*Summary of Gender Effect Analysis
 Based on Fenofibric Acid Plasma Levels*

Pharmacokinetic Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio,% (Female/Male)	90% Confidence interval*	Probability
	Female (N = 13)	Male (N = 12)			
Weight (kg)	64.8 (15)	75.6 (10)	85.68	77.56 – 93.81	0.0061
<i>Phase 1 (Single-Dose)</i>					
AUCI (h·µg/ml)	64.53 67.93 (35)	70.26 75.56 (47)	91.84	72.21 – 116.81	0.5501
Cmax (µg/ml)	3.97 4.08 (26)	4.30 4.33 (10)	92.24	81.18 – 104.80	0.2894
Tmax (h)	5.05 (15)	4.38 (21)	115.08	101.79 – 128.38	0.0641
Kel (1/h)	0.0471 (18)	0.0405 (24)	116.11	100.58 – 131.63	0.0886
Half-life (h)	15.17 (17)	18.48 (35)	82.09	63.97 – 100.22	0.1039
<i>Phase 2 (Steady-State)</i>					
AUCτ (h·µg/ml)	87.70 91.48 (31)	105.35 113.26 (48)	83.24	66.23 – 104.63	0.1825
Cmax (µg/ml)	6.63 6.77 (22)	7.77 8.23 (38)	85.35	70.22 – 103.73	0.1771
Tmax (h)	4.85 (18)	4.76 (25)	101.81	86.98 – 116.65	0.8359
Cmin (µg/ml)	1.86 2.01 (41)	2.40 2.73 (68)	77.78	57.44 – 105.33	0.1689
DF (%)	132.27 (26)	126.07(38)	104.91	82.44 – 127.39	0.7113

* Estimated through one-way ANOVA on log-transformed AUC and Cmax and on raw data for Tmax, Kel and Half-life.

** Contrast between the AUCτ at steady-state and AUCI after single-dose administration.

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Study Report, Fenofibrate Capsules 200 mg – Single and Multiple Dose
Protocol No. 01-401 (FENPK.01.01) Version 2.00

May 2002

Study No: 01-401 (FENPK.01.01)

Test: Fenofibrate Capsules, 200 mg (Cipher Pharmaceuticals Ltd.)
Lot No.: 16D01

Phase 1: Single-Dose Administration

Phase 2: Multiple-Dose Administration for Steady-State

*Summary of Gender Effect Analysis
Based on Fenofibrate Plasma Levels*

Pharmacokinetic Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio, % (Female/Male)	90% Confidence interval*	Probability
	Female (N = 13)	Male (N = 12)			
Weight (kg)	64.8 (15)	75.6 (10)	85.68	77.56 – 93.81	0.0061
<i>Phase 1 (Single-Dose)</i>					
AUCI*** (h·ng/ml)	10.56 11.19 (37)	15.29 16.52 (33)	69.08	47.54 – 100.37	0.1031
Cmax (ng/ml)	5.56 6.19 (46)	9.47 8.31 (46)	66.85	45.84 – 97.49	0.0804
Tmax (h)	3.73 (21)	3.68 (35)	101.48	81.91 – 121.04	0.8982
Kel*** (1/h)	1.3177 (67)	1.3774 (43)	95.67	50.46 – 140.89	0.8689
Half-life*** (h)	1.18 (120)	0.71 (91)	165.46	40.90 – 290.02	0.3715
<i>Phase 2 (Steady-State)</i>					
AUC τ (h·ng/ml)	9.29 10.69 (56)	14.95 17.18 (48)	62.17	41.84 – 92.39	0.0513
Cmax (ng/ml)	4.02 4.94 (65)	7.73 9.08 (50)	52.07	32.79 – 82.70	0.02396
Tmax (h)	3.50 (34)	3.84 (30)	91.04	70.04 – 112.05	0.4721

* Estimated through one-way ANOVA on log-transformed AUC and Cmax and on raw data for Tmax, Kel and Half-life.

** Contrast between the AUC τ at steady-state and AUCI after single-dose administration.

*** Due to incomplete definition of the terminal linear phase kel, half-life and AUCI parameters were not estimated on all subjects. There are only 7 values for females and 10 values for males.

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**An Open-Label, Single-Dose, Randomized, 3-Way Crossover Bioavailability Study of
Tricor[®] Tablets (Fenofibrate) in Healthy Subjects under Fed & Fasted Conditions**

Sponsor: Cipher Pharmaceuticals Ltd.
11A High Park, St. James
Barbados, W.I.

Test Product: Tricor[®] (Fenofibrate) Tablets, 160 mg (Abbott Laboratories); Lot
No. 671502E21; Expiration Date: 1FEB2003.

Number of Subjects: Twelve (12) subjects were dosed in Period I and all 12 subjects
completed the study.

Study (Dosing) Dates: Period I: November 13, 2001
Period II: November 20, 2001
Period III: November 27, 2001

Blood Sampling Times: Pre-dose (0 hour), and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours
post-dose.

Adverse Events: No adverse events were reported during the study.

Analytical: Analyte: Fenofibric Acid
Assay: LC/MS/MS
Calibration Range _____ µg/mL

Plasma samples from the 12 subjects who completed the study
were assayed.

b(4)

Study Conclusions:

The presence of food in the gastrointestinal tract and its content of fat influences considerably the bioavailability of fenofibric acid from Tricor[®] Tablets 160 mg (Abbott Laboratories). The food effect increases with the fat content of the meal: the larger the lipid content, the larger the increase in fenofibric acid bioavailability. The low fat meal triggered an increase of approximately 50% and 80% in the average AUC_t and C_{max}, respectively, compared to the fasting state.

The high fat meal almost doubled this effect; it lead to approximately 80% and 150% increase in the mean AUC_t and C_{max}, respectively, compared to the same fasting state.

All these differences reached statistical significance. This demonstrates that when Tricor[®] Tablets 160 mg are given with food, the absorption of fenofibrate is significantly increased. The extent of increase is positively related to the fat and calorie content of meals.

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**A Single-Dose, Randomized, 2-Way Crossover Bioequivalence Study of CIPHER
Fenofibrate Capsules and Tricor® Tablets 160 mg in Healthy Subjects, under Fed
Conditions**

Sponsor: CIPHER Canada Inc.
6560 Kennedy Road
Mississauga, Ontario L5T 2X4
Canada

Test Product: Fenofibrate Capsules, 1 x 160 mg (CIPHER Pharmaceuticals Ltd., Manufactured by Galephar P.R. Inc.); Lot No. 24E01

Reference Product: Tricor® (fenofibrate) Tablets, 1 x 160 mg (Abbott Laboratories Limited, Manufactured by Laboratoires Fournier S.A.); Lot No. 671502E21; Expiry Date: 1FEB2003

Number of Subjects: Twenty-four (24) subjects were dosed in Period I, 23 subjects completed the study.

Study (Dosing) Dates: Period I: January 15, 2002
Period II: January 22, 2002

Blood Sampling Times: Pre-dose (0 hour), and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, and 72 hours post-dose (N = 15 time points).

Adverse Events: Eleven adverse events involving five subjects were reported. All adverse events were mild and resolved without medication; eight were possibly related to the study drugs and three were unrelated to the study drugs.

No serious adverse events were reported during the study.

Analytical: Analytes: Fenofibric acid
Assay: LC-MS/MS
Calibration Range: _____ µg/mL

Plasma samples from the 23 subjects who completed the study were assayed.

b(4)

Study Conclusions:

Based on ln-transformed data, the 90% confidence intervals of ratios of geometric means (test: reference) for AUC_t, AUC_i, and C_{max} were within the 80-125% acceptance range. Therefore, CIPHER's Fenofibrate Capsules, 160 mg were found to meet the FDA's criteria for bioequivalence when compared to Tricor[®] (fenofibrate) Tablets, 160 mg (Abbott Laboratories Limited), under single-dose, fed conditions.

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**Summary of Study Results
(Test vs. Reference)**

(N = 23)

Test (A): Fenofibrate Capsules, 1 x 160 mg (Cipher Pharmaceuticals Ltd., Manufactured by Galephar P.R. Inc.); Lot No. 24E01.

Reference (B): Tricor[®] (fenofibrate) Tablets, 1 x 160 mg (Abbott Laboratories Limited, Manufactured by Laboratoires Fournier S.A.); Lot No. 671502E21; Expiry Date: 1FEB2003.

Analyte: Fenofibric Acid

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean (%CV)				
AUCt (µg·h/mL)	153.35 161.29 (32)	151.32 156.41 (24)	101.34	96.48 - 106.44	9.69
AUCi (µg·h/mL)	162.14 172.04 (35)	158.64 164.48 (26)	102.21	96.93 - 107.77	10.46
Cmax (µg/mL)	10.44 10.81 (30)	11.02 11.30 (22)	94.73	88.24 - 101.70	14.05
Tmax ^a (h)	5.00 (3.00-6.00)	3.00 (2.00-7.00)	-	-	-
Kel (h ⁻¹)	0.0434 (21)	0.0471 (24)	-	-	-
Thalf (h)	16.71 (22)	15.46 (22)	-	-	-

^aTmax is expressed as median (range).

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EXECUTIVE SUMMARY

**An Open-Label, Single-Dose, Two-way Crossover Relative Bioavailability Study of
Two Formulations of Fenofibrate 160 mg in Healthy Subjects, Under Fasting
Conditions**

Sponsor: Cipher Canada Inc.
6560 Kennedy Rd.
Mississauga, Ontario
L5T 2X4 Canada

Test Product: FENOFIBRATE 160 mg Capsules (Manufactured for
Cipher Canada Inc. by GALEPHAR P.R. Inc.);
Lot No.: 24E01; Expiration Date: N/A

Reference Product: TRICOR[®] (fenofibrate tablets) 160 mg (Manufactured for
Abbott Laboratories, North Chicago, IL 60064, U.S.A. by
Laboratoires Fournier, S.A., 21300 Chenôve, France. Made
in France);
Lot No.: 875012E21; Expiration Date: 1OCT2004

Number of Subjects: Thirty-six (36) subjects were dosed in Period I, and 35
subjects completed the entire study.

Study (Dosing) Dates: Period I: August 10, 2002
Period II: August 17, 2002

Blood Sampling Times: Blood samples were collected at pre-dose (0.0 hour), and at
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48 and 72 hours
following drug administration.

Adverse Events: Eight (8) adverse events involving 4 subjects were
reported. All were mild in severity and all were possibly
related to the study drugs and all adverse events resolved
without medication.

No serious adverse events were reported during the study.

b(4)

Analytical: Analyte: Fenofibric Acid
Calibration Range: _____ $\mu\text{g/mL}$

b(4)

Fenofibric acid plasma concentrations were measured.
Plasma samples were assayed from the 35 subjects who
completed the study.

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b(4)

**Summary of Results for Plasma Fenofibric Acid
(N = 30)**

Test (A): FENOFIBRATE 160 mg Capsules (GALEPHAR P.R. Inc.);
Lot No.: 24E01; Expiration Date: N/A

Reference (B): TRICOR[®] (fenofibrate tablets) 160 mg (Manufactured for Abbott
Laboratories, North Chicago, IL 60064, U.S.A. by _____)

b(4)

Lot No.: 875012E21; Expiration Date: 1OCT2004

Analyte: Fenofibric Acid

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geometric Confidence Interval (%)	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean (CV,%)				
AUC _t (µg·h/mL)	84.872 91.488 (39)	97.918 104.049 (37)	86.68	81.00 - 92.75	15
AUC _i (µg·h/mL)	104.703 114.041 (51)	109.889 117.256 (40)	95.28	86.45 - 105.01	20
C _{max} (µg/mL)	2.692 3.034 (45)	4.114 4.425 (41)	65.43	57.09 - 74.99	32
T _{max} ^a (h)	6.00 (3.00 - 48.23)	4.00 (2.00 - 7.00)	-	-	-
K _{el} ^b (h ⁻¹)	0.0265 (41)	0.0319 (36)	-	-	-
T _{half} ^b (h)	31.52 (47)	24.83 (39)	-	-	-

^a T_{max} is presented as median (range).

^b Presented as arithmetic mean (CV%) only.

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b(4)

October 2002

Study Conclusions: Based on ln-transformed fenofibric acid data, the 90% confidence intervals of ratios of geometric means (test:reference) for AUC_t and AUC_i are within the 80-125% range. Therefore the extent of absorption from the two drug-products is equivalent. However, the 90% confidence intervals of ratios of geometric means (test:reference) for C_{max} is not within the 80-125% range. Furthermore, the test formulation exhibited a longer median T_{max} value than the reference formulation.

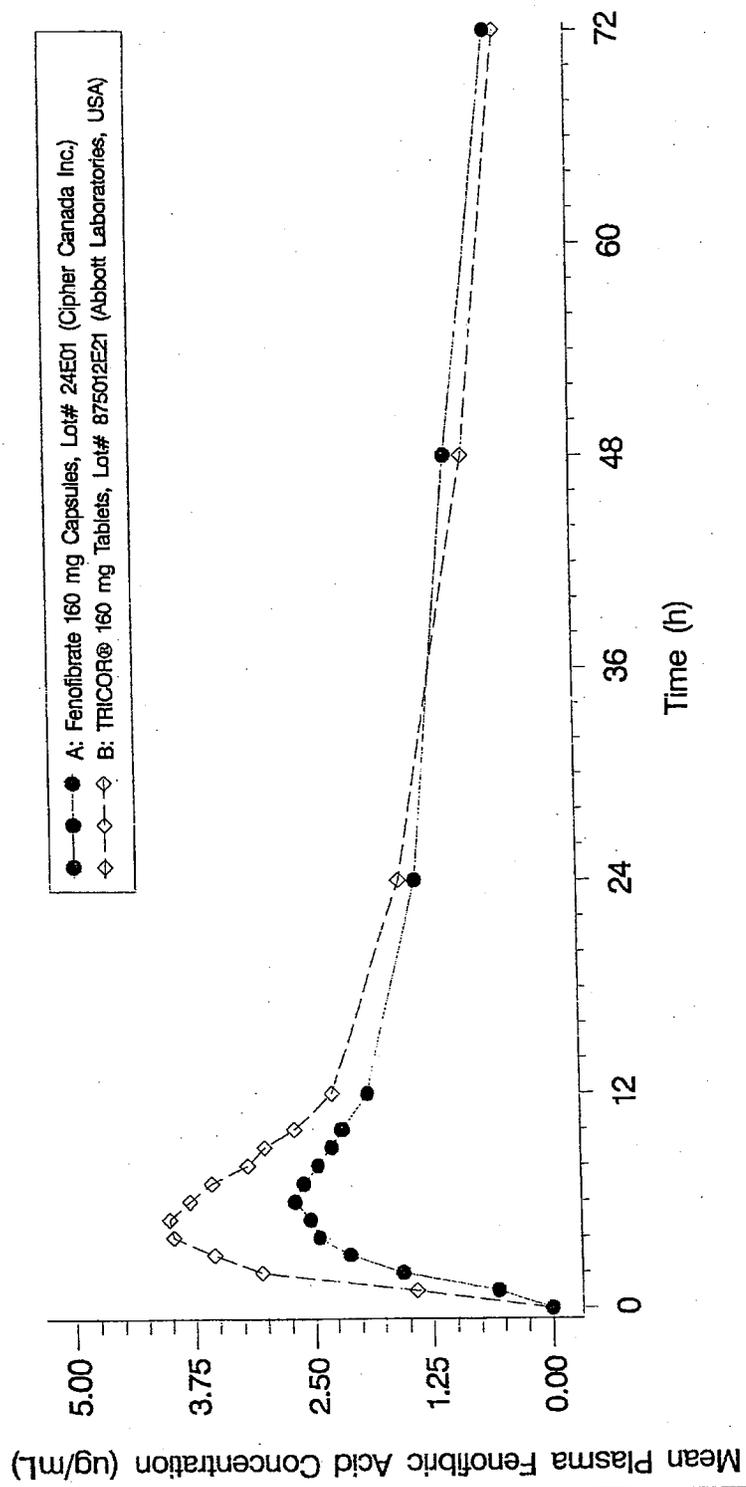
Therefore, it appears that GALEPHAR P.R. Inc.'s FENOFIBRATE 160 mg Capsules deliver the same amount of fenofibric acid as Abbott Laboratories TRICOR[®] (fenofibrate tablets) 160 mg Capsules under single-dose and fasting conditions, but at a lower rate of absorption.

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STUDY No.: 02--557

MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES

N=30

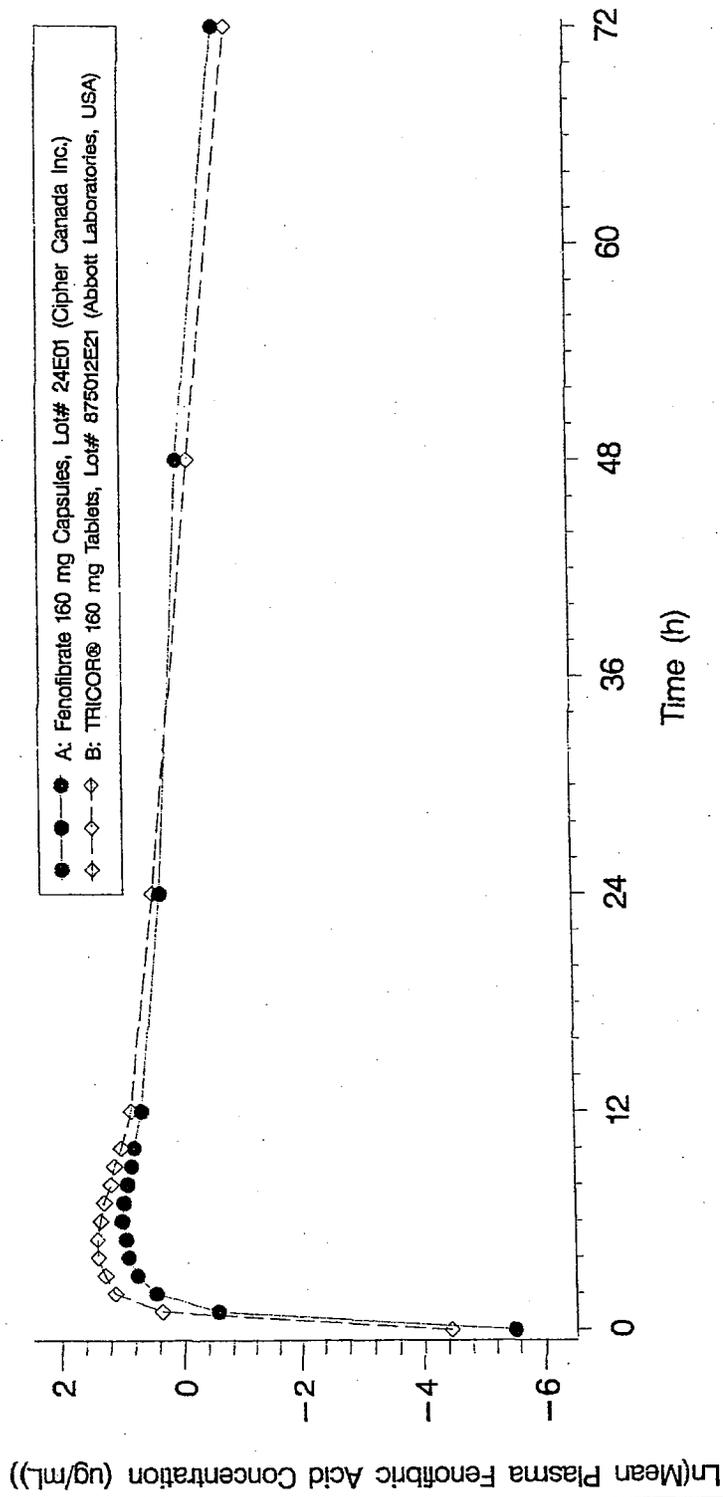


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STUDY No.: 02-557

LOG MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES

N=30



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b(4)

October 2002

EXECUTIVE SUMMARY

An Open-Label, Single-Dose, Two-Way Crossover Comparative Bioavailability Study of Fenofibrate 50 mg and 200 mg Capsules in Healthy Subjects, Under Fed Conditions

Sponsor: Cipher Canada Inc.
6560 Kennedy Rd.
Mississauga, Ontario
L5T 2X4 Canada

Treatment A (Test): Fenofibrate Capsules 50 mg [4 x 50 mg] (Lot# 17D01)
(Manufactured by GALEPHAR P.R. Inc. on behalf of
Cipher Canada Inc.); Expiration Date: N/A

Treatment B (Reference): Fenofibrate Capsules 200 mg [1 x 200 mg] (Lot# 3E01);
(Manufactured by GALEPHAR P.R. Inc. on behalf of
Cipher Canada Inc.); Expiration Date: N/A

Number of Subjects: Eighteen (18) subjects: 6 males and 12 females.

Study (Dosing) Dates: Period I: August 18, 2002
Period II: August 25, 2002

Blood Sampling Times: Blood samples were collected at pre-dose (0 hour) (2 x 7 mL), and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24, 48 and 72 hours following drug administration (1 x 7 mL) (n=19 time points).

Adverse Events: Seven (7) adverse events involving 4 subjects were reported. All adverse events were mild in severity, possibly related to the study drugs, and resolved without medication.

No serious adverse events were reported during the study.

Analytical: Analyte: Fenofibric Acid
Assay: LC-MS/MS
Calibration Range: _____ µg/mL

b(4)

b(4)

October 2002

**Summary of Results for Plasma Fenofibric Acid
(N = 18)**

Treatment A (Test): Fenofibrate 50 mg Capsules [4 x 50 mg] (Manufactured by GALEPHAR P.R. Inc. on behalf of Cipher Canada Inc.); Lot# 17D01; Expiration Date: N/A

Treatment B (Reference): Fenofibrate 200 mg Capsules [1 x 200 mg] (Manufactured by GALEPHAR P.R. Inc. on behalf of Cipher Canada Inc.); Lot# 3E01; Expiration Date: N/A

Analyte: Fenofibric Acid

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geometric Confidence Interval (%)	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUC _t (µg·h/mL)	191.68 197.33 (25)	184.26 190.70 (27)	104.03	98.27 – 110.12	10
AUC _i (µg·h/mL)	210.09 217.40 (28)	203.25 212.08 (31)	103.37	98.52 – 108.45	8
C _{max} (µg/mL)	12.09 12.43 (24)	11.39 11.52 (16)	106.16	95.25 – 118.32	19
T _{max} ^a (h)	4.50 (3.50 – 8.00)	4.50 (3.00 – 7.00)	-	-	-
K _{el} ^b (h ⁻¹)	0.0379 (29)	0.0344 (22)	-	-	-
T _{half} ^b (h)	19.87 (30)	21.05 (22)	-	-	-

^aT_{max} is expressed as median (range).

^bExpressed as arithmetic mean (CV%) only.

Study Conclusions: Based on log-transformed fenofibric acid data, the 90% confidence intervals of ratios of geometric means (Treatment A:Treatment B) for AUC_t, AUC_i and C_{max} are within the 80-125% range. Furthermore, both Treatment A and Treatment B formulations exhibited the same median T_{max} value.

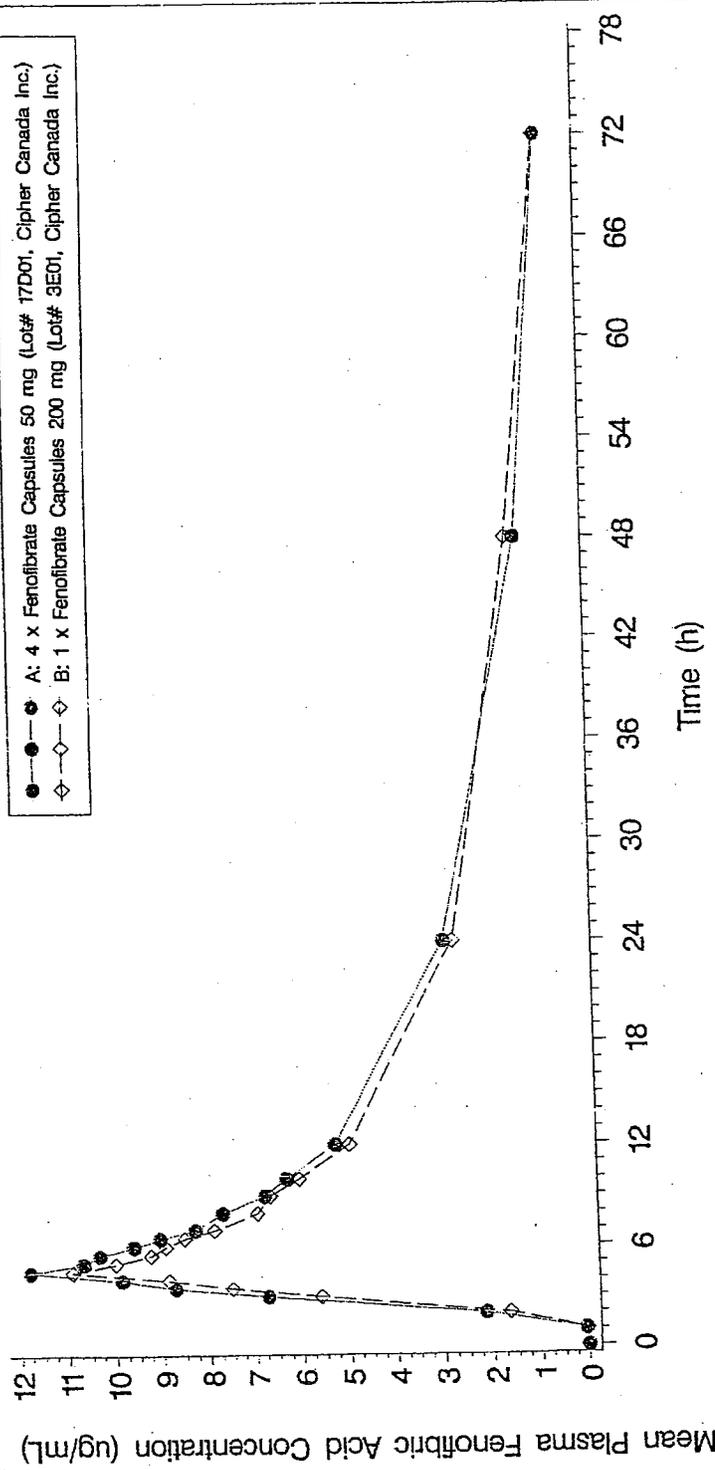
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In conclusion the 4 x 50 mg dose of Fenofibrate Capsules 50 mg (Cipher Canada Inc.) exhibited equivalent rate and extent of absorption to the 1 x 200 mg dose of Fenofibrate Capsules 200 mg (Cipher Canada Inc.) under fed conditions.

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STUDY No.: 02--558
 MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES
 N=18

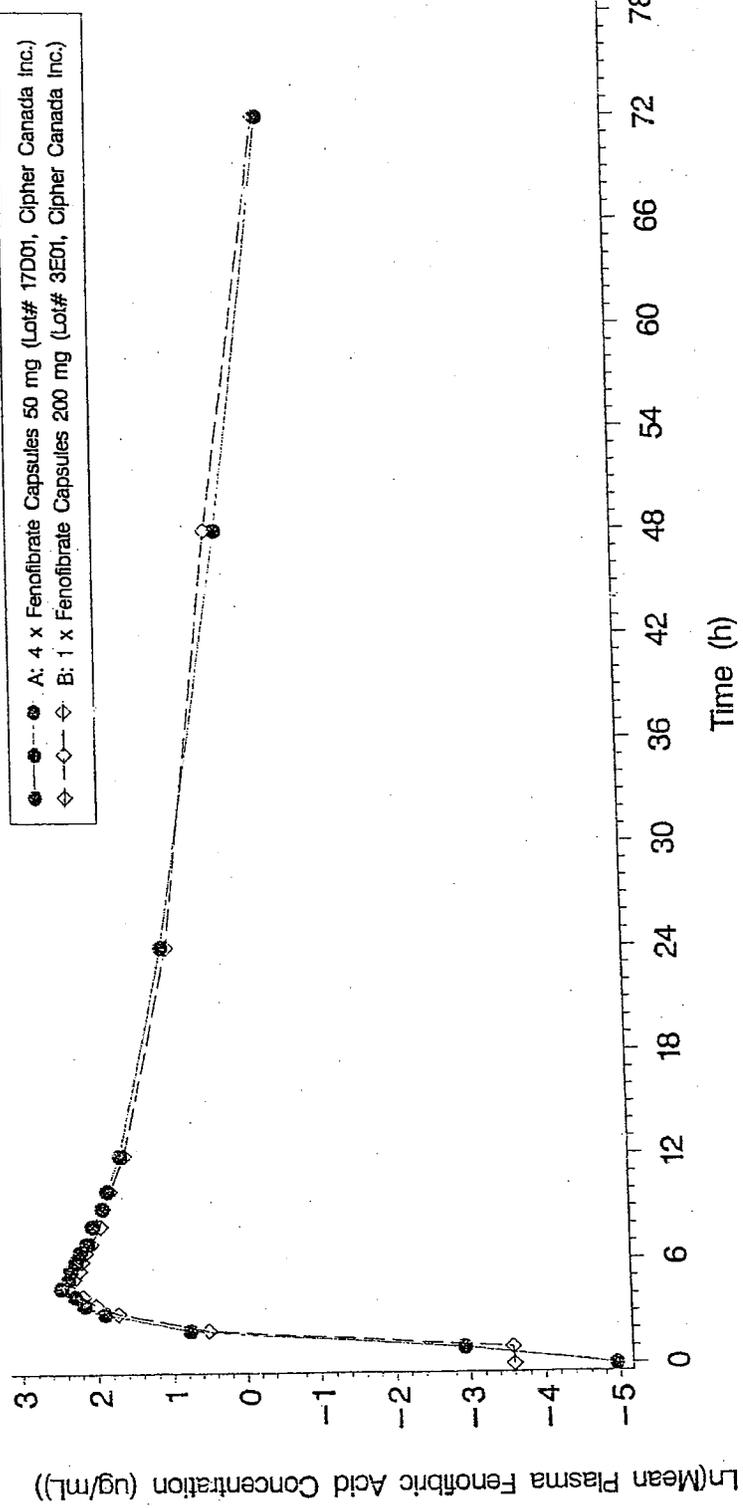


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STUDY No.: 02-558

LOG MEAN PLASMA FENOFIBRIC ACID CONCENTRATION VERSUS TIME CURVES

N=18



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BIOPHARMACEUTICS

Hae-Young Ahn
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BIOPHARMACEUTICS

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

General Information About the Submission

Information		Information	
NDA Number	2512	Brand Name	CIP-Fenofibrate
OCPB Division (I, II, III)	II	Generic Name	fenofibrate
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Type IV and V hypercholesterolemia
OCPB Team Leader	Hae-Young Ahn	Dosage Form	capsules
Related IND(s)		Dosing Regimen	50, 100, 150. mg
Date of Submission	Dec. 24, 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Cipher Pharmaceuticals Limited
PDUFA Due Date	Dec. 26, 2003	Priority Classification	regular
Division Due Date			

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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:		1		
multiple dose:		1		Same study for single dose
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
Mutual:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Meta Analysis:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2; proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:	x	2		
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm ?	x	<p>In general, the _____ paddle speed is not acceptable. The sponsor is recommended to investigate lower paddle speed and other USP apparatus such as basket. In order to obtain an appropriate dissolution method and specification for this product and to be granted for biowaivers for strengths lower than 160 mg, the sponsor must submit dissolution profiles for the 50, 100, and 150 mg tablets from _____ batches under three different conditions.</p>		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Relative bioavailability compared with Tricor micronized tablets 2. Dose proportionality 3. Food effect 		
Other comments or information not included above		<p>Since no clinical trial was conducted with the subject of this NDA submission, it is desirable to conduct DSI inspection on pivotal studies FENPK01.07 and FENPK02.01. Both studies were conducted at the same site.</p> <p>Clinical facility: L L</p> <p>Clinical Laboratory: L L</p> <p>Analytical, Statistical, and Report Issuina Facility: L L</p>		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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On Dec 24, 2002, Cipher Pharmaceuticals Limited submitted an original NDA for CIP-fenofibrate™ (fenofibrate) capsules for the treatments of Type IV and V hypercholesterolemia.

There were 7 PK studies conducted in support of this application that are provided. In addition, dissolution data for the 160 mg capsules and analytical validation reports were included. However, the dissolution data for other strengths were not provided. The compositions of the finished products are strength proportional. The strengths are varied only by the fill weight of the blend filled into the different capsule sizes.

1. FENPK.01.01 Single dose and multiple dose study of CIP-fenofibrate 200 mg capsules under high-fat fed condition
2. FENPK.01.02 Food effect on single dose of CIP-fenofibrate 200 mg capsuels
3. FENPK.01.03 Dose proportionality within the range of 50 to 200 mg under high-fat fed conditions
4. FENPK.01.06 Food effect on single dose of Tricor® 160 mg tablet

5. **FENPK.01.07** BE study comparing single dose of CIP-fenofibrate 160 mg capsules and Tricor® 160 mg tablets under high-fat fed conditions
6. **FENPK.02.01** Relative BA study comparing single dose of CIP-fenofibrate 160 mg capsules and Tricor® 160 mg tablet under fasting conditions
7. **FENPK.02.02** Relative BA study comparing single dose of CIP-fenofibrare 4x50 mg capsules and CIP-fenofibr-
1x200 mg capsules under low-fat fed conditions.

The pharmacokinetic results of CIP-fenofibrate are summarized as follows:

1. The AUC_{0-t} of CIP-fenofibrate 200 mg capsules at steady state was on average 42% larger than AUC_{inf} after a single dose. The corresponding C_{max} was 73% higher at steady state.
2. Dose proportionality was not observed in the range of 50 to 200 mg.
3. The high-fat and low-fat meals increased the AUC(0-inf) of CIP-fenofibrate 200 mg capsules by 58% and 25%, respectively, compared to the fasting condition. The high-fat and low-fat meals increased the C_{max} by 265% and 126%, respectively, compared to the fasting condition.
4. The high-fat and low-fat meals increased the AUC(0-inf) of Tricor® 160 mg tablets by 26% and 10%, respectively, compared to the fasting condition. The high-fat and low-fat meals increased the C_{max} by 148% and 77%, respectively, compared to fasting condition.
5. CIP-fenofibrate 160 mg capsules were found to be bioequivalence to Tricor® 160 mg tablets under high-fat fed condition.
6. The extent of absorption of CIP-fenofibrate 160 mg capsules and Tricor® 160 mg tablets was equivalent under fasting condition. However, The CIP-fenofibrate 160 mg capsules exhibited lower C_{max}, 65% on average when compared to Tricor®.
7. The 4x50 mg dose of CIP-fenofibrate capsule 50 mg exhibited equivalent rate and extent of absorption to the 1x200 mg dose of CIP-fenofibrate capsule 200 mg under low-fat fed condition.

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/s/

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4/16/03 03:43:19 PM
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Hae-Young Ahn
4/17/03 09:05:37 AM
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