CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-118

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-118
Submission Date(s)	September 28, 2006
Brand Name	LCP-FenoChol®
Generic Name	Fenofibrate tablets
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Sally Choe, Ph.D. (Acting)
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor	LifeCycle Pharma A/S
Submission Type	505(b)(2)
Formulation Strength(s)	Oral tablets: 40 mg and 120 mg
Indication	[redacted] or mixed dyslipidemia [redacted] and hypertriglyceridemia [redacted]
Dosage & Administration	40 – 120 mg per day

b(4)

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA22-118 for LCP-FenoChol® and concludes that LCP-FenoChol® 120 mg tablet is not bioequivalence to Antara™ 130 mg capsule

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor submitted the NDA 22-118 for LCP-FenoChol® (fenofibrate) tablet as a 505(b)(2) referencing Antara™ (fenofibrate) capsule (NDA 21-695). In this submission, there were no clinical studies conducted evaluating the efficacy and safety for LCP-FenoChol® but one pivotal bioequivalence (BE) / food effect study (PK 120-04) and two supportive BE studies (PK 120-01 and 120-03). Antara™ capsule was initially approved by the Agency as a 505(b)(2) referencing Tricor® (micronized) capsule (NDA 19-304) without any efficacy and safety clinical trials conducted for Antara™ capsule. Tricor® (micronized) capsule marketing has been discontinued and Tricor® (micronized) capsule is currently not listed as RLD in the Orange Book.

Food has been known to affect the bioavailability of fenofibric acid and the effect is dependent on fat composition (i.e., high and low fat) and formulations as indicated in the Antara® labeling. Tricor® capsule is to be taken with food to have optimum exposure. Antara™ capsule was also to be taken with food because Antara™ capsule was bioequivalent to Tricor® capsule only under low fat fed condition following multiple doses. Antara™ capsule labeling, however, is subsequently updated that it can be taken without regard to meals based on the result of Efficacy Supplement for food effect.

Fenofibric acid after LCP-FenoChol® 120 mg tablet administration was not bioequivalent to that of Antara™ 130 mg capsule administration under fasting condition because the 90% confidence interval (CI) (1.32-1.61) of least-squares means (LSM) ratio (1.46) for Cmax did not meet the bioequivalence (BE) criteria. However, the 90% CI (1.05-1.14) of LSM ratio (1.10) for AUC0-inf met the criteria. The 46% mean Cmax increase after LCP-FenoChol® administration compared to that of Antara™ implies that the Cmax of LCP-FenoChol® may be at least 2-fold higher than that of Tricor® because 72% higher mean Cmax after Antara™ administration was observed compared to that of Tricor®.

Fenofibric acid after LCP-FenoChol® 120 mg tablet administration was bioequivalent to that of Antara™ 130 mg capsule administration under high fat fed condition with LSM ratios (90% CI) for AUC0-inf and Cmax of 0.932 (0.896-0.970) and 1.11 (1.00-1.22), respectively. The BE study results under fed condition are not generally regarded as the

pivotal information because the study condition is not rigorous enough for the formulation comparability test particularly for the serial bridging BE studies (e.g., A is bioequivalent to B, B is bioequivalent to C, and thus A is beioquivalent to C).

Regarding the food effect on finofibric acid, the high-fat meal did not affect AUC0-inf after LCP-FenoChol® 120 mg tablet administration but it increased mean Cmax by 44% compared to those of fasting condition.

The pivotal study, FenoChol PK 120-04 was conducted by [redacted] between March 25, 2006 and May 10, 2006. Division of Scientific Inspections (DSI) investigated the clinical and analytical portions of the study and its review concluded that the study results were acceptable from the DSI perspectives (see Appendix 4.1). b(4)

2 Question Based Review

2.1 General Biopharmaceutics

Three comparative pharmacokinetic studies were conducted for LCP-FenoChol® (fenofibrate) tablet; one pivotal study (FenoChol PK 120-04) with the commercial production scale batch and two supportive studies (FenoChol PK 120-01 and FenoChol PK 120-03) with a formulation manufactured on pilot scale batch with lower amount of magnesium stearate [redacted] compared to that of the commercial production scale batches b(4)

2.1.1 What is the fenofibric acid relative bioavailability after LCP-FenoChol® administration compared to that after Antara™ administration?

FenoChol PK 120-04 Study:

The relative bioavailability and food effect of fenofibric acid were estimated in an open-label, single dose, four-way crossover study (n=36 healthy subjects; FenoChol PK 120-04). Test product was LCP-FenoChol® 120 mg tablet (Lot No., 306005, manufactured on January 25, 2006) and reference product was Antara™ 130 mg capsule (Lot No., 5ED0036 with expiration data of March 2007). The treatments were administered in either overnight fasting condition or in fed condition within 30 minutes of starting a high-fat breakfast. The high fat breakfast consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 ml of whole milk. The high fat meal was to provide approximately 127 calories (13.1%), 287 calories (23.6%), and 546 calories (56.3%) from protein, carbohydrate, and fat, respectively. The washout was at least 10 days between the treatments and blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose. The plasma fenofibric acid concentrations were measured by LC/MS/MS. The plasma concentration-time profiles of fenofibric acid are shown in Figure 1 and pharmacokinetic parameters are summarized in Table 1.

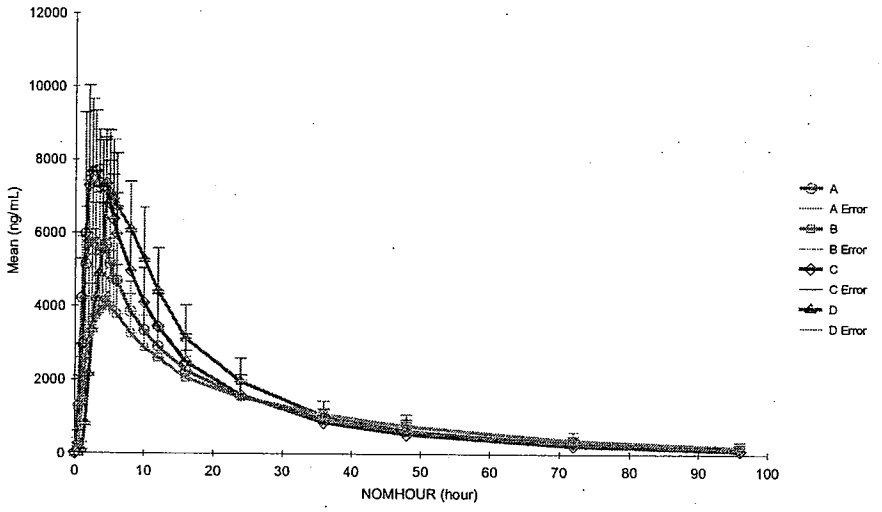

Figure 1 **Mean (SD) plasma fenofibric acid-time profiles by treatments (A: LCP-FenoChol® under fasting, B: Antara™ under fasting, C: LCP-FenoChol® under fed, D: Antara™ under fed)**

Table 1 **Fenofibric acid plasma mean (CV) pharmacokinetic parameters (n=36)**

PK parameter	LCD-FenoChol® 120 mg		Antara™ 130 mg	
	fasting	fed	fasting	fed
AUC 0-t (ng·h/mL)	112940.45 (24.8%)	122100.26 (27.7%)	102938.77 (29.6%)	130968.18 (25.6%)
AUC inf (ng·h/mL)	118051.35 (27.2%)	124976.92 (28.6%)	108966.98 (32.4%)	134247.54 (26.8%)
Cmax (ng/mL)	6049.95 (29.8%)	8736.00 (18.9%)	4152.98 (45.4%)	7888.89 (14.3%)
tmax (h)	2.50 (1.0-6.0)	2.5 (1.5-5.5)	4.5 (1.5-8.09)	5.0 (2.5-10.0)
half-life (h)	22.05 (35.4%)	18.34 (23.1%)	22.32 (32.5%)	18.42 (24.0%)

The 90% CI for the ratios of LSM were obtained from the Analyses of Variance model with sequence, formulation and period as fixed effects and subject nested within sequence as a random effect using the SAS® GLM procedure. The result of statistical analyses for BE assessment are summarized in Table 2. The fenofibric acid AUC after LCP-FenoChol® 120 mg tablet administration was bioequivalent to Antara™ 130 mg administration under fasting and high-fat fed conditions. The fenofibric acid Cmax after LCP-FenoChol® 120 mg was bioquivalent to Antara™ 130 mg administration under high-fat fed condition but was 46% higher than that after Antara™ 130 mg administration under fasting condition.

Table 2 **LSM ratios (LCP-FenoChol®/Antara™) and 90% confidence interval (red indicates out of BE criteria)**

Parameters	high-fat fed condition (N=36)	fasting condition (N=36)
AUC 0-t	93.2 % (89.6-97.0)	109.7% (105.4-114.2)
AUCinf	93.1% (89.5-96.9)	108.3% (104.1-112.7)
Cmax	110.7% (100.3-122.3)	145.7% (131.9-160.9)

Food effect on fenofibric acid bioavailability was evaluated using the statistical analyses for BE assessment. High fat meal did not affect the fenofibric acid AUC after LCP-FenoChol® administration but increased the mean Cmax by 44% compared to those under fasting condition (Table 3).

Table 3 **Food effect: LSM ratios (high fat fed/fasting) and 90% CI (red indicates out of BE criteria)**

Parameters	LCP-FenoChol® (N=36)	Antara™ (N=36)
AUC 0-t	108.1% (103.9-112.5)	127.2% (122.2-132.4)
AUCinf	105.9% (101.8-110.1)	123.2 (118.4-128.2)
Cmax	144.4% (130.8-159.4)	190.% (172.0-209.8)

FenoChol PK 120-01 Study:

The sponsor conducted a four-way crossover, single dose, bioavailability and food effect study (FenoChol PK 120-01) in healthy subjects (n=42) with a pilot scale batch formulation. The pilot scale batch formulation was manufactured with lower amount of magnesium stearate [redacted] compared to that of the commercial production scale batches [redacted]. Test product was LCP-FenoChol® 120 mg tablet (Batch No.; 305041) and the reference product was Antara™ capsule 130 mg (Lot No.; 5ED0026). General study design was comparable to the Study FenoChol PK 120-04. The study results are summarized in Table 4. b(4)

The study results were comparable to those of Study FenoChol PK 130-04. However, the Study FenoChol PK 120-01 was regarded as a supportive study due to the small size of batch and formulation difference from the to-be-marketed formulation.

Table 4 **Summary of fenofibric acid pharmacokinetic parameters and results of statistical analyses for BE assessment (red indicates out of BE criteria)**

		LCP-FenoChol® 120 mg	Antara™ 130 mg	LSM ratio	90% CI
high-fat fed condition	AUC 0-t (ng·h/mL)	135995 (33.41)	147678.21 (34.59)	92.27	88.68-96.01
	AUC 0-inf (ng·h/mL)	140729.71 (36.40)	152916.32 (37.49)	92.23	88.55-96.06
	Cmax (ng/mL)	8266.80 (18.73)	7530.35 (20.98)	110.24	100.90-120.44
fasting condition	AUC 0-t (ng·h/mL)	126269.65 (32.35)	111828.93 (36.74)	112.89	108.49-117.47
	AUC 0-inf (ng·h/mL)	130855.20 (34.72)	119403.99 (39.86)	110.76	106.31-115.40
	Cmax (ng/mL)	6335.94 (32.11)	4354.77 (29.53)	145.36	133.05-158.82

FenoChol PK 120-31 Study:

The fenofibric acid bioavailability of LCP-FenoChol® 120 mg tablet (Lot No.; 305041) was compared to that of Antara™ 130 mg capsule (Lot No.; 5ED0026) at steady-state (Day 8) under low fat fed condition in a two-way crossover study with the pilot scale batch formulation (n=40 healthy subjects). The treatments were administered once daily for 8 days under low fat fed condition. The low fat breakfast consisted of 1 medium bagel with 2 teaspoons of low fat cream cheese, 1.5 cups shredded wheat cereal, 1 small banana, 240 mL of 1% milk, and ¾ cup orange juice. The low fat breakfast was provided on Day 1 and Day 8 and subjects were to conform to the low fat requirement on other days. General study design was comparable to those of Study FenoChol PK 120-04. The steady-state fenofibric acid pharmacokinetic parameters and results of statistical analysis for BE assessment are summarized in Table 5. The PK parameters that were evaluated for LCP-FenoChol® 120 mg tablet were comparable to those of Antara™ 130 mg capsule at steady-state under low fat fed condition. The study results were, however, regarded as a supportive due to the small size of batch and formulation difference from the to-be-marketed formulation.

Table 5 **Summary of steady-state fenofibric acid pharmacokinetic parameters (Day 8) under low-fat fed condition and results of statistical analysis for BE assessment**

	LCP-FenoChol® 120 mg	Antara™ 130 mg	LSM ratio	90% CI
AUC 0-τ (ng·h/mL)	142167.55 (37.0%)	140943.85 (37.0%)	100.9	98.1-103.7
Cmax (ng/mL)	11647.02 (23.3%)	10508.99 (26.6%)	110.8	107.0-114.8

Composition of LCP-FenoChol® tablets are summarized in Table 6. The composition of 40 mg tablet was proportionally similar to that of 120 mg tablet.

Table 6 Composition of LCP-FenoChol® tablets

	amount (mg/tablet)		amount (% composition)	
Strength	**40 mg**	**120 mg**	**40 mg**	**120 mg**
fenofibrate (active)	40.0	120.0	[redacted]	
lactose monohydrate	[redacted]			
polyethylene Glycol 6000				
poloxamer 188				
magnesium stearate				
Total	211	634	100	100

b(4)

Summary (Section 2.7.1.3.1) indicates that *in vitro* dissolution profile of 40 mg tablets (Batch No.; 0600422) were comparable to those of 120 mg tablets (Batch No.; 0600418) with the similarity factor (f2) of 62.2. (refer Chemistry review by Dr. Xavier Ysern, Ph.D.).

2.2 Analytical Section

2.2.1 What bioanalytical methods are used to assess concentrations?

Plasma fenofibric acid concentrations were measured using LC/MS/MS method and QC run data are summarized in Table 7. The analytic method was acceptable.

Table 7 QC run data (n=49) from bioanalytical report (Study FenoChol PK 120-04)

Standard curve concentrations (ng/mL)	20.4-20200
QC concentrations (ng/mL)	[redacted]
QC intra-run accuracy (%)	100.3-102.8
QC intra-run precision (%)	3.5-4.1

b(4)

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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Withheld Track Number: Clin Pharm/Bio-1

13 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

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_____ Deliberative Process (b5)

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Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-118	Brand Name	LCP-FenoChol
OCP Division (I, II, III, IV, and V)	II	Generic Name	Fenofibrate
Medical Division	510	Drug Class	Metabolism
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia
OCP Team Leader	Hae-Young Ahn	Dosage Form	Tablets
		Dosing Regimen	40 and 120 mg
Date of Submission	28 September, 2006	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	LifeCycle Pharma A/S
PDUFA Due Date	10 August, 2007	Priority Classification	
Division Due Date	1 July, 2007		

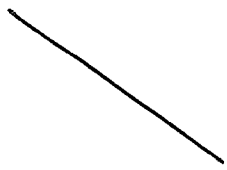
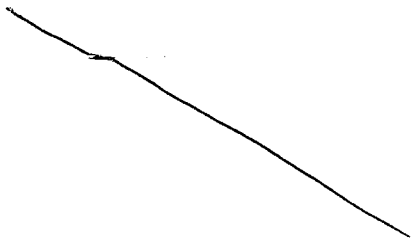
b(4)

Clin. Pharm. and Biopharm. Information

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

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	3		1 pivotal using commercial batch; 2 supportive using pilot scale batches.
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
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				

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	x	
Comments sent to firm ?		DSI inspection is recommended for the pivotal study (Study No. FenoChol PK 120-04) Title: Comparative, Randomized, Single-Dose, 4-Way Crossover Bioavailability Study of LifeCycle Pharma 120 mg Fenofibrate Tablets (FenoChol) and Reliant Pharmaceuticals, Inc. 130 mg Fenofibrate capsules (Antara™) in Healthy Adult Volunteers under Fed and Fasting Conditions Clinical Site:  b(4) Sample analysis for fenofibric acid in plasma was performed at  b(4)
QBR questions (key issues to be considered)		**1. Is FenoChol 120 mg tablet bioequivalent to Antara 130 mg capsule?** **2. Can biowaiver request for the FenoChol 40 mg tablet be granted?** **3. Does food affect the bioavailability of FenoChol tablet?**
Other comments or information not included above		

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

This 505(b)(2) application is submitted as a paper NDA. The reference drug is Antara™ (NDA 21-695), which was approved through the 505(b)(2) pathway on November 30, 2004 in 43, 87, and 130 mg capsules. The reference product for NDA 21-695 was Tricor® 200 mg capsules.

This application relies on one pivotal, single-dose bioequivalence study conducted on a commercial scale batch of LCP-FenoChol (fenofibrate) tablets, 120 mg and two supportive studies conducted on pilot scale batches of LCP-FenoChol (fenofibrate) Tablets, 120 mg. The pilot scale batches were manufactured with a slightly lower amount of the excipient magnesium stearate — compared to the commercial production scale batches —— magnesium stearate). All three studies used the reference drug, AntaraTM (fenofibrate) Capsules, 130 mg as a comparator product. b(4)

During the pre-NDA meeting, the sponsor stated that LifeCycle has successfully shown bioequivalence of FenoChol (fenofibrate) Tablets, 120 mg to AntaraTM (fenofibrate) Capsules, 130 mg. LifeCycle intended to request a waiver for providing evidence of in vivo bioequivalence for FenoChol (fenofibrate) Tablets, 40 mg based on similarity of the dissolution profiles. Agency's response was that a waiver can be granted with —dissolution conditions ——————— with the similarity of the profiles determined based on similarity factor (f2) calculations. The data supports the applicant's waiver request is included in Module 1. b(4)

Due to the exclusivity for the use of AntaraTM (fenofibrate) Capsules without regards to meals until 21 October, 2008, the proposed labeling for LCP-FenoChol (fenofibrate) Tablets does not direct for administration of the product without regards to meals.

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/s/

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