

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-118**

**MEDICAL REVIEW(S)**

8/10/07

## MEMORANDUM

August 3, 2007

NDA: 22-118

DRUG: Fenofibrate (FenoChol) Tablet 40 mg and 120 mg

INDICATION: Treatment of \_\_\_\_\_ hyperlipidemia

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COMPANY: Lifecycle Pharma

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The sponsor has submitted a 505b2 application seeking approval of 40 mg and 120 mg fenofibrate based on reference to NDA 21-695, an approved fenofibrate tradenamed Antara. Antara was approved as a 505b2 application based on reference to the Tricor NDA 19-304.

As detailed and summarized in reviews by Dr. Sang Chung and Dr. Julie Golden, respectively, three clinical pharmacology studies were conducted to compare the pharmacokinetic parameters of FenoChol to Antara.

In two single-dose studies, FenoChol 120 mg was bioequivalent to Antara 130 mg under fed but not fasting conditions. In the fasted state, the  $C_{max}$  for FenoChol was approximately 46% higher than Antara. Because the 90% confidence interval for the least squared means ratio for  $C_{max}$  did not fall within the established bioequivalency boundaries of 80%-125%, FenoChol is not bioequivalent to Antara in the fasted state.

In a multiple-dose study, FenoChol 120 mg was bioequivalent to Antara 130 mg under low-fat fed conditions. Since this study used FenoChol from a pilot scale batch, the clinical pharmacology reviewer considers the study supportive rather than pivotal.

Compared with the fasted state, a high-fat meal increased the  $C_{max}$  for FenoChol by 44%. This indicates a food effect for FenoChol.

It should be noted that the average  $C_{max}$  for fenofibric acid following a single-dose of Tricor 200 (RLD for the Antara NDA) mg under high-fat conditions was 12829 ng/mL and under fasting conditions it was 3413 ng/mL. The average  $C_{max}$  for fenofibric acid following a single-dose of FenoChol 120 mg under high-fat conditions was 8266 ng/mL and under fasting conditions it was 6335 ng/mL. Given that the largest absolute value for fenofibric acid was observed with 200 mg Tricor under fed conditions, I do not believe that the increased  $C_{max}$  for FenoChol relative to Tricor under fasting conditions represents a safety concern.

All told, the results of the submitted studies indicate that Fenochol should be taken with meals. If the sponsor wants labeling that states that Fenochol can be taken without regard to meals, they would need to conduct a clinical study to demonstrate that the effects of Fenochol on lipoprotein lipid levels are similar when the drug is taken with and without food. Oscient's exclusivity on the food effect labeling would also have to expire before such language could be added to the Fenochol labeling.

With the assistance of the SEALD team, we have drafted the Fenochol labeling in PRL format. We have added important safety data from the FIELD study. All fenofibrate NDA holders will be asked to include this information in their labeling.

Dr. Golden's review adequately addresses additional regulatory issues such as DSI audits, financial disclosure information, and pediatric study requirements.

I recommend that this 505(b)(2) NDA be approved.

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Eric Colman, MD  
Deputy Director, DMEP

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Eric Colman  
8/10/2007 11:11:01 AM  
MEDICAL OFFICER

8/9/07

**Medical Officer 505(b)(2) NDA Review  
Division of Metabolism and Endocrine Products**

**NDA – 22-118**

**Name of drug – LCP-FenoChol**

**Sponsor – LifeCycle Pharma A/S**

**Date of Submission – September 29, 2006**

**PDUFA Goal Date – August 10, 2007**

**Medical Reviewer – Julie Golden, M.D.**

**BACKGROUND**

**Regulatory**

On May 12, 2006, DMEP received correspondence from LifeCycle Pharma requesting a meeting to discuss plans to submit a 505(b)(2) NDA. On June 22, 2006, the Division and the sponsor had a pre-NDA teleconference under pre-IND 73,213. The Division agreed that the proposed drug product was appropriate for a 505(b)(2) pathway, assuming there were no patent issues. Antara, the reference listed drug, has exclusivity for no food effect. The company was informed during this meeting that the Dosage and Administration section of the package insert could be silent on the food effect, and the study could be described under the Clinical Pharmacology section. There was some discussion regarding one of the excipients, poloxamer 188, to be used in doses greater than what is listed in the FDA Inactive Ingredients Guide. After the meeting, the company submitted an article supporting its safety, but the company was informed that a full review would be made only upon NDA submission. Other issues addressed during the meeting included the planned submission of stability data, the *in vivo* bioequivalence waiver for the 40 mg dose, and agreement that no additional pre-clinical and clinical studies were required.

LifeCycle Pharma submitted a 505(b)(2) NDA for fenofibrate tablets (LCP-FenoChol) in dosage strengths of 40 mg and 120 mg for the treatment of dyslipidemia on September 29, 2006. As stated above, the reference listed product is Antara™ Capsules manufactured by Oscient, approved under NDA 21-695. Of note, NDA 21-695/S-001 was approved October 20, 2005, which allowed for inclusion of efficacy data in the Clinical Studies section of the Antara label. Antara is the only fenofibrate with clinical data specific to the approved and marketed product (the label for

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the reference listed product, Tricor®, contains lipid-altering efficacy data based on clinical studies of a fenofibrate formulation that was approved in 1993 but never marketed in the United States). These clinical data also supported the approval of the statement in the Dosage and Administration section that Antara fenofibrate can be taken without regard to meals, given that Antara 130 mg under fed and fasted conditions demonstrated similar efficacy despite not finding equivalence in a PK study.

On October 5, 2006, the sponsor was informed that the NDA was unacceptable for filing because no user fee was received. On October 10, 2006, \_\_\_\_\_

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A 74-day letter was issued December 19, 2006.

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#### **Drug in study**

The chemical name of the drug substance is isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate, with a molecular formula of  $C_{20}H_{21}ClO_4$  and a molecular weight of 360.8.

The drug product is LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg. Excipients are lactose monohydrate, polyethylene glycol 6000, poloxamer 188, and magnesium stearate.

#### **Biopharmaceutical Studies Submitted to NDA 22-118**

- PK 120-04 – Single-dose BE study under fed and fasting conditions (pivotal study)
- PK 120-01 – Single-dose BE study under fed and fasted conditions (supportive study)
- PK 120-03 – Multiple-dose BE study under fed conditions (supportive study)

These studies were reviewed in detail by Dr. Sang Chung from the Office of Clinical Pharmacology.

#### **STUDY SUMMARIES**

##### ***PK 120-04***

This was an open-label, single-dose, relative bioavailability and food effect study of LCP-FenoChol 120 mg tablet and Antara 130 mg capsule. Treatments were administered under fasting and high-fat conditions. The following tables were taken from Dr. Chung's review:

LSM Ratios (LCP-FenoChol <sup>®</sup> /Antara <sup>™</sup> ) 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: LSM ratios (high fat fed/fasting) and 90% CI (red indicates out of BE criteria)		
Parameters	LCP-FenoChol <sup>®</sup> (N=36)	Antara <sup>™</sup> (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)

LCP-FenoChol 120 mg was BE to Antara 130 mg, based on fenofibric acid AUC under fasting and high-fat fed conditions and fenofibric acid C<sub>max</sub> high-fat fed conditions. However, under fasting, the C<sub>max</sub> after FenoChol administration was 46% higher than after Antara. Re-review of historical data by Dr. Chung indicates that C<sub>max</sub> after Antara administration under fasting conditions was 172% that of TriCor fasting. Although C<sub>max</sub> is generally not as clinically important a parameter as AUC when medications are administered chronically, the fact that FenoChol's C<sub>max</sub> is extrapolated as 221% that of TriCor under fasting conditions indicates that FenoChol should be taken with meals for a more reliable PK profile.

**PK 120-01**

This was a comparative bioavailability and food effect single-dose study with a pilot scale batch formulation, testing LCP-FenoChol 120 mg tablet against reference product Antara 130 mg capsule. The study design and results were similar to those of PK 120-04.

**PK120-03**

This was a multiple-dose (8 day) bioavailability study of LCP-FenoChol 120 mg tablet (pilot scale batch) against Antara 130 mg capsule under low-fat fed conditions. The results are presented in the table below (taken from Dr. Chung's review):

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- $\tau$ (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

Under the low-fat fed condition, LCP-FenoChol and Antara are bioequivalent in steady state, although given the batch and formulation, this study was considered supportive.

#### AUDITS

A DSI audit of the pivotal BE study found that \_\_\_\_\_ - the firm that conducted all the clinical pharmacology studies - failed to retain validation data for the analytical method used to measure fenofibrate concentrations and selectively reported validation data for the analytical method without justification. Nevertheless, DSI concluded that the findings should not significantly impact the outcome of the study. DMEP requested the inspection because of a lack of domestic data to support approval and in light of recent FDA inspections that found significant deficiencies at two \_\_\_\_\_ facilities in Canada.

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#### CMC

No CMC deficiencies were identified.

#### PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology deficiencies were identified. The pharm/tox review indicates that published literature provided by the sponsor support the safety of the excipient poloxamer 188.

#### FINANCIAL DISCLOSURE

The sponsor provided a signed form FDA 3454, certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

#### LABELING

FenoChol will be the first fenofibrate to be in Physician Labeling Rule format. A detailed labeling review will be conducted separately from this document. There are two issues of note with respect to the label. First, because the reviewed data do not demonstrate bioequivalence to Antara with fasting, the company will be required to include in the labeling that FenoChol must be taken with food. Second, results for the

Golden, J.  
NDA 22-118

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study have been recently published. Given that the results of other outcome trials with fibrates are included in fenofibrate labeling, FIELD should also be included. The approval of this new fenofibrate provides the opportunity for such an inclusion in a timely fashion.

### PROPRIETARY NAME

The sponsor of this NDA and Sciele, the sponsor of Triglide, have entered into a licensing agreement, and therefore the sponsor requests feedback on acceptability of the tradenames \_\_\_\_\_ is currently marketed in \_\_\_\_\_ and \_\_\_\_\_ mg doses). This reviewer thinks that the many \_\_\_\_\_ on the market will be confusing to consumers, prescribers, and pharmacists, and would recommend that another one of the suggested names \_\_\_\_\_ be considered.

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### PEDIATRIC STUDY REQUIREMENTS

The sponsor has requested a pediatric waiver for FenoChol. Justification for the waiver request, per the sponsor, includes:

1. For indication of treatment of \_\_\_\_\_ *The standard of care indicates therapy with another class of agents is more effective than fenofibrate.*
2. For indication of treatment of \_\_\_\_\_ *Pediatric population is too small to study.*

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Other approved fenofibrates (NDAs 19-304, 21-350, 21-612, 21-656, and 21-695), including the RLD, Antara (NDA 21-695), have received pediatric waivers.

This reviewer is in agreement with the request. The medical treatment of hypercholesterolemia is predominantly indicated for adults. Pediatric patients with severe hypercholesterolemia warranting intervention with drug treatment are uncommon, and represent small numbers of patients nationally. In the one indication (heterozygous familial hypercholesterolemia) that is treated medically in the pediatric population, fenofibrate has not been demonstrated to be effective; other drugs are standard-of-care in this condition.

For the indication of hypertriglyceridemia, there are very few pediatric patients who have high enough triglyceride concentration to warrant drug treatment.

### RECOMMENDATION

This reviewer recommends approval of this 505(b)(2) fenofibrate product to be taken under *fed* conditions. Labeling should reflect the PK findings and the results of the FIELD study.

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Julie Golden  
8/9/2007 09:18:15 AM  
MEDICAL OFFICER

Eric Colman  
8/9/2007 09:28:23 AM  
MEDICAL OFFICER  
Concur. Labeling should include a statement that FenoChol should  
be taken with meals