

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-118

PHARMACOLOGY REVIEW(S)

7/12/07



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-118
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 10/2/06
PRODUCT: LCP-Fenochol (fenofibrate)
INTENDED CLINICAL POPULATION: dyslipidemia
SPONSOR: LifeCycle
DOCUMENTS REVIEWED: Vol. 1, 2, 6
REVIEW DIVISION: Division of Metabolism & Endocrine Drug
Products (HFD-510)
PHARM/TOX REVIEWER: Davis-Bruno
PHARM/TOX SUPERVISOR: Davis-Bruno
DIVISION DIRECTOR: Parks
PROJECT MANAGER: Kati Johnson

Date of review submission to Division File System (DFS): 7/12/07

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APPENDIX/ATTACHMENTS ERROR! BOOKMARK NOT DEFINED.

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: approval (AP) based on 505(b)2 status of application referencing the agency's previous determination of safety for Antara NDA 21-695
- B. Recommendation for nonclinical studies: none
- C. Recommendations on labeling: none as the proposed label for nonclinical sections is identical to NDA 21-695.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings: fenofibrate is a well established anti-hyperlipemic agent based on extensive nonclinical and clinical experience. The sponsor has provided a review of published literature to support the safety of the excipients (i.e. Poloxamer 188) used in their product formulation.
- B. Pharmacologic activity: The mechanism of action is not firmly established although fenofibrate has a range of effects on synthesis and catabolism of triglycerides and cholesterol. Fibrates have been shown to modify the expression of a variety of genes involved in lipoprotein and fatty acid metabolism via PPAR α receptor activation. The major effect of fenofibrate is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. Fenofibrate inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in the rat liver. Decreased cholesterol biosynthesis may in turn enhance LDL clearance by increased LDL receptor activity and mobilization of cholesterol deposition in peripheral tissues may also occur.
- C. Nonclinical safety issues relevant to clinical use: none

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-118

Review number: 1

Sequence number/date/type of submission: 000, 10/2/06; 505(b)2 referencing NDA 21-695

Information to sponsor: Yes () No (x)

Sponsor and/or agent: LifeCycle Pharma

Manufacturer for drug substance: _____

Reviewer name: Davis-Bruno

Division name: DMEP

HFD #: 510

Review completion date: 7/12/07

b(4)

Drug:

Trade name: LCP-FenoChol

Generic name: fenofibrate

Chemical name: isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

CAS registry number: 49562-28-9

- **Chemical Structure**

- **Molecular Formula**
C₂₀H₂₁ClO₄
- **Molecular Weight**
360.8

Relevant INDs/NDAs/DMFs: NDA 21-695 (Antara); DMF _____ for _____
fenofibrate

b(4)

Drug class: antihyperlipemic

Intended clinical population: hypercholesterolemia or _____
(mixed dyslipidemia), hypertriglyceridemia _____

b(4)

Clinical formulation: note Poloxamer 188 _____
_____ Tablets in 40 and 120 mg strengths

Table 2.3.P-1: Quantitative Composition of LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg

Component	Amount (mg/Tablet)		Amount (% Composition)		Function	Reference
	40 mg Strength	120 mg Strength	40 mg Strength	120 mg Strength		
Fenofibrate	40.0 mg	120.0 mg	100%	100%	Active	USP
Lactose Monohydrate	---	---	---	---	---	NF
Polyethylene Glycol 6000	---	---	---	---	---	NF
Poloxamer 188	---	---	---	---	---	NF
Magnesium Stearate	---	---	---	---	---	NF
Total	211 mg	634 mg	100%	100%	-	-

b(4)

Route of administration: oral

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

Data reliance : Any information or data necessary for approval that LifeCycle does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that LifeCycle does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-118.

Studies reviewed within this submission: none

Studies not reviewed within this submission: N/A

Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

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2.6.2.1 Brief summary

Fenofibrate has a range of effects on synthesis and catabolism of triglycerides and cholesterol. Fibrates have been shown to modify the expression of a variety of genes involved in lipoprotein and fatty acid metabolism via PPAR α receptor activation. The major effect of fenofibrate is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. Fenofibrate inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in the rat liver. Decreased cholesterol biosynthesis may in turn enhance LDL clearance by increased LDL receptor activity and mobilization of cholesterol deposition in peripheral tissues may also occur. Decreased platelet hyper-aggregation and PDGF as well as increased esterification of cholesterol in plasma may all contribute to an inhibitory effect on atherogenesis.

2.6.2.2 Primary pharmacodynamics**2.6.2.3 Secondary pharmacodynamics****2.6.2.4 Safety pharmacology****2.6.2.5 Pharmacodynamic drug interactions****2.6.3 PHARMACOLOGY TABULATED SUMMARY****2.6.4 PHARMACOKINETICS/TOXICOKINETICS****2.6.4.1 Brief summary**

A literature review of Poloxamer 188 identified urinary excretion as the primary clearance route. Tissue distribution studies with Poloxamer 188 revealed that the highest levels were found in the kidneys, lymph nodes, liver, spleen and urinary bladder. Poloxamer 188 lacked metabolic inhibition across various cytochrome P450 isozymes in human liver microsomes.

2.6.4.2 Methods of Analysis**2.6.4.3 Absorption****2.6.4.4 Distribution****2.6.4.5 Metabolism****2.6.4.6 Excretion****2.6.4.7 Pharmacokinetic drug interactions****2.6.4.8 Other Pharmacokinetic Studies**

2.6.4.9 Discussion and Conclusions

Based on literature, Poloxamer 188 is primarily excreted in urine following IV administration to rats, dogs and humans (Grindel et al 2002). Tissue distribution studies revealed the highest levels of Poloxamer 188 were found in the kidneys, lymph nodes, liver, spleen and urinary bladder. Poloxamer 188 lacked metabolic inhibition with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4.

b(4)

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Poloxamer 188 has been used as a pharmaceutical excipient as well as for development of an IV therapeutic. A literature review has been provided by the sponsor principally in rats and dogs.

The sponsor references nonclinical safety of Antara (fenofibrate) capsules NDA 21-695 for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.2 Single-dose toxicity

The acute oral LD50 for pluronic F68 was > 15 g/kg in rat, mouse, rabbit, guinea pig and dog.

2.6.6.3 Repeat-dose toxicity

In a 12-week study in rats which were exposed to pluronic F-68 in drinking water at 5% and 10% (2857, 5714 mg/kg/day respectively)¹. At 5714 mg/kg/day, body weight gain was decreased, sugar absorption was increased and intestinal changes including mitochondria deformity, goblet cell hyper-secretion and short villi were noted. No effect was seen at 2857 mg/kg/day suggesting this is a NOEL (Rodriguez & Singer 1991).

Data from 6-month studies conducted with pluronic F-68 in rats and dogs (Carr, 1952) suggests limited potential for toxicity. Male rats were exposed to pluronic F-68 in the diet at 0, 3, 5% (~ 0, 1500, 2500 mg/kg/day)². There were no effects on weight, limited hematology assessment or gross pathology. Histopathology performed on liver, kidney, spleen, brain, adrenal, bladder, GI, pancreas, bone marrow, thyroid, heart, lymph nodes, lung, testes, salivary gland, prostate, parathyroid, pituitary, muscle) did not reveal any treatment related changes. Male dogs were administered 0, 0.05, 0.1 g/kg pluronic F-68 in gelatin capsules. Dosing did not produce adverse clinical signs, nor affect body weight, hematology or gross pathology. Histopathology (same organs assessed as in rat)

¹ 5% drinking water is equivalent to 50,000 mg/L; rats ingest 20 ml/day water (Gold et al 1984) and are ~350 g

² 3% diet is 30,000 ppm and 1ppm in the diet of a rat is ~ 0.05 mg/kg/day (WHO 1990) or 30,000 ppm X 0.05/1=1500 mg/kg/day

did not reveal any changes. In rats and dogs, the NOEL of 2500 and 100 mg/kg/day respectively was established.

Table 2.6-1: Comparison of Human and Animal Data

Species	NOEL (mg/kg/day)	Route	Duration of Treatment	Margin of Safety*
Rat	2500	Oral	6 Months	1786
Dog	100	Oral	6 Months	71
Human	1.4	Oral	--	--

* Margin of safety is calculated by dividing the animal NOEL by the human dose.

Intravenous toxicology studies with poloxamer 188 have been reported. Female rats were treated with IV doses of pluronic F-68 at 0, 10, 20, 50, 100, 200, 500 and 1000 mg/kg/day for 30 days (Magnusson et al 1086). Histopathology revealed an increased presence of mononuclear cells with foamy cytoplasm in the alveolar spaces of the lung (slight-moderate) at doses ≥ 500 mg/kg/day and dose related increases in renal cortical degenerative changes with vacuolation (minimal-slight) at ≥ 100 mg/kg/day. The lowest dose reported suggests a NOEL of 50 mg/kg/day following IV administration in the rat.

2.6.6.4 Genetic toxicology

The sponsor references nonclinical safety of Antara (fenofibrate) capsules for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.5 Carcinogenicity

The sponsor references nonclinical safety of Antara (fenofibrate) capsules for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.6 Reproductive and developmental toxicology

The sponsor references nonclinical safety of Antara (fenofibrate) capsules for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.7 Local tolerance

The sponsor references nonclinical safety of Antara (fenofibrate) capsules for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.8 Special toxicology studies

The sponsor references nonclinical safety of Antara (fenofibrate) capsules for the active ingredient. No new toxicology studies have been conducted by the sponsor relative to fenofibrate.

2.6.6.9 Discussion and Conclusions

The recommended maximal daily dose of LifeCycle's product is 120 mg. Poloxamer is present as an excipient at _____ and _____ in the 40 and 120 mg tablet strengths respectively. Based on the literature review of the Poloxamer 188 data it is concluded that these levels of Poloxamer 188 do not represent a safety risk. **b(4)**

2.6.6.10 Tables and Figures**2.6.7 TOXICOLOGY TABULATED SUMMARY****OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Conclusions: This application is a 505(b)2 NDA which references NDA 21-695 (fenofibrate; Antara). No new nonclinical studies have been conducted by LifeCycle for this application. The safety profile of fenofibrate has been well established. One of the excipients present in LifeCycle's formulation of fenofibrate, Poloxamer 188 exceeds the levels used in products previously approved in the US. The proposed drug product formulation contains levels of _____ and _____ in the 40 and 120 mg LCP-FenoChol tablets respectively. These levels are higher than the maximum levels 18 mg for oral tablet formulations listed in the FDA Inactive Ingredients Guide. A safety evaluation using published literature on Poloxamer 188 has been provided. **b(4)**

The literature review on Poloxamer 188 incorporates a risk assessment which compares the proposed exposure in the therapeutic product (100 mg/day) to the NOEL reported in the literature. This comparison suggests that the level of Poloxamer 188 is at safe levels. Toxicity findings were noted at doses ≥ 5000 mg/kg/day Poloxamer 188 which exceeds the exposure in the LifeCycle fenofibrate tablets. The recommended maximal daily dose of LifeCycle's product is 120 mg. Poloxamer is present as an excipient at _____ and _____ in the 40 and 120 mg tablet strengths respectively. Based on the literature review of the Poloxamer 188 data it is concluded that these levels of Poloxamer 188 do not represent a safety risk. **b(4)**

Unresolved toxicology issues (if any): none

Recommendations: approval

Suggested labeling: none

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/s/

Karen Davis-Bruno
7/12/2007 09:20:33 AM
PHARMACOLOGIST
AP

12/4/06

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

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA. (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? N/A 505(2)NDA

ITEM	YES	NO	COMMENT
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<p>5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?</p>			N/A
<p>6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?</p>	X		
<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>			N/A
<p>8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m² or comparative serum/plasma AUC levels?</p>	X		

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

Reviewing Pharmacologist

Supervisory Pharmacologist Davis-Bruno

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Karen Davis-Bruno
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