

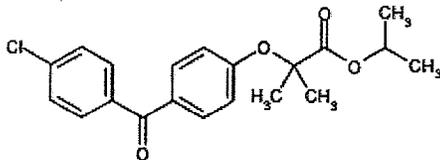
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-118

CHEMISTRY REVIEW(S)

isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate. The empirical formula is $C_{20}H_{21}ClO_4$ and molecular weight is 360.831 Da. The chemical structure is shown below:



Fenofibrate is a white to off-white crystalline powder and has only one known crystalline form. It is very soluble in _____ soluble in _____ and insoluble in water. Its melting point is 79 °C to 82 °C.

The drug substance is a chemically synthesized and well characterized product as described in the supplier's drug master file (DMF), _____ DMF _____ for fenofibrate. The proposed specifications for the drug substance, which are based on the tests and acceptance criteria in the USP and Ph. Eur. monographs, meet both USP and Ph. Eur.

Fenofibrate drug substance, manufactured and supplied by _____ is labeled _____ The retest of _____ period was based on satisfactory stability data.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product, LCP-FenoChol, is available in two strengths, 40-mg and 120-mg, as immediate release tablets for oral administration,

- The 40-mg tablets, which contain 40 mg of fenofibrate, are white to off-white oval shaped tablets, debossed "FLO", and weigh 211 mg.
- The 120-mg tablets, which contain 120 mg of fenofibrate, are white to off-white oval shaped tablets, debossed "FLH", and weigh 634 mg

The two dosage strengths are prepared from the same granulate and the tablet composition is proportional. The commercial formulation is a _____ have been used to improve drug solubility and bioavailability of low water-soluble compounds. Each 40-mg tablet core tablet contains 40 mg of fenofibrate USP (drug substance), _____ lactose monohydrate NF _____ polyethylene glycol NF _____ poloxamer 188 NF _____ and _____ magnesium stearate NF _____ for a total tablet weight of 211 mg.

b(4)

b(4)

b(4)

b(4)

b(4)

Drug product specifications include Description (appearance), Identification (active by IR and HPLC), Dissolution (Q = — at 45 minutes, USP paddle, 75 rpm, 900 mL, 0.75 % SDS), Impurities Content ————, Water Content, Microbial Testing, Assay ———— and Uniformity of Dosage Units ————

Adequate stability data was provided to support the proposed expiration dating of 24 months for 40 mg and 120 mg tablets stored in 30- and 100-count packaging configurations and 18 months for 40 mg and 120 mg tablets stored in 7-count packaging configurations under the proposed storage conditions: "Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)."

Conclusion: Drug product is acceptable.

Additional Items:

- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The applicant committed to placing at least one commercial production lot of the drug product per year on stability for each strength and package configuration following the approved stability protocol.
- The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**, pending agreement on product labeling.

Ali Al-Hakim, Ph.D.
Chief, Branch 2
Division of Pre-Marketing I
ONDQA

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/s/

Ali Al-Hakim
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CHEMISTRY REVIEW



NDA 22-118

LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg

LifeCycle Pharma

**Xavier Ysern, PhD
ONDQA/ DPAI/ Branch II**

(Clinical Review Division: DMEP)



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C. CC Block	8
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III. List of Deficiencies To Be Communicated	(none)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

1. NDA: 22-118
2. REVIEW #: 2
3. REVIEW DATE: 12-Jun-2007
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 73,213 Fenochol Tablets (includes reference to preNDA meeting)	12-May-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original:	28-Sep-2006
Amendments:	01-Jun-2007
	04-Jun-2007

7. NAME & ADDRESS OF APPLICANT:

Name: LifeCycle Pharma A/S
Address: Kogle Alle 4
2970 Horsholm
Denmark
(Primary contact: Michael Beckert, MD; Executive Vice President and Chief Operating Officer)
Representative: B&H Consulting Services, Inc.
55 North Gaston Avenue
Sommerville, NJ 08876
(Primary contact: Elizabeth N. Dupras, RAC; Project Manager)
Telephone: +45 7033 3300 fax: +45 3613 0319
USA representative: 908 704 1691 fax: 908 704 1693

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LCP-FenoChol (fenofibrate) Tablets
b) Non-Proprietary Name (USAN): Fenofibrate Tablets
c) Code Name/# (ONDC only): LF-178
d) Chem. Type/Submission Priority (ONDC only):
· Chem. Type: 5 (new formulation or manufacturer)
· Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)
(Reference listed drug product: Oscient Pharmaceuticals' Antara™ (fenofibrate) Capsules)

10. PHARMACOL. CATEGORY: Antihyperliproteinemic agent

11. DOSAGE FORM: Tablets



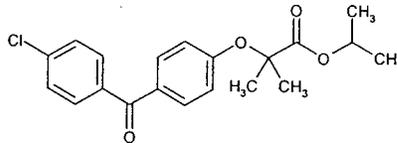
CHEMISTRY REVIEW



12. STRENGTH/POTENCY: 40 mg and 120 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fenofibrate

$C_{20}H_{21}ClO_4$
 MW: 360.831 g/mol
 CAS #: 49562-28-9



Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate
 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	LOA Date
---	---	Fenofibrate manufacture	3	Adequate		14-Sep-2006
Type III	---	---	4	Adequate		12-Oct-2005
			4	Adequate		09-Feb-2006
			4	Adequate		18-Oct-2005

¹ Action codes for DMF Table: 1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF 3 - Reviewed previously and no revision since last review 4 - Sufficient information in application
 5 - Authority to reference not granted 6 - DMF not available 7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
--	--	--

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ Comment
Biometrics	N.A.		
EES	Acceptable	16-Mar-2007	EER Summary Report Attached (see CMC Review # 1)
Pharm/Tox	N.A.		
Biopharm	Bioequivalence and adequacy of the bioequivalence waiver to be evaluated by the Office of Clinical Pharmacology		
Labeling	Labeling issues, including acceptability of the proposed trade name(s), are still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
EA	Request for categorical exclusion of an EA granted		Meet 21CFR§25.21 & §25.31(a) criteria (see CMC Review # 1)
Microbiology	N.A.		

b(4)



The Chemistry Review for NDA 22-118

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application can be APPROVED. Based on the stability data submitted, an expiry of 24 months for 40 mg and 120 mg tablets in 30- and 100-count packaging configurations and of 18 months for 40 mg and 120 mg tablets in 7-count packaging configurations is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance fenofibrate (USAN, INN) is a prodrug and after absorption it is rapidly and completely metabolized by tissue and plasma esterases to the major and active metabolite fenofibric acid. Fenofibrate is poorly soluble in water and the oral bioavailability of fenofibrate is dependent on the formulation. The chemical name of fenofibrate is isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate. The empirical formula is C₂₀H₂₁ClO₄ and its molecular weight is 360.831 Da.

Fenofibrate is white to off-white crystalline powder and stable under ordinary conditions. It is very soluble in _____, soluble in _____ and insoluble in water. Fenofibrate has no chiral center and only one known crystalline form. The melting point is 79 °C to 82 °C.

b(4)

The drug substance is well characterized and described in the supplier's drug master file (DMF), _____ DMF _____ for fenofibrate. Fenofibrate is described in the United States Pharmacopeia (USP) and the European Pharmacopoeia (Ph. Eur.). Ph. Eur. and USP monographs for fenofibrate are very similar, drug substance batches tested according to Ph. Eur. requirements also meet USP requirements. The proposed specifications for the drug substance, which are based on the tests and acceptance criteria in the USP and Ph. Eur. monographs, meet both USP and Ph. Eur.

b(4)

Fenofibrate drug substance manufactured and supplied by _____ is labeled _____
_____. The retest period is _____.

b(4)

Drug Product

The drug product, LCP-FenoChol (fenofibrate) Tablets, is proposed to be commercialized in two dosage strengths 40-mg and 120-mg immediate release non-coated tablets for oral administration. Each 40-mg tablet core contains 40 mg of fenofibrate (drug substance), _____ lactose monohydrate _____, _____ polyethylene glycol _____, poloxamer 188 _____, and _____ magnesium stearate _____. All components meet compendial requirements. The two dosage strengths are prepared from the same granulate and the tablet composition is proportional. Although the tablets are white to off white oval shaped, the two different strengths are easily distinguished by size and debossing. The 40 mg strength tablets have a total weight of 211 mg, and are debossed "FLO". The 120 mg strength tablets weight 634 mg and are debossed "FHI".

b(4)

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry- 1



Drug product specifications include Description (appearance) Identification (active by IR and HPLC), Dissolution, Impurities Content _____, Water Content, Microbial Testing, Assay: _____, and Uniformity of Dosage Units _____. Although LCP-FenoChol (fenofibrate) Tablets' specifications do not differ appreciable from those for other Fenofibrate Tablets and Capsules currently available in the market, the acceptance criteria for Single Unknown Impurities and for Dissolution are requested to be tightened (current ICH recommendations).

b(4)

Stability studies include photostability data (one lot of each strength) and primary stability data from 6 batches, (three of each strength), packaged in tablet fill counts (7, 30, and 100), in the two bottle sizes _____, stored at controlled room temperature ($25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/60\text{ } \% \text{RH} \pm 5\text{ } \% \text{RH}$), stress and accelerated conditions ($30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/65\text{ } \% \text{RH} \pm 5\text{ } \% \text{RH}$ and $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\text{ } \% \text{RH} \pm 5\text{ } \% \text{RH}$, respectively). Although the primary stability study is still ongoing, up to 12 months of stability data is provided under controlled (long term) and stress conditions, and up to 6 months under accelerated conditions. Testing of stability indicating parameters (Description, Assay, Degradation Products and Dissolution) in the primary stability study are carried out under a matrix protocol. Although the current available data confirms the remarkable stability of the fenofibrate tablets regarding degradation, the solubility properties of the drug matrix in the tablets are adversely affected by exposure to high temperatures and departures from the dissolution acceptance criteria are seen at the accelerated condition $40\text{ }^{\circ}\text{C}/75\text{ } \% \text{RH}$. Based on the provided stability data, as requested by the applicant, an expiry dating of an expiry of 24 months for 40 mg and 120 mg tablets in 30- and 100-count packaging configurations and of 18 months for 40 mg and 120 mg tablets in 7-count packaging configurations is granted under the proposed storage conditions: "Store at $25\text{ }^{\circ}\text{C}$ ($77\text{ }^{\circ}\text{F}$); excursions permitted to $15\text{-}30\text{ }^{\circ}\text{C}$ ($59\text{-}86\text{ }^{\circ}\text{F}$) [see USP Controlled Room Temperature]."

b(4)

B. Description of How the Drug Product is Intended to be Used

LCP-FenoChol (fenofibrate) Tablets, _____, 40 mg, are intended for oral usage. LCP-FenoChol Tablets are indicated as 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 _____. LCP-FenoChol (fenofibrate) Tablets, _____, 40 mg, are also indicated as adjunctive therapy for treatment of adult patients with hypertriglyceridemia: _____. The proposed indications are the same indications listed for the marketed product Antara™ (fenofibrate) Capsules, which is the reference listed drug product.

b(4)

LCP-FenoChol (fenofibrate) Tablets are supplied in _____ bottles (7, 30 and 100 count) with tamper-evident seals and child-resistant closures. Storage is at $25\text{ }^{\circ}\text{C}$ ($77\text{ }^{\circ}\text{F}$) Excursions permitted to $15\text{ - }30\text{ }^{\circ}\text{C}$ ($59\text{ - }86\text{ }^{\circ}\text{F}$) [see USP Controlled Room Temperature]. The expiration dating period is 24 months in 30- and 100-count packaging configurations and of 18 months in 7-count packaging configurations

b(4)

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow an evaluation of the quality of both drug substance (DS) and drug product (DP). LCP-FenoChol (fenofibrate) Tablets manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by the compliance to their proposed specifications, to assure their quality throughout their granted shelf live. The Agency concerns, which pertained to the drug product specifications (see CMC Review # 1), have been satisfactorily addressed by the applicant. An expiry dating of 24 months for 40 mg and 120 mg tablets in 30- and 100-count packaging configurations and of 18 months for 40 mg and 120 mg tablets in 7-count packaging configurations is granted under the recommended storage conditions: "Store at $25\text{ }^{\circ}\text{C}$ ($77\text{ }^{\circ}\text{F}$); excursions permitted to $15\text{-}30\text{ }^{\circ}\text{C}$ ($59\text{-}86\text{ }^{\circ}\text{F}$) [see USP Controlled Room Temperature]."



III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Chemist, ONDQA/ DPA I/ Branch II

See appended electronic signature page.

B. Endorsement Block

Blair Fraser, PhD Director, ONDQA/ DPA I

C. CC Block

Kati Johnson R.Ph./ Supervisory Regulatory Project Manager

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Xavier Ysern
6/12/2007 04:00:07 PM
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Blair Fraser
6/13/2007 05:34:02 AM
CHEMIST

5/17/07



CHEMISTRY REVIEW



NDA 22-118

LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg

LifeCycle Pharma

**Xavier Ysern, PhD
ONDQA/ DPAI/ Branch II**

(Clinical Review Division: DMEP)

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

1. NDA: 22-118
2. REVIEW #: 1
3. REVIEW DATE: 17-May-2007
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 73,213 Fenochol Tablets (includes reference to preNDA meeting)	12-May-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	28-SEP-2006

7. NAME & ADDRESS OF APPLICANT:

Name: LifeCycle Pharma A/S
Address: Kogle Alle 4
2970 Horsholm
Denmark
(Primary contact: Michael Beckert, MD; Executive Vice President and Chief Operating Officer)
Representative: B&H Consulting Services, Inc.
55 North Gaston Avenue
Sommerville, NJ 08876
(Primary contact: Elizabeth N. Dupras, RAC; Project Manager)
Telephone: +45 7033 3300 fax: +45 3613 0319
USA representative: 908 704 1691 fax: 908 704 1693

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LCP-FenoChol (fenofibrate) Tablets
b) Non-Proprietary Name (USAN): Fenofibrate Tablets
c) Code Name/# (ONDC only): LF-178
d) Chem. Type/Submission Priority (ONDC only): - Chem. Type: 5 (new formulation or manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)
(Reference listed drug product: Oscient Pharmaceuticals' Antara™ (fenofibrate) Capsules)

10. PHARMACOL. CATEGORY: Antihyperliproteinemic agent

11. DOSAGE FORM: Tablets



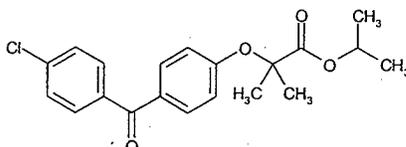
CHEMISTRY REVIEW



12. STRENGTH/POTENCY: 40 mg and 120 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fenofibrate

$C_{20}H_{21}ClO_4$
 MW: 360.831 g/mol
 CAS #: 49562-28-9



Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate
 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	LOA Date
Type II	[Redacted]	Fenofibrate manufacture	3	Adequate		14-Sep-2006
Type III	[Redacted]	[Redacted]	4	Adequate		12-Oct-2005
	[Redacted]	[Redacted]	4	Adequate		09-Feb-2006
	[Redacted]	[Redacted]	4	Adequate		18-Oct-2005

¹ Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF 3 – Reviewed previously and no revision since last review 4 – Sufficient information in application
 5 – Authority to reference not granted 6 – DMF not available 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
--	--	--

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ Comment
Biometrics	N.A.		
EES	Acceptable	16-Mar-2007	EER Summary Report Attached
Pharm/Tox	N.A.		
Biopharm	Adequacy of the bioequivalence waiver		
Labeling	Labeling issues, including acceptability of the proposed trade name, are still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
EA	Request for categorical exclusion of an EA granted		Meet 21CFR§25.21 & §25.31(a) criteria
Microbiology	N.A.		

b(4)



The Chemistry Review for NDA 22-118

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is APPROVABLE pending a satisfactory response to the Agency request regarding the acceptance criteria for drug product Single Unknowns Impurities and for Dissolution. Based on the stability data submitted, an expiry of _____ is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance fenofibrate (USAN, INN) is a prodrug and after absorption it is rapidly and completely metabolized by tissue and plasma esterases to the major and active metabolite fenofibric acid. Fenofibrate is poorly soluble in water and the oral bioavailability of fenofibrate is dependent on the formulation. The chemical name of fenofibrate is isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate. The empirical formula is C₂₀H₂₁ClO₄ and is molecular weight is 360.831 Da.

Fenofibrate is white to off-white crystalline powder and stable under ordinary conditions. It is very soluble in _____, soluble in _____, and insoluble in water. Fenofibrate has no chiral center and only one known crystalline form. The melting point is 79 °C to 82 °C.

b(4)

The drug substance is well characterized and described in the supplier's drug master file (DMF), _____, for fenofibrate. Fenofibrate is described in the United States Pharmacopeia (USP) and the European Pharmacopoeia (Ph. Eur.). Ph. Eur. and USP monographs for fenofibrate are very similar, drug substance batches tested according to Ph. Eur. requirements also meet USP requirements. The proposed specifications for the drug substance, which are based on the tests and acceptance criteria in the USP and Ph. Eur. monographs, meet both USP and Ph. Eur.

b(4)

Fenofibrate drug substance manufactured and supplied by _____ is labeled _____
_____ The retest period is: _____

b(4)

Drug Product

The drug product, LCP-FenoChol (fenofibrate) Tablets, is proposed to be commercialized in two dosage strengths 40-mg and 120-mg immediate release non-coated tablets for oral administration. Each 40-mg tablet core tablet contains 40 mg of fenofibrate (drug substance), _____ lactose monohydrate _____ polyethylene glycol _____, _____ poloxamer 188 _____, and _____ magnesium stearate _____. All components meet compendial requirements. The two dosage strengths are prepared from the same granulate and the tablet composition is proportional. Although the tablets are white to off white oval shaped, the two different strengths are easily distinguished by size and debossing. The 40 mg strength tablets have a total weight of 211 mg, and are debossed "FLO". The 120 mg strength tablets weight 634 mg and are debossed "FHI".

b(4)

b(4)



CHEMISTRY REVIEW



[Redacted content]

b(4)

Drug product specifications include Description (appearance), Identification (active by IR and HPLC),
Dissolution, Impurities Content

b(4)



III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Chemist, ONDQA/ DPA I/ Branch II Date: 17-May-2007

See appended electronic signature page.

B. Endorsement Block

Blair Fraser, PhD Director, ONDQA/ DPA I

C. CC Block

Kati Johnson R.Ph./ Supervisory Regulatory Project Manager

48 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Xavier Ysern
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Blair Fraser
5/17/2007 04:30:39 PM
CHEMIST

12/4/06

Initial Quality Assessment

OND Division of Metabolism and Endocrinology Products

NDA: 22-118

Applicant: LifeCycle Pharma

Stamp Date: 29-SEP-2006 (user fee received on 10-OCT-2006)

PDUFA Date: 10-AUG-2007

Proposed Proprietary Name: LCP-Fenochol (fenofibrate) Tablets

Established Name: fenofibrate

Dosage form and strength: tablets of 40 mg and 120 mg

Route of Administration: oral

Indications: adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, and Apo b, and to increase HDL-C in adults with primary hypercholesterolemia or mixed dyslipidemia.

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer

Time goals:

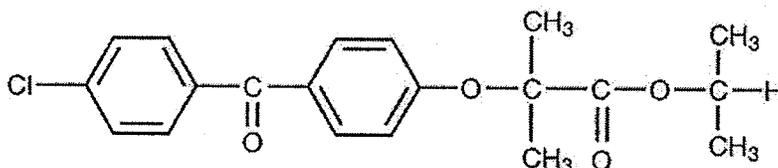
- IQA/Chemistry filing memo in DFS: by 9-DEC-2006
- Chemistry Review (DR/IR) letter if applicable: by 10-MAR-2007
- Final Chemistry Review "Month 8" in DFS: by 10-JUN-2007
- PDUFA: 10-AUG-2007

Initial Quality Assessment

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	Assessment of the biowaiver request for the 40 mg strength based on dissolution profiles. See Pre-NDA meeting minutes.
CDRH	<i>May not be applicable</i>
EA	Categorical exclusion request to be assessed by Primary Reviewer
EES	Sent to Office of Compliance on 31-OCT-2006.
DMETS	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	To be assessed by Primary Reviewer.
Microbiology	<i>May not be applicable</i>
Pharm/Tox	Assessment of high quantities of excipients Poloxamer 188 and polyethylene glycol 600 in the product composition. See Pre-NDA meeting minutes.

Summary:

- This is a paper NDA. The associated IND is IND 73,213. The NDA is filed as a 505(b)(2) application.
- The drug substance is fenofibrate USP/EP. Reference is made to DMF _____ for all CMC information on the drug substance.



- The drug product is an immediate release tablet in 40 mg and 120 mg strengths for once-a-day dosing. Both tablets are manufactured from the same final blend (i.e., the strengths are dose proportional). The commercial formulation is a _____ used to increase the bioavailability of this drug substance with low solubility in water. Polyethylene glycol 6000: _____, and lactose monohydrate: _____. Tablets are formulated by _____, polyethylene glycol 6000 at _____, poloxamer 188. Note that the melting point of the drug substance is 79-82 °C. _____

LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg are white to off white oval tablets. The 40 mg strength is debossed "FLO" and has a tablet weight of approximately 211 mg. The 120 mg strength is debossed "FHI" and has a tablet weight of approximately 634 mg. The composition of the drug product is provided in Table 2.3.P-1.

Initial Quality Assessment

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	—	—	Active	USP
Lactose Monohydrate	—	—	—	—	—	NF
Polyethylene Glycol 6000	—	—	—	—	—	NF
Poloxamer 188	—	—	—	—	—	NF
Magnesium Stearate	—	—	—	—	—	NF
Total	211 mg	634 mg	100%	100%	—	—

- Container closure systems for product distribution:

LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg will be supplied in _____ or _____ containers with tamper-evident aluminum inner seals and child-resistant _____ closures as indicated in Table 2.3.P-2.

Table 2.3.P-2: Container Closure Systems for LCP-FenoChol (fenofibrate) Tablets, 40 mg and 120 mg

Presentation	Bottle	Closure	Inner Seal
40 mg, 7-count	—	—	Tamper-Evident Aluminum
40 mg, 30-count	—	—	Tamper-Evident Aluminum
40 mg, 100-count	—	—	Tamper-Evident Aluminum
120 mg, 7-count	—	—	Tamper-Evident Aluminum
120 mg, 30-count	—	—	Tamper-Evident Aluminum
120 mg, 100-count	—	—	Tamper-Evident Aluminum

- Shelf life: A _____ shelf life at room temperature is proposed, based on _____ long-term, accelerated, and intermediate data. The stability program is per ICH guidelines. Each dosage strength has 3 commercial-scale and commercial-formulation (including debossing) batches, each packaged in 3 bottles for 7-count, 30-count and 100-count. A matrix design is used for the _____

Initial Quality Assessment

- Batches of interest:

Function	Packaging	Batch number
120 mg Biobatch (pivotal clinical study PK 120-04)	Unknown	0600418
40 mg Primary stability	7-count bottle	306019, 306016, 306022
	30-count bottle	306018, 306015, 306021
	100-count bottle	306017, 306014, 306020
120 mg Primary stability	7-count bottle	306007 (=biobatch 0600418), 306010, 306013
	30-count bottle	306006 (=biobatch 0600418), 306009, 306012
	100-count bottle	306005 (=biobatch 0600418), 306008, 306011

Critical Issues (this is not an exhaustive list of critical issues. See Chemistry Review by Primary Reviewer for additional critical issues):

- Has all information requested during the IND phases, and at the pre-NDA meetings been included?

YES

Pre-NDA chemistry comments were conveyed to the sponsor on 22-JUN-2006 (refer to meeting minutes in DFS). The applicant includes information in the NDA to address these issues discussed at the meeting:

- High quantities of excipients Poloxamer 188 and polyethylene glycol in the product composition will be addressed by the Pharm.Tox. review team.
 - Primary 6-month stability data are included in the NDA for long-term, accelerated, and intermediate conditions. The stability program is per ICH guidelines.
 - is included in the primary stability study.
- The most recent review (Chem. Rev. of DMF for the drug substance fenofibrate USP on 17-FEB-2005 found it adequate for a different approved drug product. The primary review will evaluate any new (not yet reviewed) amendment and annual report submitted to this DMF.
- During process development, particle size in the range of was found to be important to product processability. Instead of testing for the size distribution, the applicant proposes as critical process controls these parameters that affect the particle size:

The primary reviewer will evaluate the adequacy of this proposal as supported by reports such as " and "
- No uniformity testing is performed to ensure the homogeneity of the drug substance in the. The primary reviewer will evaluate the adequacy of this proposal as supported by reports such as
- The primary reviewer may seek input on Dissolution from the Clin. Pharm. review team because
- Because of the poor aqueous solubility of fenofibrate, the process is used in the manufacture of the drug product in order to improve dissolution and bioavailability. This process

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3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Initial Quality Assessment

CHEMISTRY NDA FILEABILITY CHECKLIST NDA 22-118 (fenofibrate) tablets 40 mg and 120 mg

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			Not applicable.

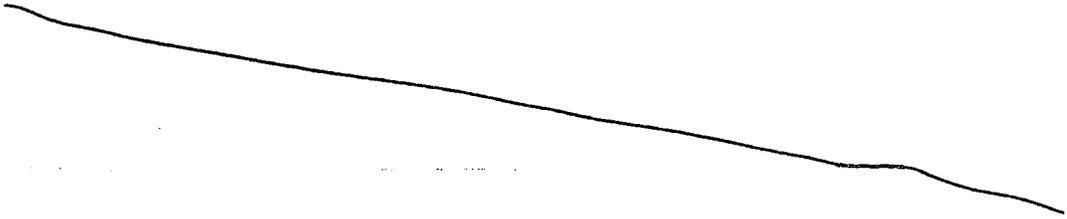
Comments for the 74-day letter:

- We note your acknowledgment that dissolution of the 40 mg strength packaged in the 7-count bottle shows significant decreasing trend during the stability study under the accelerated conditions (40 °C/75% RH). In addition, available stability data appear to show that this trend also occurs, to the same or a lesser extent, in the 40 mg strength packaged in the 30-count and 100-count bottles and in the 120 mg strength packaged in all three bottle presentations, under all stability storage conditions. While the results may be within your proposed dissolution acceptance criteria of $Q = \text{---}$, at 45 minutes, the regulatory criteria will be finalized as part of FDA's review of the NDA, and be advised that this time point may not be adequately discriminating because the earlier time points may show more significant changes in dissolution with respect to storage time under all stability conditions. Because dissolution is shown to be an attribute critical to the performance of the product, and a decreasing trend in dissolution is observed during the stability study that has a matrix design, an extrapolation of shelf life beyond the period covered by long-term data may not be appropriate.

b(4)

Initial Quality Assessment

- Clarify your statement regarding the head-space volume of the 7-count bottle being a possible cause for the decreasing trend in dissolution. If the head-space volume of the 7-count bottle is a stability issue, then the stability of the product in the open larger-count bottles (i.e., during patient use) should present concerns.



b(4)

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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

/s/

Suong Tran
12/4/2006 11:35:31 AM
CHEMIST

paper sign-off 11/8/6

Blair Fraser
12/4/2006 04:06:06 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22118/000 Sponsor: LIFECYCLE PHARMA A/S
 Org Code : 510 NO CITY, , XX
 Priority : 5

Brand Name : LCP FENOCHOL TABS. 40MG,120MG.
 Stamp Date : 29-SEP-2006 Estab. Name:
 PDUFA Date : 10-AUG-2007 Generic Name: FENOFIBRATE
 Action Goal : Dosage Form: (TABLET)
 District Goal: 11-JUN-2007 Strength : 40 MG AND 120 MG

FDA Contacts: K. JOHNSON Project Manager 301-796-1234
 X. YSERN Review Chemist 301-796-2410
 S. TRAN Team Leader 301-796-1764

Overall Recommendation: ACCEPTABLE on 16-MAR-2007by S. FERGUSON(HFD-322) 301-827-9009

Establishment : CFN : _____ FEI : _____

DMF No: AADA:

Responsibilities: _____

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 08-NOV-06
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

b(4)

b(4)

Establishment : CFN : _____

FEI : _____

b(4)

JMF No:

AADA:

Responsibilities: _____

b(4)

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-OCT-06

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : _____

FEI : _____

b(4)

JMF No:

AADA:

Responsibilities: _____

b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TCM OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 16-MAR-07
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : _____ FEI : _____

(Handwritten mark)

b(4)

DMF No: _____ AADA:

Responsibilities: _____

b(4)

Profile : CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 16-NOV-06
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION