

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-612

CHEMISTRY REVIEW(S)

**Lipofen (fenofibrate) capsules
NDA 21-612**

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Cipher Pharmaceuticals, Ltd
Suite 201
Lauriston, Collymore Rock
St. Michaels, Barbados

Indication: Treatment of type IV and V hypercholesterolemia

Presentation: 50 mg, 100 mg, 150 mg hard gelatin capsules

EER Status: Acceptable for all sites 15-DEC-2005

Consults: Pharm/Tox – Adequate
Biopharm - Acceptable
Methods Validation – Methods Validation package requested

Original Submission: 24-DEC-2002

Post-Approval Agreements:

No Post-Approval Agreements for CMC information have been proposed.

Drug Substance:

Bulk drug substance is Fenofibrate, EP. Fenofibrate is a non-chiral, crystalline material with no polymorphic forms. The compound is nearly insoluble in water at pH 1-10, but is soluble in polar organic solvents and short chain alcohols. The supplier is _____ and the CMC information is supplied in DMF _____. The application's acceptance specification is EP monograph plus tests for appearance and residual isopropanol. Data supports the proposed acceptance criteria; low levels of impurities are observed. A _____ stability study indicates that bulk drug substance in solution is sensitive to hydrolysis, near-UV light and oxidation. The solid material is stable for 60 months at room temperature.

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Conclusion: Drug substance is acceptable.

Drug Product:

Drug product is _____

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contained in a standard hard gelatin (HG) capsule. The matrix includes components: Gelucire® 44/14, / _____, PEG 20,000, NF; PEG 8000, NF; Hydroxypropylcellulose, NF; and Sodium Starch Glycolate, NF. The hard gelatin capsule contains the solidified matrix. The dissolution mechanism is described as / _____

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_____ Thermal analysis studies
establish tha^t _____

b(4)

Conclusion: Drug product is satisfactory.

Additional Items:

- The product presents no microbiology issues.
- All supporting DMFs are adequate for their intended purpose.
- TSE issues for HG capsules are satisfactorily addressed.
- All listed manufacturing and control sites are in GMP compliance.
- There are no comparability protocols.

-The sponsor has adequately responded to all CMC labeling comments. The package insert and container cartons are acceptable from chemistry standpoint. However, it should be noted that the firm's currently proposed trade name, Lipofen, was not recommended by the Office of Drug Safety (ODS). Incidentally, one of the firm's previously proposed trade names, Luxacor, was found acceptable by ODS.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**

/s/

Blair Fraser
1/3/2006 07:34:20 AM
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NDA 21-612

LIPOFEN
[Fenofibrate Capsules]

Cipher Pharmaceutical, Ltd.

William M. Adams
Office of New Drug Quality Assessment
(ONDQA)

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Chemistry Review Data Sheet

1. NDA 21-612
2. REVIEW #3
3. REVIEW DATE: 06-Dec-2005
4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N-000	24-Dec-2002
N-000 (AZ)	30-Mar-2004
N-000 (BC)	14-May-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N-000 (BZ)	30-Nov-2004
N-000 (AZ)	04-Jul-2005
N-000 (C)	19-Oct-2005
N-000 (BL)	15-Dec-2005

7. NAME & ADDRESS OF APPLICANT:

Name	Cipher Pharmaceuticals, Ltd
	Suite 201
Address	Lauriston, Collymore Rock St. Michaels, Barbados Arthur M. Duboeck Galephar PR, Inc.
Representative	Road 198, No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873, PR
Telephone	(787) 713-0340
FAX	(787) 713 0344

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lipofen
- b) Non-Proprietary Name (USAN): Fenofibrate Capsules
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only): 5P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

10. PHARMACOLOGICAL CATEGORY: type IV and V hypercholesterolemia

11. DOSAGE FORM: HG capsule

12. STRENGTH/POTENCY: 50,100,150 mg

13. ROUTE OF ADMINISTRATION: oral, immediate release

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

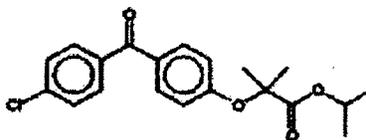
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula/Weight : C₂₀H₂₁ClO₄; 360.8 awu

Molecular Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	---	---
					Adequate	pending	IR request AR
					N/A	---	---
					Adequate	20-May-2003	CMC #4
					Adequate	May-2004	---
					Adequate	May-2004	---

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:

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Document	Application Number	Description
IND	62,780	bioequivalence studies for the proposed dosage form and Tricor® tablets

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Acceptable for all sites	12/15/05	OC conclusion based on inspections
Pharm/Tox	Adequate	May-2004 review	I.Antonipillai
Biopharm	Acceptable with comments	05/13/04 review	W.Qui
DMETS	"CIP Fenofibrate" rejected "Luxacor" accepted _____ rejected "Lipofen" rejected	07/25/03 review 10/21/03 review 03/19/04 review 12/16/05 review	C.Hoppes A.Mahmad K.Culley D.Toyer
Methods Validation	MV package submitted	---	M.Adams
EA	N/A	---	---
Microbiology	N/A	---	---

b(4)

19. ORDER OF REVIEW : N/A

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Chemistry Review for NDA 21-612

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The submitted CMC information is now complete and adequate to support APPROVAL (AP) of the proposed new drug application.

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

No phase 4 commitments for CMC information have been proposed in the NDA.

II. Summary of Chemistry Assessments

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

This is a 505(b)(2) submission for 50mg, 100mg and 150mg Fenofibrate capsules as a new oral, immediate release formulation in 30-count and 90-count bottles for the treatment of hyperlipidemia and hypertriglyceridemia in adults.

The proposed product is claimed to be bioequivalent to Tricor[®] and Lipidil Supra[®] tablets. Bioequivalence trials are addressed in IND 62,780. While Tricor[®] and Lipidil Supra[®] use a micronized drug substance/dispersant matrix to enhance the bioavailability of the water insoluble drug, the proposed formulation uses

The proposed formulation was developed by Galephar Puerto Rico, Inc and is addressed by patent 5,545,628.

DRUG PRODUCT

The proposed drug product is contained in a standard hard gelatin (HG) capsule. The matrix includes 5 components. Gelucire[®] 44/14,

The dissolution mechanism is described as Thermal analysis studies establish that

Galephar Puerto Rico Inc (Juncos, Puerto Rico) is proposed for drug product manufacture and control. The manufacturing process consists of

The market package is a

Example executed batch records (EBR) which match the proposed master production records are provided for the clinical lots of each proposed strength as well as for 200mg capsules which were used in the bioequivalence studies. Blend lots were used to prepare encapsulation lots and packaging lots

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CHEMISTRY REVIEW



Chemistry Assessment Section

B. Endorsement Block

M.Adams/ONDQA/CMC Reviewer
S.Moore/ONDQA/PAL

C. CC Block

M.Simoneau/DMEP/PM
B.Fraser/ONDQA/Chief Branch II
R.Lostritto/ONDQA/Dir DPME I

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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Mike Adams
12/22/2005 03:59:58 PM
CHEMIST

Stephen Moore
12/22/2005 05:03:49 PM
CHEMIST

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5/21/04



NDA 21-612

LUXACOR
[Fenofibrate Capsules]

Cipher Pharmaceutical, Ltd

William M. Adams
Division of Metabolism and Endocrine Drug Products
HFD-510

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Chemistry Review Data Sheet

1. NDA 21-612
2. REVIEW #2
3. REVIEW DATE: 20-May-2004
4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed
N-000

Document Date
24-Dec-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
N-000 (BC)
N-000 (BC)

Document Date
30-Mar-2004
14-May-2004

7. NAME & ADDRESS OF APPLICANT:

Name	Cipher Pharmaceuticals, Ltd
	Suite 201
Address	Lauriston, Collymore Rock St. Michaels, Barbados Arthur M. Duboeck Galephar PR, Inc.
Representative	Road 198, No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873, PR
Telephone	(787) 713-0340
FAX	(787) 713-344

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Luxacor
- b) Non-Proprietary Name (USAN): Fenofibrate Capsules
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chemical. Type: 3
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: type IV and V hypercholesterolemia

Chemistry Review Data Sheet

11. DOSAGE FORM: HG capsule
12. STRENGTH/POTENCY: 50,100,150. ~~5~~mg
13. ROUTE OF ADMINISTRATION: oral, immediate release
14. Rx/OTC DISPENSED: Rx

b(4)

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

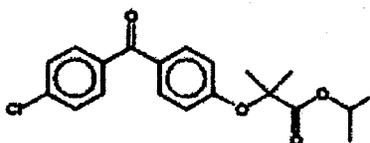
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula/Weight : C₂₀H₂₁ClO₄; 360.8 awu

Molecular Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	---	---
					Adequate	pending	IR request AR
					N/A	---	---
					Adequate	20-May-2003	CMC #4
					Adequate	May-2004	---
					Adequate	May-2004	---

b(4)

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

IND	62,780	bioequivalence studies for the proposed dosage form and Tricor [®] tablets
-----	--------	---

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Acceptable for all sites	11/25/03	OC conclusion based on inspections
Pharm/Tox	Adequate	May-2004 review	I.Antonipillai
Biopharm	Acceptable with comments	05/13/04 review	W.Qui
DMETS	Trade Name accepted	10/30/03 review	A.Mahmud
Methods Validation	MV package submitted	---	M.Adams
EA	N/A	---	---
Microbiology	N/A	---	---

19. ORDER OF REVIEW : N/A

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Chemistry Review for NDA 21-612

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information has been reviewed and found to be satisfactory, therefore I recommend that the application be APPROVED (AP).

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

No phase 4 commitments for CMC information have been proposed in the NDA.

II. Summary of Chemistry Assessments

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

The NDA is a 505(b)(2) submission for 50mg, 100mg, 150mg _____ Fenofibrate as a new oral, immediate release formulation in _____, 30-count and 90-count bottles for the treatment of hyperlipidemia and hypertriglyceridemia in adults. The proposed product is claimed to be bioequivalent to Tricor[®] and Lipidil Supra[®] tablets. Bioequivalence trials are addressed in IND 62,780. While Tricor and Lipidil Supra use a micronized API/dispersant matrix to enhance the bioavailability of the water insoluble drug, the proposed formulation uses _____

_____ The proposed formulation was developed by Galephar Puerto Rico, Inc and is covered by patent #5,545,628.

The proposed bulk drug substance is Fenofibrate, EP (European Pharmacopeia). There is no USP monograph for this material. Fenofibrate is a non-chiral, crystalline material that does not form polymorphs and is nearly insoluble in water at pH 1-10. It is soluble in polar organic solvents and in short chain alcohols. The supplier is _____, with type _____ DMF _____. The NDA acceptance specifications are EP monograph plus appearance and residual IPA. A validated _____ HPLC method is used for assay and impurity analysis. A validated _____ GC method is used for residual solvent analysis. Example data is provided to support the proposed acceptance criteria; low levels of _____ are observed. A _____ stability study indicates that bulk drug substance in solution is sensitive to hydrolysis, nearUV light and oxidation and the solid material is stable for 60 months at room temperature.

The proposed drug product is _____ and contained in a standard HG capsule. The matrix includes _____ components. Gelucire[®] 44/14 _____



CHEMISTRY REVIEW



Chemistry Assessment Section

The dissolution mechanism is described as

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DTA studies are provided to establish that Gelucire®

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Galephar Puerto Rico Inc (Juncos, PR) is proposed for drug product manufacture and control. The manufacturing process consists

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Differing amounts of a single blend formulation is filled into differing sized capsules to obtain the various strengths. There are no overages. The market package is a white

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The application proposes unit commercial lots for each capsule strength. Example executed batch records (EBRs) which match the proposed master production records are provided for the clinical lots of each proposed strength as well as for the 200mg capsules which were used in the bioequivalence studies. blend lots, were used to prepare encapsulation lots and packaging lots. Process validation data for blending, encapsulation and packaging of the EBR lots is also provided. These lots were used for the bioequivalence and stability studies.

b(4)

Product release specifications are presented in two parts; chemical testing of bulk capsules and inspection of packaged product. Identity, assay and impurity analyses use a validated -HPLC method whose mobile phase differs from that used for drug substance analysis. Content uniformity and dissolution analyses use a validated UV absorbance assay method. As there is no in vivo model for bioavailability, the dissolution medium was developed empirically. The dissolution criterion and procedure accepted by the Division of Biopharmaceutics is Q= in 120 minutes with USP paddle at 75 rpm and pH 6.8 buffer with 0.1% Pancreatin plus 2% Tween 80. The criterion is based on the USP monograph for Clofibrate since there is no USP monograph for fenofibrate capsules and its EP monograph does not include dissolution. The method validation studies include stress degradation of bulk drug substance and capsule fill material which conclude that drug product degradation parallels that for drug substance; sensitivity to light, oxidation and hydrolysis in solution. An ICH stability protocol and study are provided to support the proposed label storage statement at USP CRT. Draft package insert and bottle labels for the 30-count and 90-count packaging configuration are provided. Revisions have been requested in the print size for the trade and established name on the bottle labels.

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b(4)

The application presents no microbiology issues. All supporting DMFs are adequate for their intended purpose. TSE issues for are satisfactorily addressed by the COA. No other material presents TSE issues. All listed manufacturing and control sites are in GMP compliance. There are no comparability protocols.

b(4)



CHEMISTRY REVIEW



Chemistry Assessment Section

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

The proposed drug product is provided as 50mg, 100mg, 150mg _____ oral, immediate release HG capsules in _____ 30-count or 90-count package. The drug is indicated for the treatment of hyperlipidemia and hypertriglyceridemia in adults; there is no pediatric dosing information in the package insert. The patients are to be placed on a lipid lowering diet for the duration of the 4-8 weeks of treatment. Dosing is typically 50mg-_____ initially, then adjustments are made according to patient need and tolerance. Doses are taken with the meal to enhance fenofibrate absorption. _____ The product in its market package is stated to be stable for _____ are USP CRT.

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C. Basis for Approvability or Not-Approval Recommendation

With respect to CMC information, the application can be APPROVED in that complete and acceptable information has been provided. The firm is requested to revise the print size for the established name and trade name on the final printed bottle labels.

III. Administrative

A. Reviewer's Signature

William M. Adams, CMC Reviewer, HFD-510

B. Endorsement Block

M.Adams/CMC Reviewer/20-May-2004

S.Moore/CMC TL

V.Jimenez/PM

C. CC Block

E.Duffy/DNDC II Dir

B.Fraser/DNDC II Dep Dir

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Mike Adams
5/20/04 04:07:20 PM
CHEMIST

Stephen Moore
5/21/04 02:05:42 PM
CHEMIST

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12/2/03



CHEMISTRY REVIEW



NDA 21-612

**LUXACOR
[Fenofibrate Capsules]**

Cipher Pharmaceutical, Ltd

**Mike Adams
Division of Metabolism and Endocrine Drug Products
HFD-510**

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Chemistry Review Data Sheet

1. NDA 21-612
2. REVIEW #1
3. REVIEW DATE: 03-Nov-2003
4. REVIEWER: Mike Adams
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u> N-000	<u>Document Date</u> 24-Dec-2002
--	-------------------------------------
7. NAME & ADDRESS OF APPLICANT:

Name	Cipher Pharmaceuticals, Ltd
	Suite 201
Address	Lauriston, Collymore Rock St. Michaels, Barbados Arthur M. Duboeck Galephar PR, Inc.
Representative	Road 198, No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873, PR
Telephone	(787) 713-0340
FAX	(787) 713—344
8. DRUG PRODUCT NAME/CODE/TYPE:
 - a) Proprietary Name: Luxacor
 - b) Non-Proprietary Name (USAN): Fenofibrate Capsules
 - c) Code Name/# (ONDC only): None
 - d) Chem. Type/Submission Priority (ONDC only):
 - Chemical. Type: 3
 - Submission Priority: Standard
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOLOGICAL CATEGORY: type IV and V hypercholesterolemia
11. DOSAGE FORM: HG capsule



CHEMISTRY REVIEW



Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 50,100,150 mg **b(4)**

13. ROUTE OF ADMINISTRATION: oral, immediate release

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____ SPOTS product – Form Completed

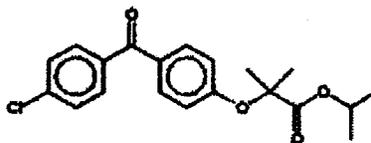
X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula/Weight : C₂₀H₂₁ClO₄; 360.8 awu

Molecular Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	---	---
					Adequate	pending	IR request AR
					N/A	---	---
					Adequate	20-May-2003	CMC #4

b(4)

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
IND	62,780	bioequivalence studies for the proposed dosage form and Tricor [®] tablets

18. STATUS:

CONSULTS/CMC	RECOMMENDATION	DATE	REVIEWER
--------------	----------------	------	----------



CHEMISTRY REVIEW



Chemistry Review Data Sheet

RELATED REVIEWS			
Biometrics	N/A	---	---
EES	Acceptable for all sites	11/25/03	OC conclusion based on inspections
Pharm/Tox	Adequate	10/07/03 review	I.Antonipillai
Biopharm	Acceptable with comments	11/12/03 review	W.Qui
DMETS	Trade Name accepted	10/30/03 review	A.Mahmud
Methods Validation	MV package requested	---	M.Adams
EA	N/A	---	---
Microbiology	N/A	---	---

19. ORDER OF REVIEW : N/A

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Chemistry Review for NDA 21-612

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information has been reviewed and found deficient with respect to some CMC information, therefore I recommend that the application be found APPROVABLE (AE). An action letter detailing the deficiencies listed in section III of this review should be sent to the applicant.

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

No phase 4 commitments for CMC information have been proposed in the NDA.

II. Summary of Chemistry Assessments

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

The NDA is a 505(b)(2) submission for 50mg, 100mg, 150mg _____ Fenofibrate as a new oral, immediate release formulation in 30-count and 90-count bottles for the treatment of hyperlipidemia and hypertriglyceridemia in adults. The proposed product is claimed to be bioequivalent to Tricor[®] and Lipidil Supra[®] tablets. Bioequivalence trials are addressed in IND 62,780. While Tricor and Lipidil Supra use a micronized API/dispersant matrix to enhance the bioavailability of the water insoluble drug, the proposed formulation uses _____

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_____ The proposed formulation was developed by Galephar Puerto Rico, Inc and is covered by patent 5,545,628.

The proposed bulk drug substance is Fenofibrate, EP. There is no USP monograph for this material. Fenofibrate is a non-chiral crystalline material which does not form polymorphs and is nearly water insoluble at pH 1-10. It is soluble in polar organic solvents and in short chain alcohols. The supplier is _____ with type _____ DMF DMF _____. The NDA acceptance specifications are EP monograph plus appearance and residual IPA. A validated _____ -HPLC method is used for assay and impurity analysis. A validated _____ GC method is used for residual solvent analysis. Example data is provided to support the proposed acceptance criteria; low levels of _____ are observed. A _____ stability study indicates that bulk drug substance in solution is sensitive to hydrolysis, near UV light and oxidation and the solid material is stable for 60 months at room temperature.

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The proposed drug product is _____

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_____ The matrix includes _____ components. Gelucire[®] 44/14 _____

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CHEMISTRY REVIEW



Chemistry Assessment Section

[Redacted]

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The dissolution mechanism is described as

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DTA studies are provided to establish that Gelucire®

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Galephar Puerto Rico Inc (Juncos, PR) is proposed for drug product manufacture and control. The manufacturing process consists of

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[Redacted]

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There are no overages. The market package is a white

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The application proposes [redacted] unit commercial lots for each capsule strength. Example executed batch records which match the proposed master production records are provided for clinical lots of each proposed strength and 200mg capsules which were used in the bioequivalence studies. Blend lots used to prepare encapsulation lots and packaging lots. Process validation data for blending, encapsulation and packaging of the EBR lots is also provided. These lots were used for the bioequivalence and stability studies.

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Product release specifications are presented in two parts; chemical testing of bulk capsules and inspection of packaged product. Identity, assay and impurity analyses use a validated HPLC method whose mobile phase differs from that used for drug substance analysis. Content uniformity and dissolution analyses use a validated UV absorbance assay method. As there is no *in vivo* model for bioavailability, the dissolution medium was developed empirically. The proposed dissolution procedure and criterion is

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The criterion is based on the USP monograph for Clofibrate since there is no USP monograph for fenofibrate capsules and its EP monograph does not include dissolution. The Division of Biopharmaceutics has accepted the proposed criterion. The method validation studies include stress degradation of bulk drug substance and capsule fill material which conclude that drug product degradation parallels that for drug substance; sensitivity to light, oxidation and hydrolysis in solution. An ICH stability protocol and study are provided to support the proposed label storage statement. Draft package insert and bottle labels for the 90-count packaging configuration are provided.

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The application presents no microbiology issues. All supporting DMFs are adequate for their intended purpose. [redacted] are satisfactorily addressed by the COA. No other material presents TSE issues. All listed manufacturing and control sites are in GMP compliance. There are no comparability protocols.

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CHEMISTRY REVIEW



Chemistry Assessment Section

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

The proposed drug product is provided as 50mg, 100mg, 150mg _____, oral, immediate release HG capsules in a 30-count and 90-count package. The drug is indicated for the treatment of hyperlipidemia and hypertriglyceridemia in adults; there is no pediatric dosing information in the package insert. The patients are to be placed on a lipid lowering diet for the duration of the 4-8 weeks of treatment. Dosing is typically 50mg- _____ initially, then adjustments are made according to patient need and tolerance. Doses are taken with the meal to enhance fenofibrate absorption. _____ The product in its market package is stated to be stable for _____ are USP CRT.

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C. Basis for Approvability or Not-Approval Recommendation

The application is APPROVABLE in that:

1. The drug substance acceptance and drug product release specifications are deficient. Revisions are needed for the tests, methods, acceptance criteria and validation studies. In addition, the Division of Biopharmaceutics has recommended _____
2. The drug substance and drug product stability information is deficient. A stability protocol has not been provided for drug substance. Insufficient drug product stability data has been provided to support the proposed initial expiry period.
3. The description of the drug product manufacturing process and controls is deficient. The excipient controls are incomplete. _____
_____ The manufacturing process does not address _____
4. The packaging information is deficient. _____
_____ Information to address packaging suitability is not provided.
5. The capsule does not include an imprinted identifier code as required under 21 CFR 206.10.
6. The labeling is deficient. The ingredient list and storage statement need to be corrected.

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III. Administrative

A. Reviewer's Signature

Mike Adams, CMC Reviewer, HFD-510

B. Endorsement Block

M.Adams/CMC Reviewer/03-Nov-2003

S.Moore/CMC TL/Date

V.Jimenez/PM/Date

C. CC Block

E.Duffy/DNDC II Dir/date

D.Wu/DNDC II Dep Dir/date

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Mike Adams
12/2/03 01:01:39 PM
CHEMIST

Stephen Moore
12/2/03 03:53:38 PM
CHEMIST

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