

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-612**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED UPON AND  
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation or  
Composition) and/or Method of Use*

NDA NUMBER

**21-612**

NAME OF APPLICANT / NDA HOLDER

**Cipher Pharmaceuticals Ltd.**

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME  
**LIPOFEN™**

ACTIVE INGREDIENT(S)

**Fenofibrate**

STRENGTH(S)

**50 mg, 100 mg, and 150 mg**

DOSAGE FORM

**Oral capsule**

APPROVAL DATE OF NDA OR SUPPLEMENT

**January 11, 2006**

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

**For hand-written or typewriter versions of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number  
**5,545,628**

b. Issue Date of Patent  
**August 13, 1996**

c. Expiration Date of Patent  
**January 10, 2015**

d. Name of Patent Owner  
**Galephar P.R. Inc.**

Address (of Patent Owner)  
**Road 198 No. 100 KM 14.7  
Juncos Industrial Park**

City/State  
**Juncos, Puerto Rico**

ZIP Code  
**00777-3873 Puerto Rico**

FAX Number (if available)  
**(787) 713-0344**

Telephone Number  
**(787) 713-0340**

E-Mail Address (if available)  
**adeboeck@galephar.com**

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.a.)  
**RAKOCZY MOLINO MAZZOCHI SIWIK LLP  
6 West Hubbard Street, Suite 500**

City/State  
**Chicago, Illinois**

ZIP Code  
**60610**

FAX Number (if available)  
**(312) 222-6321**

Telephone Number  
**(312) 222-6301**

E-Mail Address (if available)  
**wrakoczy@rmmlegal.com**

**William A. Rakoczy, RAKOCZY  
MOLINO MAZZOCHI SIWIK  
LLP**

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes  No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

## 2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). **N/A**  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

**N/A**

2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) **N/A**  Yes  No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes,"
- the answer to 2.7 is "No."

## 3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) **N/A**  Yes  No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

## 4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?  Yes  No

4.2 Patent Claim Number (as listed in the patent) **Claims 11, 12, 13, 14, and 15** Does the patent claim referenced in 4.2 claim an approved method of use of the approved drug product?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) **Claims 11, 12, 13, 14, and 15 claim an approved method of use of the approved drug product, LIPOFEN™ (fenofibrate capsules), in particular the method of use of LIPOFEN™ (fenofibrate capsules) for the treatment of hypercholesterolemia and/or the treatment of hypertriglyceridemia, which are the only approved indications for the product, as denoted in the Indications and Usage section of the approved labeling.**

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.

Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

**Treatment of hypercholesterolemia and/or hypertriglyceridemia**

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

### 5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

N/A

### 6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

January 30, 2006

Larry Andrews, President, Cipher Pharmaceuticals Ltd.

*Larry Andrews*

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Cipher Pharmaceuticals Ltd.

Address

409 Matheson Blvd. E

City/State

Mississauga, Ontario, Canada

ZIP Code

L4Z 2H2 Canada

Telephone Number

(905) 602-5840 (extension 24)

FAX Number (if available)

(905) 602-0628

E-Mail Address (if available)

landrews@cipherpharma.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## EXCLUSIVITY SUMMARY

NDA # 21-612

SUPPL #

HFD # DMEP

Trade Name Lipofen

Generic Name fenofibrate capsules 50, 100 and 150 mg

Applicant Name Cipher

Approval Date, If Known Jan. 11, 2006

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The only studies were submitted as bioequivalence studies.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-304 Tricor Capsules, 67, 134, and 200mg

NDA# 21-203 Tricor Tablets 54, 160 mg

NDA# 21-656 Tricor Tablets 48, 145 mg

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

!

YES

!

! NO

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

---

Name of person completing form: Margaret Simoneau  
Title: RPM  
Date: January 11, 2006

Name of Office/Division Director signing form: Mary Parks, M.D.  
Title: Acting Director, DMEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

-----  
Mary Parks

1/24/2006 04:30:25 AM

Appears This Way  
On Original

**EXCLUSIVITY STATEMENT**

The period of marketing exclusivity for the listed drug expires April 24, 2003.



\_\_\_\_\_  
Dr. Ian W. French Ph.D.  
Chairman and Chief Scientific Officer

Dec 18/02

Date

Appears This Way  
On Original



LD= May 5, 2004  
SD= May 6, 2004

Full waiver granted in  
AC letter of 5/21/04

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Sponsor: CIPHER Pharmaceuticals Limited  
Product: Luxacor (Fenofibrate capsules) 50, 100, 150, ~~200~~ mg strengths  
Indication(s): Type IIa, IIb, IV and V dyslipidemia

b(4)

1. What age ranges are included in your waiver?  
All pediatric age groups.
2. Reasons for waiving pediatric studies:
  - (a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients
  - (b) Studies are impossible or highly impractical because of the number of patients is so small or geographically dispersed
  - (c) The product would be ineffective or unsafe in all pediatric age groups
  - (d) Attempts to develop a pediatric formulation for a specific age group have failed
  - (e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)
    - Alzheimer's disease, Age-related macular degeneration
    - Prostate cancer, Breast cancer
    - Renal cell cancer, Non-germ cell ovarian cancer
    - Hairy cell cancer, Pancreatic cancer, Colorectal cancer
    - Osteoarthritis, Squamous cell cancers of the oropharynx
    - Uterine cancer, Basal cell and Squamous cell cancer
    - Endometrial cancer, Small cell and Non-small-cell lung cancer
    - Parkinson's disease, Amyotrophic lateral sclerosis
    - Arteriosclerosis, Symptoms of menopause
    - Infertility Other (please state and justify)

3. Justification for waiver (not necessary if category 2(e) is checked):  
Fenofibrate is typically not beneficial until patients reach maturity.

  
\_\_\_\_\_  
Ian French, PhD  
Chief Scientific Officer

May 5, 2004  
Date

Suite 201, Lauriston, Collymore Rock  
St. Michael, Barbados  
Tel: (246) 228-9663 Fax: (246) 228-8329

BEST POSSIBLE COPY

**DEBARMENT CERTIFICATION**

Fenofibrate Capsules of 50, 100, 150 \_\_\_\_\_mg

b(4)

Galephar PR, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

*Arthur M. Deboeck*

Arthur M. Deboeck

VP & General Manager

Galephar Pharmaceutical Research, Inc.

*April 21. 2003*

Date

Appendix 21

Appendix 22

Appendix 23

Appendix 24



**DEBARMENT CERTIFICATION**

Fenofibrate Capsules of 50, 100, 150 \_\_\_\_\_ng

**b(4)**

In accordance with the requirements of Section 306 (k) of the Federal Food Drug and Cosmetic Act I, the undersigned, certify that to the best of my knowledge. Galephar Pharmaceutical Research, Inc. did not use any person debarred under subsection (a) or (b) of 306 (k) in any capacity in connection with this application, nor will Galephar Pharmaceutical Research, Inc. use any such person in connection with this application.

Furthermore, I certify that to the best of my knowledge, neither the applicant nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of Section 306.

Arthur M. Deboeck

Arthur M. Deboeck

VP & General Manager

Galephar Pharmaceutical Research, Inc.

March 17, 2003

Date



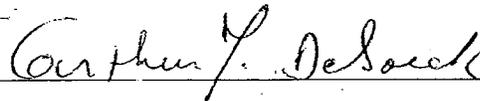
**DEBARMENT CERTIFICATION**

Fenofibrate Capsules of 50, 100, 150 ~~mg~~ mg

b(4)

In accordance with the requirements of Section 306 (k) of the Federal Food Drug and Cosmetic Act I, the undersigned, certify that to the best of my knowledge. Galephar Pharmaceutical Research, Inc. did not use any person debarred under subsection (a) or (b) of 306 (k) in any capacity in connection with this application, nor will Galephar Pharmaceutical Research, Inc. use any such person in connection with this application.

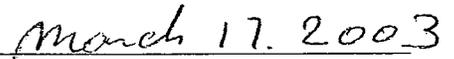
Furthermore, I certify that to the best of my knowledge, neither the applicant nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of Section 306.



Arthur M. Deboeck

VP & General Manager

Galephar Pharmaceutical Research, Inc.



Date



**DEBARMENT CERTIFICATION**

I certify that Cipher Pharmaceuticals Ltd. did not and will not use the services of any person debarred under Section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act, in connection with the development of this drug product and the preparation of this New Drug Application.

I further certify that neither Cipher Pharmaceuticals Ltd. nor any affiliated person responsible in any capacity for providing services or generating information for this New Drug Application for Fenofibrate Capsules 50, 100, 150 ~~mg~~ mg, has been convicted of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act during the past five years.

b(4)

At this time Cipher Pharmaceuticals Ltd. has no person to list who have been convicted during the last five years of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act.

Dr. Ian W. French Ph.D.  
Chairman and Chief Scientific Officer

Dec 18/02  
Date

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached list of Investigators / Sub-Investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Larry Andrews	TITLE President
FIRM / ORGANIZATION Cipher Pharmaceuticals Ltd.	
SIGNATURE 	DATE 5/21/04

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

2 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
		
		

b(6)

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Dr. Ian W. French	TITLE Chairman and Chief Scientific Officer
FIRM / ORGANIZATION Cipher Pharmaceuticals Ltd.	
SIGNATURE 	DATE 3/24/03

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

25 Page(s) Withheld

\_\_\_\_\_ Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

\_\_\_\_\_ Privacy (b6)

RECEIVED RECEIVED

January 30, 2006

FEB - 1 2006

JAN 31 2006

CDR/CDER

**CDER White Oak DR1**

David G. Orloff, M.D.  
Director  
Division of Metabolism and Endocrinology Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg 22 Rm 3360  
Silver Spring, MD 20993

ORIGINAL AMENDMENT

*NCPD*

Re: **NDA 21-612**  
**LIPOFEN™ (fenofibrate capsules) 50 mg, 100 mg and 150 mg**  
**Time Sensitive Patent Information**

Dear Dr. Orloff:

Reference is made to Cipher Pharmaceuticals' New Drug Application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. Reference is also made to the approval of this NDA on January 11, 2006.

With regard to this approved NDA, enclosed herewith is form FDA 3542, "Patent Information Submitted Upon and After Approval of an NDA or Supplement", for United States patent number 5,545,628. This correspondence is provided in triplicate, and an additional copy is being submitted directly to the Orange Book Staff, at the following address: Office of Generic Drugs, OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.

If you have any questions or comments, please do not hesitate to call me at 905 602 5840 x 24.

Yours sincerely,

*Larry Andrews*

Larry Andrews  
President  
Cipher Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY  
APPLICATION NUMBER **RECEIVED**

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Ltd.	DATE OF SUBMISSION 30/1/06	FEB - 1 2006
TELEPHONE NO. (Include Area Code) 905 602 5840	FACSIMILE (FAX) Number (Include Area Code) 905 602 0628	CDER White Oak DR1
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, Barbados	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park, Juncos 00777-3873	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21,612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY LIPOFEN™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:  
For Type IIa, IIb, IV and I dyslipidemia

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Tricor Tablets</u> Holder of Approved Application <u>Abbott Laboratories</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION

Patent Information
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1 (in triplicate)</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached sheet for Establishment Information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA # 21,612

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one)       Draft Labeling       Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) \_\_\_\_\_

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

*Ray Andrews*  
*Arthur M. Deboeck*

TYPED NAME AND TITLE

Ray Andrews, President, Cipher Pharmaceuticals Ltd.  
Arthur M Deboeck, VP & Gen Mgr, Galephar PR Inc.

DATE:

30/1/06

ADDRESS (Street, City, State, and ZIP Code)

US Agent, Galephar PR Inc., Juncos, Puerto Rico, 00777-3873

Telephone Number

( 787 ) 713-0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**Division of Metabolic and Endocrine Drug Products**

**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 21-612

**Name of Drug:** Lipofen (fenofibrate capsules), 50, 100 and 150 mg

**Applicant:** Cipher Pharmaceuticals LTD

**Material Reviewed:**

**Submission Date(s):** January 11, 2006 Package Insert

**Background and Summary**

This was a new drug application (NDA) dated December 24, 2002, received February 26, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lipofen (fenofibrate capsules) 50, 100, and 150 mg.

The July 4, 2005, resubmission constituted a complete response to the Agency's July 15, 2004, tentative approval letter.

The new drug application was approved on January 11, 2006, for the use of Lipofen (fenofibrate capsules) as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Frederickson Type IIa, IIb) in addition to the treatment of adult patients with hypertriglyceridemia (Frederickson Types IV and V hyperlipidemia).

There were numerous labeling changes during previous review cycles recommended by the Agency and are attached to prior action letters. The sponsor submitted draft labeling on December 15, 2005, which included the most recent Agency recommendations from the July 4, 2005 resubmission. However, during the labeling review it was noted that there were numerous changes from the Reference Listed Drug, RLD, NDA 21-203 Tricor (fenofibrate tablets, 54 and 160 mg). An internal labeling meeting took place with members of the review team, specifically Clinical (Dr. Parks), Biopharm (Wei Qiu), Pharm Tox (Karen Davis-Bruno) and Enid Galliers to discuss the specific changes between the last approved label for NDA 21-203, approved September 4, 2001, and Cipher's December 15, 2005 Draft label. The proposed changes that did not belong exclusively to Cipher's submission were noted. Cipher was notified to make the corrections and a new label was submitted on January 11, 2006. Additionally, correspondences took place between Kim Dettelbach and the Division requesting authorization for legal clearance for approval of this 505B2 NDA. E-mail clearances are in the DFS system.

**Review**

Attached to this label review is the approved label for Lipofen, NDA 21-612, with yellow highlighting added. All highlighted text is that which does not match the text in the RLD, NDA 21-203, Tricor 54/160mg package insert. The changes from the RLD were accepted by the reviewing team (Dr. Parks, Wei Qui, and Karen Davis-Bruno).

**Package Insert:**

The draft labeling (submitted January 11, 2006) was compared to the RLD, NDA 21-203 Tricor (fenofibrate tablets), approved September 4, 2001, [(Identifier Nos. 4009, 4013), label attached to the approval letter, archived in DFS].

**Conclusions**

An approval letter issued. The currently approved labeling is as follows:

Package Insert: Identifier: January 2006; Galephar Pharmaceutical Research, Inc, Juncos, Puerto Rico 00777-3873

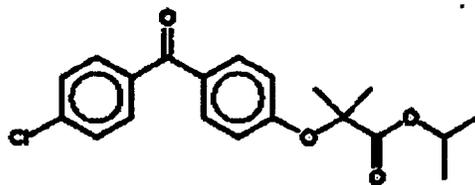
Margaret Simoneau/Regulatory Project Manager/January 11, 2006

Appears This Way  
On Original

**LIPOFENT<sup>TM</sup>**  
**(fenofibrate capsules)**  
**Rx only**

**DESCRIPTION**

LIPOFENT<sup>TM</sup> (fenofibrate capsules), is a lipid regulating agent available as hard gelatin capsules for oral administration. Each hard gelatin capsule contains 50, 100 or 150 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is  $C_{20}H_{21}O_4Cl$  and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

**Inactive Ingredients:** Each hard gelatin capsule contains Gelucire 44/14 (lauroyl macrogol glyceride type 1500), polyethylene glycol 20,000, polyethylene glycol 8000, hydroxypropylcellulose, sodium starch glycolate, gelatin, titanium dioxide, shellac, propylene glycol, may also contain sodium hydroxide, povidone, red iron oxide, black iron oxide, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, D&C Yellow #10.

**CLINICAL PHARMACOLOGY**

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich

lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor  $\alpha$  (PPAR $\alpha$ ). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR $\alpha$  also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

### **Pharmacokinetics/Metabolism**

The extent and rate of absorption of fenofibric acid after administration of 150 mg LIPOFENT™ capsules are equivalent under low-fat and high-fat fed conditions to 160 mg Tricor® tablets.

#### **Absorption**

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces.

The absorption of fenofibrate is increased when administered with food.

**With LIPOFENT™, the extent of absorption** is increased by approximately 58% and 25% under high-fat fed and low-fat fed conditions as compared to fasting conditions, respectively.

In a single dose and multiple dose bioavailability study with LIPOFENT™ capsules 200 mg, the extent of absorption (AUC) of fenofibric acid, the principal metabolite of fenofibrate, was 42% larger at steady state compared to single-dose administration. The rate of absorption ( $C_{max}$ ) of fenofibric acid was 73% greater after multiple-dose than after single-dose administration.

The extent of absorption of LIPOFENT™ in terms of AUC value of fenofibric acid increased in a less than proportional manner while the rate of absorption in terms of  $C_{max}$  value of fenofibric acid increased proportionally related to dose.

### Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved after 5 days of once a day dosing and demonstrated a mean 2.4-fold accumulation following multiple dose administration. Steady-state plasma levels of fenofibrate demonstrated no accumulation. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

### Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; unchanged fenofibrate is detected at low concentrations in plasma compared to fenofibric acid over most of the single dose and multiple dosing periods.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

*In vivo* metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant degree.

### Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in feces.

Fenofibric acid is eliminated with a half-life between 10 and 35 hours (mean approximately 20 hours) allowing once daily administration in a clinical setting.

### Special Populations

#### Geriatrics

In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

#### Pediatrics

Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.

#### Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

#### Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

#### Renal insufficiency

In a study of patients with severe renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibric acid was greatly reduced and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of **LIPOFEN™** should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

#### Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

#### Drug-drug interactions

*In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. **Therefore, LIPOFEN™ should be** taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

## **Clinical Trials**

Clinical trials have not been conducted with LIPOFEN™.

**Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)**

The effects of fenofibrate at a dose equivalent to 150 mg per day of LIPOFEN™ were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1

**Mean Percent Change in Lipid Parameters at End of Treatment<sup>+</sup>**

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid				
Values (n= 646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid				
Values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C >160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid				
Values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

<sup>+</sup> Duration of study treatment was 3 to 6 months.

\* p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

**Hypertriglyceridemia (Fredrickson Type IV and V)**

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials<sup>1</sup> of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 150 mg LIPOFENT™ per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

**Table 2**  
**Effects of *Fenofibrate* in Patients With**  
**Fredrickson Type IV/V Hyperlipidemia**

Study 1		Placebo			Fenofibrate			
Baseline TG Levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*

Study 2		Placebo			Fenofibrate			
Baseline TG Levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

\* = P<0.05 vs. Placebo

The effect of fenofibrate on cardiovascular morbidity and mortality has not been determined.

## INDICATIONS AND USAGE

### Treatment of Hypercholesterolemia

**LIPOFENT™** is 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 or mixed dyslipidemia (Fredrickson Types IIa and IIb).

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological intervention alone has been inadequate (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

### Treatment of Hypertriglyceridemia

**LIPOFENT™** is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually

reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of LIPOFEN™ therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia<sup>2</sup>.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet (see WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation	
		Major	Minor
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔C

C = cholesterol

TG = triglycerides

LDL = low density lipoprotein

VLDL = very low density lipoprotein

IDL = intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at which to Consider Drug Therapy (mg/dL)
<b>CHD† or CHD risk equivalents (10-years risk &gt; 20%)</b>	<100	≥100	≥130 (100-129; drug optional)††
<b>2+ Risk Factors (10-year risk ≤20%)</b>	<130	≥130	10-year risk 10%-20%: ≥130 10-Year risk <10%: ≥160
<b>0-1 Risk Factor†††</b>	<160	≥160	≥190 (160-189: LDL-Lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%: thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

## CONTRAINDICATIONS

**LIPOFEN™ is contraindicated in patients** who exhibit hypersensitivity to fenofibrate.

**LIPOFEN™ is contraindicated** in patients with hepatitis or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

**LIPOFEN™ is contraindicated** in patients with preexisting gallbladder disease (see WARNINGS).

## WARNINGS

**Liver Function:** Fenofibrate at doses equivalent to 100 mg to 150 mg **LIPOFEN™ per day** has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 100 mg to 150 mg **LIPOFEN™ per day** and was 0% in those receiving dosages equivalent to 50 mg or less **LIPOFEN™ per day, or placebo**. **Hepatocellular**, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver functions, including serum ALT (SGPT) should be performed for the duration of therapy with **LIPOFEN™**, **and therapy discontinued** if enzyme levels persist above three times the normal limit.

**Cholelithiasis:** Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. **LIPOFEN™ therapy should be discontinued** if gallstones are found.

**Concomitant Oral Anticoagulants:** Caution should be exercised when anticoagulants are given in conjunction with **LIPOFEN™** because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

**Concomitant HMG-CoA Reductase Inhibitors:** The combined use of LIPOFEN™ and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of fenofibrate and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3 $\alpha$ -hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including LIPOFEN™, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving LIPOFEN™ and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, LIPOFEN™ should be stopped.

**Mortality:** The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

**Other Considerations:** In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between LIPOFEN™ (fenofibrate capsules), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to LIPOFEN™.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%,  $p < 0.01$ ). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5

years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance ( $p=0.19$ , 95% confidence interval for relative risk G:P=0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group ( $p=0.11$ ), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A second prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between the study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%,  $p=0.07$ ). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317,  $p=0.029$ ).

## PRECAUTIONS

**Initial Therapy:** Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting LIPOFEN™ therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

**Continued therapy:** Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of LIPOFEN™. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 150 mg per day.

**Pancreatitis:** Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

**Hypersensitivity Reactions:** Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

**Hematologic Changes:** Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of LIPOFEN™ administration.

**Skeletal muscle:** The use of fibrates alone, including LIPOFEN™, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

### **Drug Interactions**

**Oral Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPOFEN™. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

**HMG-CoA reductase inhibitors:** The combined use of LIPOFEN™ and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

**Resins:** Since bile acid sequestrants may bind other drugs given concurrently, patients should take LIPOFEN™ at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

**Cyclosporine:** Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPOFEN™, there is a risk that an interaction will lead to deterioration. The benefits and risks of using LIPOFEN™ with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45 and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD, based on mg/m<sup>2</sup> of surface area). At a dose of 200 mg/kg/day (at 6 times MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/m<sup>2</sup> surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg; 2 times the human dose), and gemfibrozil (250 mg/kg; 2 times the human dose, multiples based on mg/m<sup>2</sup> surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular nodules in females. Gemfibrozil increased hepatic neoplastic nodules in females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45 and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/m<sup>2</sup> surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at same doses, fenofibrate 10, 45 and 200 mg/kg/day (approximately 0.2, 0.7 and 3 times the MRHD on the basis of mg/m<sup>2</sup> surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

### **Pregnancy Category C:**

Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/m<sup>2</sup> surface area). There are no adequate and well

controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternbrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight at birth, as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams, and death in 7% of fetuses at 18 times the MRHD.

**Nursing mothers:** Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

**Pediatric Use:** Safety and efficacy in pediatric patients have not been established.

**Geriatric Use:** Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

## ADVERSE REACTIONS

**CLINICAL:** Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
<b>BODY AS A WHOLE</b>		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
<b>DIGESTIVE</b>		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>		
SGPT Increased	3.0%	1.6%
Creatinine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
<b>RESPIRATORY</b>		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

\* Dosage equivalent to 150 mg LIPOFEN™

\*\* Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

**BODY AS A WHOLE:** Chest pain, (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

**CARDIOVASCULAR SYSTEM:** Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular

disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

**DIGESTIVE SYSTEM:** Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

**ENDOCTRINE SYSTEM:** Diabetes mellitus

**HEMIC AND LYMPHATIC SYSTEM:** Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

**METABOLIC AND NUTRITIONAL DISORDERS:** Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

**MUSCULOSKELETAL SYSTEM:** Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

**NERVOUS SYSTEM:** Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

**RESPIRATORY SYSTEM:** Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

**SKIN AND APPENDAGES:** Rash, pruritus, eczema, herpes, zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

**SPECIAL SENSES:** Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

**UROGENITAL SYSTEM:** Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

## **OVERDOSAGE**

There is no specific treatment for overdose **with LIPOFEN™**. **General** supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

## **DOSAGE AND ADMINISTRATION**

Patients should be placed on an appropriate lipid-lowering diet before receiving **LIPOFEN™**, and should continue this diet during treatment **with LIPOFEN™**. **LIPOFEN™ capsules** should be given with meals, thereby optimizing the absorption of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, **the initial dose of LIPOFEN™ is 150 mg per day.**

For adult patients with hypertriglyceridemia, the initial dose is 50 to 150 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determination at 4 to 8 week intervals. The maximum dose is 150 mg per day.

**Treatment with LIPOFEN™ should be initiated** at a dose of 50 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 50 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of LIPOFEN™ if lipid levels fall significantly below the targeted range.

## **HOW SUPPLIED**

LIPOFEN™ (fenofibrate capsules) is available in three strengths:

50 mg: Size 3 white opaque/white opaque gelatin capsule, imprinted in black ink with **“50” between lines on the body, “G 246” on the cap** and containing a white to almost white paste, available in bottles of 30 (NDC 66277-246-02) and 90 (NDC 66277-246-03).

100 mg: Size 2 white opaque/white opaque gelatin capsule, imprinted in brown-red (rust) ink with **“100” between lines on the body, “G 247” on the cap** and containing a white to almost white paste, available in bottles of 30 (NDC 66277-247-02) and 90 (NDC 66277-247-03).

150 mg: Size 1 white opaque/white opaque gelatin capsule, imprinted in green ink with **“150” between lines on the body, “G 248” on the cap** and containing a white to almost white paste, available in bottles of 30 (NDC 66277-248-02) and 90 (NDC 66277-248-03).

## **Storage**

Store at controlled room temperature, 15°-30°C (59°-86°F). Keep out of the reach of children. Protect from moisture and light.

## **REFERENCES**

1. GOLDBERG AC, et al. Fenofibrate for the treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics*, 11, pp. 69-83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5<sup>th</sup> edition, McGraw-Hill. 1983, Chap. 30, pp. 622-642.

3. BROWN WV, et al. Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. Arteriosclerosis. 6, pp. 670-678, 1986.

January 2006

Galephar Pharmaceutical Research Inc.,  
Juncos, Puerto Rico 00777-3873

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/

-----  
Margaret Simoneau  
1/30/2006 08:53:51 AM  
CSO

Appears This Way  
On Original

## Simoneau, Margaret A

---

**From:** Simoneau, Margaret A  
**Sent:** Tuesday, January 24, 2006 10:43 AM  
**To:** Simoneau, Margaret A  
**Subject:** FW: Medical Team Leader Memo

-----Original Message-----

**From:** Dettelbach, Kim  
**Sent:** Wednesday, January 11, 2006 2:23 PM  
**To:** Galliers, Enid M; Simoneau, Margaret A  
**Subject:** RE: Medical Team Leader Memo

Assuming I am right about my summary of the reprotox data (in previous email), and there is no safety issue re: the elimination of the drug interaction information, the labeling issues should not be a bar to approval.

-----Original Message-----

**From:** Galliers, Enid M  
**Sent:** Wednesday, January 11, 2006 11:02 AM  
**To:** Dettelbach, Kim  
**Cc:** Simoneau, Margaret A; Parks, Mary H  
**Subject:** RE: Medical Team Leader Memo

Kim:

Would you please send us an email with the go-ahead to approve whenever you and Mary reach agreement on her memo? We need it for the record.

Thanks,

Enid

-----Original Message-----

**From:** Dettelbach, Kim  
**Sent:** Wednesday, January 11, 2006 8:54 AM  
**To:** Galliers, Enid M; Dettelbach, Kim; Parks, Mary H  
**Subject:** RE: Medical Team Leader Memo

I went to the most recent atorvastatin and pravastatin labeling in the PDR and it appears that neither is cross labeled with the drug-drug interaction with fenofibrate. This seems to lend additional support for the proposition that the drug interaction information is not critical safety information in this case. We should consider whether Dr. Parks wants to include this fact as additional support in her memo. Thanks.

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/

-----  
Margaret Simoneau  
1/24/2006 10:57:29 AM  
CSO

Appears This Way  
On Original

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST #4

(Information on checklist #4 will be updated information contained in the July 4, 2005 resubmission)

Application Information		
NDA 21-612	Efficacy Supplement Type SE-	Supplement Number
Drug: Lipofen (fenofibrate capsules) 50, 100, and 150 mg		Applicant: Cipher Pharmaceuticals
RPM: E. Galliers and M. Simoneau		HFD- DMEP <span style="float: right;">Phone # 301-796-1295</span>
<p>Application Type: ( ) 505(b)(1) (X) 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p>(X) Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 21-203Tricor 54 and 160 mg Tablets</p> <p>Clearance for this 505b2 application came from Kim Dettelbach on 12.6.05 and 1.11.06.</p>	
<b>❖ Application Classifications:</b>		
<ul style="list-style-type: none"> <li>• Review priority</li> </ul>		(x) Standard ( ) Priority Class 2 (6-month resubmission)
<ul style="list-style-type: none"> <li>• Chem class (NDAs only)</li> </ul>		
<ul style="list-style-type: none"> <li>• Other (e.g., orphan, OTC)</li> </ul>		
<b>❖ User Fee Goal Dates</b>		January 11, 2006
<b>❖ Special programs (indicate all that apply)</b>		( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
<b>❖ User Fee Information</b>		
<ul style="list-style-type: none"> <li>• User Fee</li> </ul>		( ) Paid UF ID number
<ul style="list-style-type: none"> <li>• User Fee waiver</li> </ul>		( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>		



(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes ( ) No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	( ) Yes, Application # _____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	(see previous #1-3 AP checklists)
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	January 11, 2006 final
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	December 15, 2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	none
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Dr. Mary Parks
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	Dr. Mary Parks
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet <i>(NME approvals only)</i>	
❖ Statistical review(s) <i>(indicate date for each review)</i>	
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	Wei Qiu
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	Not required for the July 4 <sup>th</sup> , 2005 resubmission
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	William Adams
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	

Appears This Way  
On Original

**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**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/

-----  
Margaret Simoneau  
1/23/2006 02:06:46 PM

Appears This Way  
On Original

**Simoneau, Margaret A**

---

**From:** Fraser, Blair  
**Sent:** Wednesday, January 11, 2006 2:41 PM  
**To:** Simoneau, Margaret A  
**Subject:** RE: NDA 21-612 Cipher PI REVISED

Approved.

-----Original Message-----

**From:** Simoneau, Margaret A  
**Sent:** Wednesday, January 11, 2006 9:30 AM  
**To:** Fraser, Blair  
**Subject:** FW: NDA 21-612 Cipher PI REVISED

Blair,  
This should be the Lipofen PI, if the NDA gets approved.

Thanks.

-----Original Message-----

**From:** Julia Nash [mailto:jnash@cipherpharma.com]  
**Sent:** Tuesday, January 10, 2006 6:54 PM  
**To:** Simoneau, Margaret A  
**Cc:** Larry Andrews; Jan Sedgeworth  
**Subject:** NDA 21-612 Cipher PI REVISED

Dear Ms. Simoneau,

As per my discussion with Enid Galliers and yourself this afternoon, please find attached the revised package insert for NDA 21-612 LIPOFEN™ (fenofibrate capsules). It has been provided in MS Word format, as both tracked and clean versions, and also in rendered PDF format as a clean version. The associated cover letter and Form FDA 356h will be provided by email in scanned PDF format tomorrow, January 11, 2005.

The changes discussed today have all been included as requested. We would like to note, however, that the wording in the PRECAUTIONS section, referred to below, which does not appear in the RLD Tricor 54/160 mg package insert (NDA 021203), was included in Cipher's package insert in the March 30, 2004 response to FDA's December 18, 2003 letter, in which it was requested. Following today's discussion, this wording remains in Cipher's LIPOFEN™ package insert, as per the Agency's request.

- Carcinogenesis, Mutagenesis, Impairment of Fertility – paragraphs 1-3.
- Pregnancy Category C – first sentence.
- Pregnancy Category C – use of the word “\_\_\_\_\_” in paragraphs 2 and 4, and also paragraph 3, which has been added in this version as requested in today's discussion.
- Pregnancy Category C – use of the acronym “MRHD” (instead of expanded wording) in each paragraph.
- Pregnancy Category C – last paragraph.

In addition to the Agency's requested changes, four minor corrections have been made, mainly typographical:

- CLINICAL PHARMACOLOGY, Special Populations, Drug-drug interactions – Third paragraph, second sentence, “\_\_\_\_\_” changed to “LIPOFEN™”.
- WARNINGS, Other Considerations – Fourth paragraph, third sentence, change from “\_\_\_\_\_”

b(4)

b(4)

b(4)

## Simoneau, Margaret A

---

**From:** Fraser, Blair  
**Sent:** Wednesday, January 11, 2006 2:42 PM  
**To:** Simoneau, Margaret A  
**Subject:** RE: NDA 21-612 Lipofen DRAFT Approval letter

Letter is acceptable.

-----Original Message-----

**From:** Simoneau, Margaret A  
**Sent:** Wednesday, January 11, 2006 9:21 AM  
**To:** Adams, William M; Fraser, Blair  
**Subject:** NDA 21-612 Lipofen DRAFT Approval letter

Mike and Blair,

Attached is the Draft Lipofen approval letter with an action due today! Please let me know if you have any problems, concerns or issues with approving this.  
Thank you.

<< File: 21612APItr.doc >>

Margaret Simoneau, M.S., R.Ph.  
FDA/CDER/DMEP  
301-796-1295  
simoneaum@cder.fda.gov

Appears This Way  
On Original

**Memo to the File for NDA 21-612**

The Division has no objections to the tradename Lipofen®.

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/  
-----

Mary Parks  
1/11/2006 01:43:22 PM  
MEDICAL OFFICER

Appears This Way  
On Original

**RECEIVED**

January 11, 2006

JAN 17 2006

**CDR/CDER**

N. 000-C

David G. Orloff, M.D.  
Director  
Division of Metabolism and Endocrinology Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg 22 Rm 3360  
Silver Spring, MD 20993

**NEW CORRESP**

**RECEIVED**

JAN 19 2006

**CDER White Oak DR1**

Re: **NDA 21-612**  
LIPOFEN™ (fenofibrate capsules) 50 mg, 100 mg and 150 mg  
Response to January 11, 2006 Agency Comments on Labeling

Dear Dr. Orloff:

Reference is made to Cipher Pharmaceuticals' New Drug Application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. Reference is also made to the submissions since that time, and the discussions that took place with the Agency on January 5, 6, 10 and 11, 2006, regarding the package insert for Cipher's LIPOFEN™ product. As per the most recent discussion with Ms. Margaret Simoneau on January 11, 2006, a clean version of the revised package insert for LIPOFEN™ (fenofibrate capsules) has been provided, considered to be the final version as agreed upon with the Agency. The electronic version of this document is provided in both MS Word and rendered PDF formats.

If you have any questions or comments, please do not hesitate to call me at 905 602 5840 x 24.

Yours sincerely,



Larry Andrews  
President  
Cipher Pharmaceuticals Ltd.

Appears This Way  
On Original

CC: Arthur DeBoeck, Galephar PR Inc.

b(4)

ORIGINAL

b(4)

**RECEIVED**

January 10, 2006

JAN 19 2006

**CDER White Oak DR1**

**RECEIVED**

JAN 17 2006

**CDR/CDER**

David G. Orloff, M.D.  
Director  
Division of Metabolism and Endocrinology Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg 22 Rm 3360  
Silver Spring, MD 20993

N-000-0

Re: **NDA 21-612**  
CIP-FENO-FIBRATE (fenofibrate capsules) 50 mg, 100 mg, 150 mg NEW CONDITION  
Response to January 10, 2006 Agency Comments on Labeling

b(4)

Dear Dr. Orloff:

Reference is made to Cipher Pharmaceuticals' New Drug Application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. Reference is also made to the submissions dated January 10, March 24, April 21, May 6, October 15, 23, November 7, December 2 and 8, 2003, and January 7, 25, February 3, 9, 16, March 30, May 5, 14, 21, June 1 and 4, 2004. Further reference is made to the FDA's tentative approval letter dated July 15, 2004, the amendment to the tentatively approved NDA submitted November 30, 2004, the revised amendment to the tentatively approved NDA dated July 4, 2005, and the submissions dated September 9, October 19 and December 15, 2005.

Further reference is also made to the discussions that took place with the Agency on January 5, 6 and 10, 2006, regarding the package insert for Cipher's LIPOFEN™ product. As per the most recent discussion with Ms. Enid Galliers and Ms. Margaret Simoneau on January 10, 2005, the revised package insert for LIPOFEN™ (fenofibrate capsules) has been provided, in MS Word format, as both tracked and clean versions, and also in rendered PDF format as a clean version. The tracked changes version shows changes made to the version of the package insert included in the December 15, 2005 submission.

The changes discussed on January 10, 2006, have all been included as requested. Cipher would like to note, however, that the wording in the PRECAUTIONS section, referred to below, which does not appear verbatim in the RLD Tricor 54/160 mg package insert (NDA 021203) but does refer to the same data/studies as presented in the RLD Tricor 54/160 mg package insert, was included in Cipher's package insert in the March 30, 2004 response to FDA's December 18, 2003 letter, which requested the addition of this specific wording. Following the January 10,

ORIGINAL

2006 discussion, this wording remains in Cipher's LIPOFEN™ package insert, as per the Agency's request.

- Carcinogenesis, Mutagenesis, Impairment of Fertility – paragraphs 1-3.
- Pregnancy Category C – first sentence.
- Pregnancy Category C – use of the word \_\_\_\_\_ in paragraphs 2 and 4, and also paragraph 3, which has been added in this version as requested in today's discussion.
- Pregnancy Category C – use of the acronym "MRHD" (instead of expanded wording) in each paragraph.
- Pregnancy Category C – last paragraph.

In addition to the Agency's requested changes, four minor corrections have been made, mainly typographical:

- CLINICAL PHARMACOLOGY, Special Populations, Drug-drug interactions – Third paragraph, second sentence. \_\_\_\_\_ changed to "LIPOFEN™".
- WARNINGS, Other Considerations – Fourth paragraph, third sentence, change from \_\_\_\_\_ to "G:P=0.91-1.64".
- PRECAUTIONS, Skeletal Muscle – addition of "with" in first sentence, to match Tricor 54/160 mg package insert.
- OVERDOSAGE – addition of "s" to "precaution" to read "precautions", to match Tricor 54/160 mg package insert.

Also, in order to confirm a point that came up during the January 10, 2006 discussion, the container labels that have been provided thus far (the most up to date versions were submitted on December 15, 2005), have been for the immediate container (bottles). Cipher does not currently plan to use any additional container labeling, such as that for an outer carton.

If you have any questions or comments, please do not hesitate to call me at 905 602 5840 x 24. Alternatively, you may contact our Regulatory Affairs Manager Ms. Julia Nash at extension 26.

Yours sincerely,

*for John R. Nash*

Larry Andrews  
President  
Cipher Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

Appears This Way  
On Original

b(4)

b(4)

b(4)

b(4)

December 15, 2005

**RECEIVED**

DEC 19 2005

**CDR/CDER**

David G. Orloff, M.D.  
Director  
Division of Metabolism and Endocrinology Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg 22 Rm 3360  
Silver Spring, MD 20993

ORIGINAL AMENDMENT

N-000-BL

**RECEIVED**

DEC 21 2005

**CDER White Oak DR1**

Re: **NDA 21-612**  
CIP-FENOPIBRATE (fenofibrate capsules) 50 mg, 100 mg, 150 mg  
Response to Dec 2, 2005 Agency Comments on Labeling

b(4)

Dear Dr. Orloff:

Reference is made to Cipher Pharmaceuticals' New Drug Application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. Reference is also made to submissions to the NDA since that time, and to the FDA's tentative approval letter dated July 15, 2004. Further reference is made to the amendment to the tentatively approved NDA submitted November 30, 2004, the revised amendment to the tentatively approved NDA dated July 4, 2005, and the subsequent Agency comments on the product labeling dated December 2, 2005.

Reference is also made to the September 6, 2005 teleconference with the Agency regarding the brandnames "~~LIPOFEN~~" and "LIPOFEN" proposed in the July 4, 2005 revised amendment to the tentatively approved NDA, following receipt of preliminary feedback from the Division of Drug Marketing, Advertising and Communications (DDMAC). It is understood that while there were some objections from DDMAC regarding this name, specifically related to reminder advertising, it may still be acceptable to the review division. Cipher confirmed its intention to proceed with LIPOFEN as the proposed brandname in correspondence to the Agency dated October 19, 2005. No further issues regarding the brandname have been communicated since that time.

b(4)

In response to the Agency's Dec 2, 2005 comments on the product labeling, please find enclosed in both paper and electronic format, updated labeling for Cipher's product. We have incorporated the two minor changes requested by the Agency, as follows:

- Removal of the last sentence of the fourth paragraph under the heading Pharmacokinetics/Metabolism, Absorption
- Change in the mean half-life stated for fenofibric acid, from 17 to 20 hours, so that the second paragraph under the heading Pharmacokinetics/Metabolism, Excretion reads: "Fenofibric acid is eliminated with a half-life between 10 and 35 hours (mean approximately 20 hours) allowing once daily administration in a clinical setting."

In addition to making the changes requested by the Agency, the proposed brandname "LIPOFEN™" has been incorporated into the labeling, in both the package insert and container labels.

Further to the changes already described, very minor typographical changes have been made to the versions of the package insert and bottle labels that were submitted as part of the July 4, 2005 revised amendment to the tentatively approved NDA.

For the package insert, these minor changes are as follows:

- Indications and Usage, Treatment of Hypertriglyceridemia, paragraph 3 (page 8) – "Type 1" has been changed to "Type I"
- Clinical Trials, Table 1 (page 6) and Indications and Usage, Treatment of Hypertriglyceridemia, Table of NCEP Treatment Guidelines (page 9) – removal of superfluous symbols in these tables
- Adverse Reactions, Clinical, Table of Adverse Events (page 17) – Removal of two empty lines in the table to correct formatting

For the bottle labels, the following changes have been made:

- The name "Galephar P.R. Inc." has been replaced with "G"
- The text "package Insert" has been revised to state "package insert"

It should be noted that with regard to the bottle labels, there was unfortunately some difficulty in generating MS Word and rendered PDF files containing the bottle labels that include the image of a bar code, as shown on the SOPs included in the paper copy of the submission (Appendix 4). The MS Word and rendered pdf files provided electronically (Appendix 5) and included in hard copy in Appendix 4, as scaled mockups in color, therefore contain the words "BAR CODE" in that location on each label, but are identical in every other way. In addition, a scanned pdf file containing the images that do include the bar code image has been provided. Cipher apologizes for this inconvenience.

~~\_\_\_\_\_~~, bottle labels are still being provided for all ~~\_\_\_\_\_~~ strengths (50, 100, 150 ~~\_\_\_\_\_~~), while potential FDA approval of the proposed 150 mg claims is pending.

b(4)

One original and two (2) copies of this submission are provided. If you have any questions or comments, please do not hesitate to call me at 905 602 5840 x 24, or you may contact our ~~\_\_\_\_\_~~

b(4)

b(4)

Yours sincerely,

*Larry Andrews*

Larry Andrews  
President  
Cipher Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

b(4)

Appears This Way  
On Original

## Simoneau, Margaret A

---

**From:** Dettelbach, Kim  
**Sent:** Tuesday, December 06, 2005 3:32 PM  
**To:** Peat, Raquel; Dickinson, Elizabeth; Dettelbach, Kim  
**Subject:** RE: OCC CONSULT: 505(b)(2): NDA 21-961, Cip-Fenofibrate caps

These court decisions end the 30 month stays. Therefore, assuming there are no other issues, this application can receive a full approval.

-----Original Message-----

**From:** Peat, Raquel  
**Sent:** Tuesday, December 06, 2005 9:46 AM  
**To:** Dickinson, Elizabeth; Dettelbach, Kim  
**Cc:** Colangelo, Kim M  
**Subject:** OCC CONSULT: 505(b)(2): NDA 21-961, Cip-Fenofibrate caps

Good Morning Liz and Kim D.:

Per my meeting invitation for this Friday, I am attaching the information that the PM forwarded to me on the OCC consult for NDA 21-961, CIP-fenofibrate- TA issued 7/15/04. The applicant, Cipher Pharmaceuticals, LTD sent in a resubmission and the division plans to issue an AP around December 16, 2005. A consult was sent to OCC to review the final judgment on July 27, 2005 by the PM, Margaret Simoneau.

Please let us know if you need us to do anything else.

Kind regards,  
Raquel and Kim C.

*LT Raquel Peat, MS, MPH, USPHS*  
Regulatory Project Officer  
FDA/CDER/OND, Immediate Office  
301-796-0700 (OND IO main)  
301-796-0517 (direct)  
Fax: 301-796-9858

Address:  
10903 New Hampshire Ave.  
Bldg #22, Room 6469  
Silver Spring, MD 20993

-----Original Message-----

**From:** Simoneau, Margaret A  
**Sent:** Thursday, December 01, 2005 12:09 PM  
**To:** Peat, Raquel  
**Subject:** FW: COMIS 6966 - Cipher Pharmaceuticals LTD, Cip-Fenofibrate caps, 505(b)(2)

-----Original Message-----

**From:** Simoneau, Margaret A  
**Sent:** Friday, July 29, 2005 7:31 AM

**To:** Colangelo, Kim M  
**Subject:** FW: COMIS 6966 - Cipher Pharmaceuticals LTD, Cip-Fenofibrate caps, 505(b)(2)

Hi Kim,  
Just FYI. This is a re-submission on a Tentative Approval of a 505(b)(2) application. If you don't need to be notified of this type submission, please let me know.

Thanks.  
Margaret

-----Original Message-----

**From:** Jordan, Kathleen M  
**Sent:** Thursday, July 28, 2005 3:21 PM  
**To:** Guido, Mirna; Anselmo, Rita  
**Cc:** Fain, Kevin; Ray, Seth; Vaid, Sonal; Thakur, Emily; Schwemer, Tawni B; Simoneau, Margaret A; Dickinson, Elizabeth  
**Subject:** COMIS 6966 - Cipher Pharmaceuticals LTD, Cip-Fenofibrate caps, 505(b)(2)

Hi. Attached is the OCC consult request for COMIS 6966 - Cipher Pharmaceuticals LTD, Cip-Fenofibrate caps, 505(b)(2). This is a 60 day request. The GC goal date is 9/28/05. Supporting documents are attached. Liz Dickinson has been involved with this project.

<< File: 21612OCC.pdf >> << File: 6966.pdf >>  
Kathy

Kathleen Jordan  
Division of Regulatory Policy II  
Office of Regulatory Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[Jordank@cder.fda.gov](mailto:Jordank@cder.fda.gov) <<mailto:Jordank@cder.fda.gov>>  
(301) 443-5539  
RKW2 RM1125, HFD-007  
5515 Security Lane

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.**

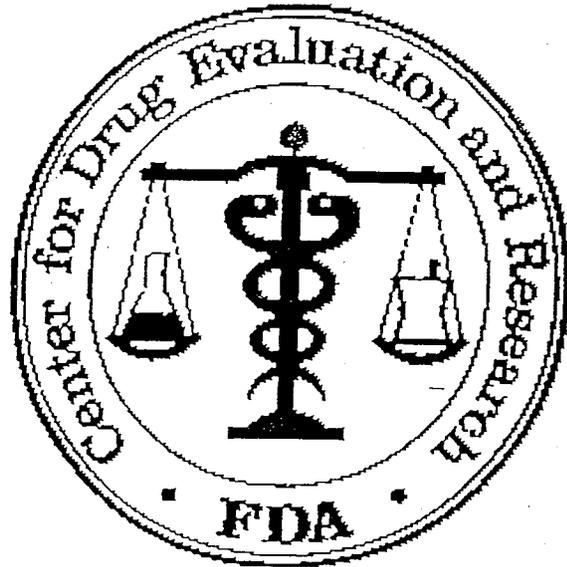
/s/

-----  
Margaret Simoneau  
1/24/2006 09:56:03 AM  
CSO

Appears This Way  
On Original

FOOD AND DRUG ADMINISTRATION  
DIVISION OF METABOLIC AND  
ENDOCRINE DRUG PRODUCTS  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE: 12/2/05



TO:

FROM:

Name: *Mr. Arthur Deboeck*  
*V/S Agent for Ciphex Pharmaceuticals*  
Fax No.: *787-713-0344*

Name: Margaret Simoneau  
Fax No.: (301) *796-9712*

Phone No.: *787 713-0340*

Phone No.: (301) *796-1295*

Location:

Location: FDA

Pages: *3* (including cover)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

*NDA 21-612 Cip-Fenofibrate  
Labeling Comments*

2 Page(s) Withheld

       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

✓ Draft Labeling (b5)

       Deliberative Process (b5)

**Simoneau, Margaret A**

---

**From:** Julia Nash [jnash@cipherpharma.com]  
**Sent:** Monday, December 05, 2005 9:06 AM  
**To:** Simoneau, Margaret A  
**Subject:** RE: Cipher Package Insert

Margaret,

As a follow up to the voice message I left you towards the end of the day on Friday (Dec 2), I just wanted to confirm that your fax with the comments on our package insert was received by Arthur Deboeck (our US Agent) on Friday and he has provided us with a copy also.

Thank you very much again for your assistance.

Kind regards,  
Julia

---

**From:** Julia Nash [mailto:jnash@cipherpharma.com]  
**Sent:** December 2, 2005 1:00 PM  
**To:** 'SIMONEAUM@cder.fda.gov'  
**Subject:** Cipher Package Insert

Margaret,

It was a pleasure speaking with you today, and the rapid feedback following the review of our package insert is much appreciated.

As discussed, I am sending this email so that you may respond and attach the comments document. Thank you for being so flexible in providing the comments via email.

Kind regards,  
Julia

*Julia Nash  
Regulatory Affairs Manager  
Cipher Pharmaceuticals Ltd.  
409 Matheson Blvd. East  
Mississauga, ON  
L4Z 2H2*

*Tel: 905 602 5840 ext 26  
Fax: 905 602 0628  
jnash@cipherpharma.com*

**Appears This Way  
On Original**

12/5/2005

## Simoneau, Margaret A

---

**Subject:** TENTATIVE NDA 21-612 Cip-Fenofibrate (Lipofen) INDUSTRY T-con  
**Location:** CDER White Oak 3376 Conference Room 3rd Floor

**Start:** Mon 12/5/2005 2:00 PM  
**End:** Mon 12/5/2005 3:00 PM

**Recurrence:** (none)

**Meeting Status:** Meeting organizer

**Required Attendees:** Simoneau, Margaret A; Parks, Mary H; Ahn, Hae Young; Qiu, Wei; Adams, William M; CDER White Oak 3376 Conference Room 3rd Floor

**Optional Attendees:** Madara, Patricia

**Resources:** CDER White Oak 3376 Conference Room 3rd Floor

Appears This Way  
On Original

**Simoneau, Margaret A**

---

**Subject:** NDA 21-612 Cip-Fenofibrate (Lipofen) INTERNAL labeling meeting  
**Location:** CDER White Oak 3376 Conference Room 3rd Floor

**Start:** Wed 11/30/2005 2:00 PM  
**End:** Wed 11/30/2005 3:00 PM

**Recurrence:** (none)

**Meeting Status:** Meeting organizer

**Required Attendees:** Simoneau, Margaret A; Parks, Mary H; Ahn, Hae Young; Qiu, Wei; Adams, William M; CDER  
White Oak 3376 Conference Room 3rd Floor

**Optional Attendees:** Madara, Patricia

**Resources:** CDER White Oak 3376 Conference Room 3rd Floor

Appears This Way  
On Original

**Simoneau, Margaret A**

---

**Subject:** NDA 21-612 Cip-Fenofibrate (Lipofen) Regulatory Status Meeting/ Pre-Action Pkg review  
**Location:** CDER White Oak 3157 Conference Room 3rd Floor  
**Start:** Fri 11/18/2005 1:00 PM  
**End:** Fri 11/18/2005 2:00 PM  
**Recurrence:** (none)  
**Meeting Status:** Meeting organizer  
**Required Attendees:** Simoneau, Margaret A; Galliers, Enid M; Madara, Patricia; CDER White Oak 3157 Conference Room 3rd Floor  
**Resources:** CDER White Oak 3157 Conference Room 3rd Floor

Appears This Way  
On Original

October 19, 2005

RECEIVED  
OCT 21 2005  
CDR / CDER

David G. Orloff, M.D.  
Director  
Division of Metabolism and Endocrinology Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg 22 Rm 3360  
Silver Spring, MD 20993

NEW CORRESP  
N-000-(C)

Re: **NDA 21-612**  
CIP-FENOFIBRATE (fenofibrate capsules) 50 mg, 100 mg, 150 mg

b(4)

Dear Dr. Orloff:

Reference is made to Cipher Pharmaceuticals' New Drug Application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. Reference is also made to submissions to the NDA since that time, and to the FDA's tentative approval letter dated July 15, 2004. Further reference is made to the amendment to the tentatively approved NDA submitted November 30, 2004, and the revised amendment to the tentatively approved NDA dated July 4, 2005.

In relation to Cipher's revised amendment to the tentatively approved NDA, a teleconference took place with Dr. Mary Parks and Ms. Margaret Simoneau on September 6, 2005. Cipher's proposed brandnames of LIPOFEN and ~~LIPOFEN~~ were discussed following preliminary feedback from the Division of Drug Marketing, Advertising and Communications (DDMAC). There were objections to the name ~~LIPOFEN~~ due to claims of efficacy implied by the ~~LIPO~~ part of the name. The brandname LIPOFEN, however, which also had some objections from DDMAC, may still be acceptable to the review division.

b(4)

b(4)

Regarding "LIPOFEN", the DDMAC considered "FEN" to be a truncated version of "fenofibrate", therefore identifying the active, and "LIPO" coming from "lipid", identifying the therapeutic area. Together, these could pose an issue for reminder advertisements. Cipher was being alerted to this fact, so that the limitations that would be placed on these promotional activities could be assessed. Dr. Parks stated, however, that even if the DDMAC objected to the name "LIPOFEN" (assuming that no new issues would be brought up by DDMAC prior to final review), the division would still accept the name. It was suggested that Cipher might consider submitting another name for consideration by the Agency, due to the potential promotional activity limitations.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-612

Galephar PR, Inc.  
Attention: Arthur M. Deboeck  
VP and General Manager  
US Representative for Cipher Pharmaceuticals, Ltd.  
Road 198 No. 100 km 14.7  
Juncos Industrial Park  
Juncos, PR 00777-3873

Dear Mr. Deboeck:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cip-Fenofibrate (fenofibrate Capsules).

We also the June 21, 2005 e-mail from ~~XXXXXXXXXX~~ to Ms. Valerie Jimenez, of this division, in which you requested responses to several questions regarding the requirements for establishing a claim that a fenofibrate product may be given without regards to meals.

b(4)

We have reviewed the submission and have the following comments. The questions are followed by our **bolded** responses.

1. Can a claim that a fenofibrate product can be taken without regard to meals be supported by a food effect study that demonstrates bioequivalence under low fat fed and fasted conditions?

**Response: No. a three-way cross-over study comparing high-fat fed, low-fat fed, and fasting condition is recommended.**

2. If yes, do both AUC and Cmax have to meet the bioequivalence criteria, or is it sufficient to only meet equivalence for AUC?

**The three-way cross-over study should be powered so that AUC would meet the bioequivalence criteria. With regard to Cmax, it would be a judgment call.**

3. Should the food effect study be single dose or multidose steady state?

**Response: a single dose study would be sufficient.**

If you have any questions, call Kati Johnson, Chief, Project Management Staff, at (301) 827-6380.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

/s/

-----  
David Orloff  
9/15/2005 05:10:36 PM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-612

Galephar PR, Inc.  
Attention: Arthur M. Deboeck  
VP and General Manager  
US Representative for Cipher Pharmaceuticals, Ltd.  
Road 198 No. 100 km 14.7  
Juncos Industrial Park  
Juncos, PR 00777-3873

Dear Mr. Deboeck:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cip-Fenofibrate (fenofibrate Capsules).

We also the June 21, 2005 e-mail from \_\_\_\_\_ to Ms. Valerie Jimenez, of this division, in which you requested responses to several questions regarding the requirements for establishing a claim that a fenofibrate product may be given without regards to meals.

b(4)

We have reviewed the submission and have the following comments. The questions are followed by our **bolded** responses.

1. Can a claim that a fenofibrate product can be taken without regard to meals be supported by a food effect study that demonstrates bioequivalence under low fat fed and fasted conditions?

**Response: No. a three-way cross-over study comparing high-fat fed, low-fat fed, and fasting condition is recommended.**

2. If yes, do both AUC and Cmax have to meet the bioequivalence criteria, or is it sufficient to only meet equivalence for AUC?

**The three-way cross-over study should be powered so that AUC would meet the bioequivalence criteria. With regard to Cmax, it would be a judgment call.**

3. Should the food effect study be single dose or multidose steady state?

**Response: a single dose study would be sufficient.**

If you have any questions, call Kati Johnson, Chief, Project Management Staff, at (301) 827-6380.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

/s/

-----  
David Orloff

9/13/2005 02:48:32 PM

Appears This Way  
On Original