CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-612

PHARMACOLOGY REVIEW

6/3/04

NDA 21-612/02

review signed off in DFS on 6/2/04

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-612
Review Number: 2

Sequence number/date/type of submission: March 30, 2004 (a complete response to our letter dated 12/18/03). 5/14/04 (BC, a pharm/tox response regarding the particle size of their fenofibrate drug product). Original application was submitted on December 26, 2003. It was a 505 (b) (2) application.
Information to sponsor: Yes ( ) No (X)

Sponsor: Cipher Pharmaceuticals Limited. St Michael, Barbados.

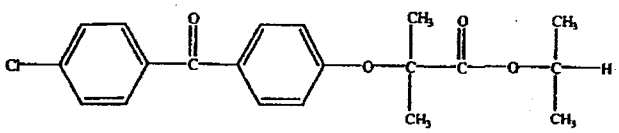
Manufacturer for drug substance: [redacted] However the manufacturer of the drug product is Galephar Pharmaceutical Research Inc, Puerto Rico. b(4)

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrine Drug products, **HFD #:** 510
Review completion date: 4/29/2004

Drug:

Trade name: Luxacor [redacted] CIP Fenofibrate capsules, 50, 100, 150, [redacted] mg strengths b(4)
Generic name (list alphabetically): Fenofibrate (BAN, rINN)
Code name: LF-178, Procetofene, CIP Fenofibrate.
Chemical name: 2-(4-(4-clorobenzoyl)phenoxy)-2-methyl-propanoic acid-1-methylethyl ester.
CAS registry number: 49562-28-9
Mole file number: N/A
Molecular formula/molecular weight: $C_{20}H_{21}O_4Cl$/360.83

Structure:



Relevant INDs/NDAs/DMFs: IND 62,780 [redacted], DMF NO. [redacted] DMF [redacted] DMF [redacted] b(4)

Drug class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester. It is a synthetic fenofibric acid prodrug used for the treatment of dyslipidemia.

Indication: Treatment of primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb), and hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

Clinical formulation: The drug is available in 50, 100, 150 ——— mg capsule strengths. [redacted] These contain the active drug and following inactive ingredients (see page). b(4)

Route of administration: oral

Proposed use: The drug is indicated alone (monotherapy), as an adjunctive therapy to diet for the reduction of elevated LDL-cholesterol, total cholesterol, TG, and Apo B and increase HDL-C in adult patients with primary hypercholestrolemia or mixed dyslipidemia (Fredrickson Types IIa, and IIb) at initial recommended dose of ——— in adults. It is also indicated in adult diabetic patients with hyper-triglyceridemia (Fredrickson Types IV, and V hyperlipidemia), at the initial recommended dose of 50 mg/day, with maximal dose of ——— b(4) b(4)

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: Sponsor has submitted a full response on 3/30/04 to our recommended changes dated 12/18/03, these are reviewed

Studies not reviewed in this submission: None

On March 30, 2004, sponsor has submitted a complete response to our letter dated 12/18/03. Original application was submitted by the sponsor on December 26, 2003. It was a 505 (b) (2) application.

Pharm/tox had recommended labeling changes under the 'Carcinogenesis and mutagenesis' and 'Teratogenic effects'. These changes have been made by the sponsor

Sponsor was also asked to provide the particle size of this fenofibrate (luxacor), as it has been shown that the particle size in the range of ——— nanometer size may have different toxicity profile compared to the initial formulation with the standard particle size. Sponsor addressed this concern on 5/14/04 by stating that the drug capsules are prepared [redacted] Particulate fenofibrate is not present according to the sponsor. Therefore, sponsor is unable to provide any information on the particle size of this fenofibrate as released in the gastrointestinal tract. Thus, from the sponsor's explanation it appears that the particle size is not a concern here since the drug remains in a ——— form. b(4) b(4) b(4)

External Recommendation: Labeling changes have been made by the sponsor in this response submission as recommended by us. From the preclinical standpoint, approval of this application is recommended.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21612/02 (CIP-fenofibrate ———) b(4)

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

/s/

Indra Antonipillai
6/2/04 12:18:46 PM
PHARMACOLOGIST
Approval of this application is recommended
Pharm/tox labeling changes have been made by the sponsor, approval of this application is recommended

Karen Davis-Bruno
6/3/04 09:13:39 AM
PHARMACOLOGIST
concur with recommendation

10/7/03

NDA 21-612

Review completed: September 29, 2003
Signed off in DFS on 10/7/03

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-612
Review Number: 1

Sequence number/date/type of submission: December 26, 2003 (original application), 4/21/03 (contained histopathology summary Table on 13-week toxicity study in dogs). 505 (b) (2) application.
Information to sponsor: Yes ( ) No (X)

Sponsor: Cipher Pharmaceuticals Limited. St Michael, Barbados. Since it is a foreign company they have appointed Galepher PR Inc. in Juncos, Puerto Rico as their agent.

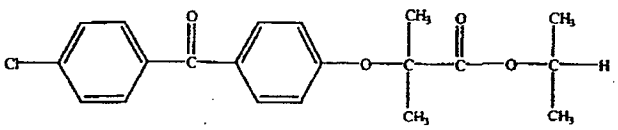
Manufacturer for drug substance: [redacted] b(4)
However the manufacturer of the drug product is Galephar Pharmaceutical Research Inc, Puerto Rico.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrine Drug products, **HFD #:** 510
Review completion date: 9/29/2003

Drug:

Trade name: CIP Fenofibrate capsules, 50, 100, 150, [redacted]mg strengths b(4
Generic name (list alphabetically): Fenofibrate (BAN, rINN)
Code name: LF-178, Procetofene.
Chemical name: 2-(4-(4-clorobenzoyl)phenoxy)-2-methyl-propanoic acid-1-methylethyl ester.
CAS registry number: 49562-28-9
Mole file number: N/A
Molecular formula/molecular weight: $C_{20}H_{21}O_4Cl/360.83$

Structure:



b(4)

Relevant INDs/NDAs/DMFs: IND 62,780 (CIP-fenofibrate), DMF NO [redacted] for the current fenofibrate, submitted by [redacted] DMF [redacted] for [redacted] DMF [redacted] for [redacted] b(4)

Drug class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester. It is a synthetic fenofibric acid prodrug used for the treatment of dyslipidemia.

Indication: Treatment of primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb), and hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

Clinical formulation: The drug is available in 50, 100, 150, [redacted] mg capsule strengths. The 200 mg capsule strength is also provided as two pivotal studies were conducted using this 200 mg strength capsules. These contain the active drug and following inactive ingredients (see page). b(4)

Route of administration: oral

Proposed use: The drug is indicated alone (monotherapy), as an adjunctive therapy to diet for the reduction of elevated LDL-cholesterol, total cholesterol, TG, and Apo B and increase HDL-C in adult patients with primary hypercholestrolemia or mixed dyslipidemia (Fredrickson Types IIa, and IIb) at initial recommended dose of [redacted] in adults. It is also indicated in adult diabetic patients with hyper-triglyceridemia (Fredrickson Types IV, and V hyperlipidemia), at the initial recommended dose of 50 mg/day, with maximal dose of [redacted] b(4) b(4)

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: A 13-week toxicity study in dogs, and two genotoxicity studies with CIP fenofibrate clinical formulation (with gelucire 44/14).

Studies not reviewed in this submission: None

Executive Summary

1. Recommendations

A. **Recommendation on approvability**

Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies:**

The preclinical studies are adequate to support the recommended doses up to [redacted]. No further pre-clinical studies are required b(4)

C. **Recommendation on Labeling:** see the labeling section on page 22 to 25

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies

Fenofibrate is an approved drug for oral use in Canada, Europe and US (as Tricor, NDA 19-304). Since extensive nonclinical studies have been conducted with the approved fenofibrate, only one non-clinical 13-week bridging toxicity study was conducted in dogs with CIP fenofibrate to compare it with the micronized fenofibrate, and two geno-toxicity studies were conducted with the current CIP fenofibrate drug product. The nonclinical findings with CIP fenofibrate in general were similar to the approved micronized fenofibrate (Tricor) in dogs.

B. Pharmacologic activity

Like other fenofibrates, it is a fibric acid derivative, it increases lipolysis and elimination of triglyceride rich particles from plasma by activating lipoprotein lipase.

C. Nonclinical safety issues relevant to clinical use

No new nonclincal safety issues relevant to the clinical use have been identified in a limited one 13-week toxicity study in dogs.

III. Administrative

A. Reviewer signature: ----------

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21612 (CIP fenofibrate)

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Fenofibrate is a fibric acid derivative, and is used as a lipid lowering agent. The underlying mechanisms of its action are not fully established. The major effect of the drug is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. It inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in rat liver. In addition the drug decreases cholesterol biosynthesis which may in turn enhance LDL clearance by increased LDL receptor activity. The drug may also mobilize cholesterol deposited in peripheral tissues, decrease hyper-aggregability and platelet derived growth factor, and increase esterification of cholesterol in plasma, all of the above actions could contribute to inhibition of atherogenesis. The potential mechanisms of action of fenofibrate are described in a Table below.

Table: Mechanisms of lipid modifying actions of fenofibrate:

Table 2.6.2.1.2 Potential Mechanisms of Action of Fenofibrate

- Inhibition of cholesterol synthesis prior to mevalonate formation (rats)
- Diminution of HMG-CoA reductase activity (rat microsomes, leukocytes of patients)
- Increased cholesterol uptake in perfused livers (rats)
- Increased lipoprotein lipase activity (patients with decreased triglyceride levels)
- Increased LCAT activity (patients with increased HDL levels)
- Improved balance between catabolism and synthesis of Apo Al (patients with decreased Apo-Al levels)
- Increased high-affinity LDL receptor activity (patients, LDL)

HMG-CoA = hydroxymethylglutaryl coenzyme A; LCAT = lecithin-cholesterol acyltransferase; HDL = high density lipoprotein; Apo Al = apolipoprotein Al; LDL = low-density lipoprotein

Fenofibrate inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in rat liver. Fenofibrate has been shown to decrease cholesterol synthesis from acetate but not mevalonate in rat liver microsomes, presumably by inhibiting HMG CoA reductase. Fenofibrate increases the ratio of apolipoprotein CII (which activates lipoprotein lipase) to apolipoprotein CIII, whose main effect is to inhibit the activity of lipoprotein lipase. (P3)

Fenofibrate is currently a marketed drug in US, as Tricor. Up to 200 mg/day are approved doses. Both micronized and non-micronized formulations are approved, but the micronized drug has increased absorption. However, the absorption is still variable/incomplete and dependent on food. The micronized 67 mg (as lypantyl 200) is equivalent to 100 mg of the conventional form. It is marketed in Canada as Lipidil Micro and Lipid Supra

Micronization of the drug is supposedly time consuming and costly operation, as the material must comply with the stringent particle size specifications. The current sponsor (Cipher Pharmaceuticals) has come up with the new formulation of the drug, which they claim has bioavailability of the micronized form, [redacted] but the manufacturer of the drug product is Galephar Pharmaceutical Research Inc, Puerto Rico. b(4)

The Clinical formulation contain the active drug and following inactive ingredients:

Table. Composition of CIP-fenofibrate:

The quantitative composition for Fenofibrate 50, 100, 150, [redacted] mg Capsules follows in the table below. b(4)

Ingredient (and Test Standard)	Amount per Capsule (mg) Strength: 50 mg	Amount per Capsule (mg) Strength: 100 mg	Amount per Capsule (mg) Strength: 150 mg	Amount per Capsule	Amount per Capsule (mg)
Fenofibrate (EP)	50	100	150		
Lauroyl Macrogol Glycerides Type 150 (Gelucire 44/14)					
Polyethylene 20,0					
Polyethylene Glycol 8,000 (NF)					
Hydroxypropylcellulose (NF)					
Sodium Starch Glycolate (Explotab) (NF)					
Total Fill weight					
Gelatine Capsule (NF)					
Weight					
Size					
Cap					
Body					

b(4)

b(4)

Physical chemical properties: CIP-fenofibrate is a white crystalline powder with melting point of 79-82°C. The particle size is irrelevant because the drug is dissolved in hot liquid blend. It is very soluble in dichloromethane, soluble in ethanol, and insoluble in water

The CIP-fenofibrate consists of hard gelatin capsules containing the active drug. [redacted] b(4)

Thus the final product [redacted] is filled in a hard gelatin capsule. This is the reason that the present drug (CIP-fenofibrate) [redacted] to exhibit the bioavailability of micronized fenofibrate like Tricor.

b(4)

This new oral formulation contains gelucire 44/14 up to doses of [redacted] Gelucire is a lipid vehicle, it consists of glycerides and polyethylene glycol esters, it [redacted] b(4)
Also new formulation uses polyethyleneglycol (PEG) 20.000 up to doses of [redacted] and PEG 8000 up to doses of [redacted] b(4)
Other inactive ingredients are hydroxy propylcellulose [redacted], and sodium starch glycolate [redacted] These latter two excipients have been used at the recommended or higher doses in other approved products in the FDA inactive ingredient guide, 1996. b(4)

The process involves [redacted]

b(4)

Since extensive non-clinical studies have been conducted with the approved fenofibrate Tricor (under NDA 19-304), no additional non-clinical studies have been considered necessary, and have not been provided for the current drug (Cipher fenofibrate).

b(4)

However, since this drug uses a new formulation (which contains gelucire 44/14 [redacted] and PEG 20000 [redacted] the sponsor was asked at a pre-IND meeting to provide adequate support for each excipient. In an IND 62,780, sponsor had provided a [redacted] in which a 13-week toxicity study with a 4-week recovery period (at 400, 1000, 2500 mg/kg/day) was conducted with gelucire 44/14 in dogs (n=3-5/dose/group, a GLP and QA study conducted by [redacted] in 1995). In this study doses up to 1000 mg/kg of gelucire 44/14 were safe with no histopath findings in dogs at the highest dose (only controls and high dosed animals were examined for histopath findings). At 2500 mg/kg/day clinical signs (diarrhea, soft and mucoid feces) were noted with gelucire 44/14 in dogs. Sponsor has also provided three genotoxicity studies with the excipient gelucire 44/14. Two of these (AMES and mouse lymphoma) were negative with gelucire 44/14, but there was a concern about the third in vivo micronucleus assay. Sponsor was asked to clarify the number of mortalities and cause of death observed following initial dosing of gelucire 44/14 (5000 µg/ml) in the 'in vivo mouse micronucleus assay (PH-309-GAF-001-95). Additionally, they were asked to clarify a dose dependent increase in MPCE that was observed in males at 24 hrs in the above assay (which appeared to be within historical background range, but sponsor was asked to address this and explain the condition used to establish historical range, see IND 62,780 review). In a subsequent submission (6/20/02) sponsor provided the mortalities in the in vivo mouse micronucleus assay as requested. In the first assay 4/5 mice died at a high dose and study required at least 6 per group, so they added new set of mice and this time they did not die. However sponsor was unable to explain the cause of death in mice in the first assay, and did not provide the historical control data for MPCE at 24 hrs harvest time in this micronucleus assay.

b(4)

b(4)

Note that in the current NDA submission sponsor has provided 2 genotox studies (in vitro chromosome aberration assay and AMES assay) containing gelucire 44/14, and both geno-toxicity assays were negative.

The excipients PEG 8000 and PEG 20000 have been used in other approved products in the FDA inactive ingredient guide at levels used in this product. For complete review of above studies including genotoxicity studies with gelucire 44/14, see IND 62,780 signed off in DFS on 7/23/01.

Following 13-week study in dogs, and two geno-toxicity studies with the present new formulation of the drug (CIP-fenofibrate) have been provided in this NDA:

IV. General Toxicology:

Study title: A 13-Week Oral Toxicity Study of Fenofibrate in Dogs (Study No. 11502)

Key study findings: Both the CIP-fenofibrate and micronized fenofibrate (240-300 mg/kg/day) produced decreases in BW in dogs (males by up to 16-20%, females by up to 28%) compared to controls. Both fenofibrates produced slight histopath findings in the female liver and in epididimys in male dogs. Note that in this study there were only 3 dogs/sex/group, plasma levels were variable, and initially AUC values and histopathology summary Table was not provided. No significant differences between CIP-fenofibrate and marketed micronized fenofibrate were observed from this limited study.

Study no: 11502
Volume #, and page #: 1.3, page 36
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 1/11/02
GLP compliance: Yes
QA report: yes (X) no ( )
Drug lot #, and % purity: Cipher fenofibrate hard gelatin capsules, lot # 3E012, manufactured by Galpher P.R. inc., 99% pure. Positive control; Apotex fenofibrate micronized capsules, lot # GA9122, purity 96.2%
Formulation/vehicle: Cipher (CIP) fenofibrate placebo gelatin capsules manufactured by Galpher P.R. inc, lot # 5L01

Methods (unique aspects):
Dosing: 2000 mg/day of the CIP-fenofibrate or micronized fenofibrate
Species/strain: Dogs, Beagle
#/sex/group or time point (main study): 3/sex/dose
Age: Approximately 4-4.5 months of age
Weight: Males 8.2-8.5 kg, females 6.3-7.0 kg.

Doses in administered units: Male and female dogs were dosed with the placebo or 2000 mg/day (five 200 mg capsules twice daily, 1000 mg twice a day, or total dose of 2000 mg/day) of the drug CIP-fenofibrate, or marketed micronized fenofibrate.

Route of administration: Oral, 5 gelatin capsules BID (or total dose of 2000 mg/day) for 13 consecutive weeks with food (high fat content of 16.3%).

Table 1. Study design:

Table 2 **Groups, Dose Levels and Dosing Schedule**

Group	Dose Level	No. M/F Per Group	Route of Administration and Frequency of Dosing
1. Control Group (Placebo Capsules – Cipher Formulation)	5 x placebo caps BID	3 / 3	Orally, twice a day (total daily dose = 0)
2. Test Fenofibrate Group (Cipher Formulation - Manufactured by Galephar P.R. Inc.)	5 x 200 mg caps BID	3 / 3	Orally, twice a day (total daily dose = 2000 mg)
3. Control Fenofibrate Group (Apotex Micronized Capsules)	5 x 200 mg caps BID	3 / 3	Orally, twice a day (total daily dose = 2000 mg)

Observations and times:
Clinical signs: Once daily
Body weights: Weekly
Food and water consumption: Daily
Ophthalmoscopy: Prior to treatment, and once during week 13.
Electrocardiography (ECG): Prior to treatment, and once during weeks 6 and 13.

Hematology: Prior to treatment, and during weeks 6 &13.
Clinical chemistry: Prior to treatment, and during weeks 6 and 13.
Urinalysis: Prior to treatment, and during weeks 6 and 13.
Gross pathology: At sacrifice.
Organs weighed: Organs weighed are shown below:

The weight of the following organs were recorded: spleen, liver, lungs, kidneys, adrenals, heart, pituitary, prostate, thymus, thyroids with parathyroids, uterus, ovaries/testes, and brain. Paired organs were weighed together.

Histopathology: This was performed at sacrifice on tissues, listed below.

Tissues collected for histopathology in the 13 week dog toxicity study:

The following tissues were preserved for histopathological examination immediately after gross necropsy was performed:

Adrenal glands	Salivary gland (major)
Aorta	Skeletal muscle
Animal identification (ear with tattoo)	Peripheral nerve (sciatic)
Brain	Skin & subcutis
Heart	Spleen
Small intestine (Duodenum, Jejunum, Ileum)	Sternum (bone marrow)
Cecum	Stomach
Colon	Thymus
Kidneys (both)	Trachea
Liver	Eyes with optic nerve
Lung	Pancreas
Lymph nodes (abdominal, mandibular and/or cervical)	Prostate
Urinary bladder	Parathyroids
Thyroid (both lobes)	Testes/Ovaries
Epididymides (both)	Uterus
Oesophagus	Vagina
Pituitary gland	Tongue
	Mammary Gland

Section of cervical, thoracic, lumbar and sacral spinal cord.

Toxicokinetics: On days 28, 56 and 84, prior to first dose

Results:
Mortality: None

Clinical signs: No drug related effects were observed.

Body weights: Body weights were lower in both fenofibrate treated groups vs controls on day 92 (males 14.0, 11.8, 11.3 kg with placebo, CIP-fenofibrate and micronized-fenofibrate respectively; females 10.0, 7.1, 7.4 kg respectively). Sponsor states that reductions in BW with fenofibrate are expected effects.

Table. Body weights in males and females

Table 3 **Group Body Weight Summaries (kg) – Means ± S.D. and Group Body Surface Area (BSA – m^2)**

Group	N	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 92
1. Placebo Control Male	3	8.5 ± 0.4 (0.466)	9.6 ± 0.5 (0.506)	10.9 ± 0.4 (0.551)	12.0 ± 0.4 (0.587)	12.9 ± 0.4 (0.616)	13.3 ± 0.6 (0.629)	14.0 ± 0.6 (0.651)
2. Test Fenofibrate Male	3	8.2 ± 0.3 (0.455)	9.2 ± 0.7 (0.492)	10.0 ± 0.9 (0.526)	10.8 ± 1.1 (0.547)	11.5 ± 1.2 (0.571)	11.9 ± 1.2 (0.584)	11.8 ± 1.4 (0.581)
3. Control Fenofibrate Male	3	8.2 ± 0.5 (0.455)	9.2 ± 0.8 (0.492)	9.8 ± 1.1 (0.513)	10.3 ± 1.3 (0.530)	10.9 ± 1.5 (0.551)	11.3 ± 1.6 (0.564)	11.3 ± 2.1 (0.564)
1. Placebo Control Female	3	7.0 ± 0.8 (0.410)	7.8 ± 1.1 (0.441)	8.3 ± 1.4 (0.459)	9.2 ± 1.6 (0.492)	9.7 ± 1.8 (0.509)	10.1 ± 2.1 (0.523)	10.0 ± 2.3 (0.526)
2. Test Fenofibrate Female	3	6.3 ± 0.3 (0.382)	6.3 ± 0.6 (0.382)	6.2 ± 0.6 (0.378)	6.4 ± 0.5 (0.386)	7.0 ± 0.7 (0.410)	7.1 ± 0.7 (0.414)	7.1 ± 0.6 (0.414)
3. Control Fenofibrate Female	3	6.6 ± 0.4 (0.394)	7.3 ± 0.4 (0.421)	7.4 ± 0.3 (0.425)	7.7 ± 0.4 (0.437)	7.9 ± 0.4 (0.444)	8.0 ± 0.5 (0.448)	7.4 ± 0.4 (0.425)

Note: Group mean BSA's (m^2) are presented in brackets.

Figure. Mean Body weights in males

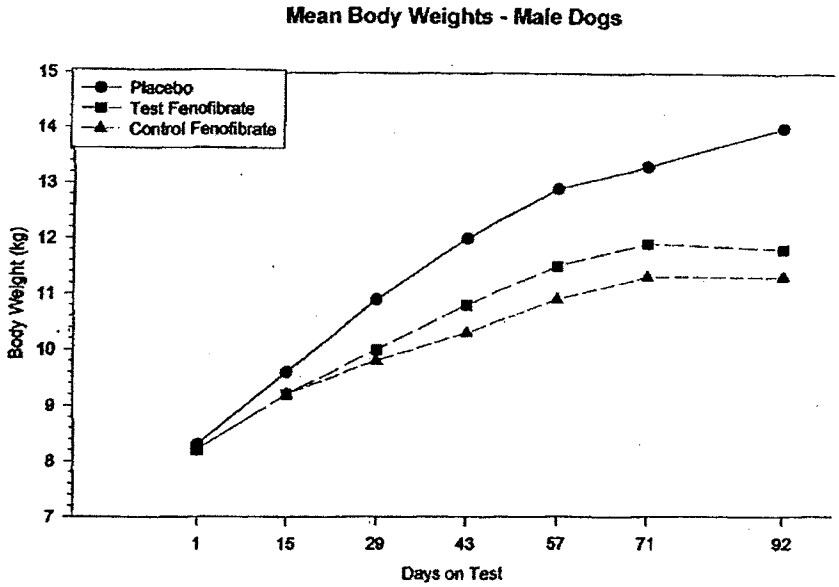
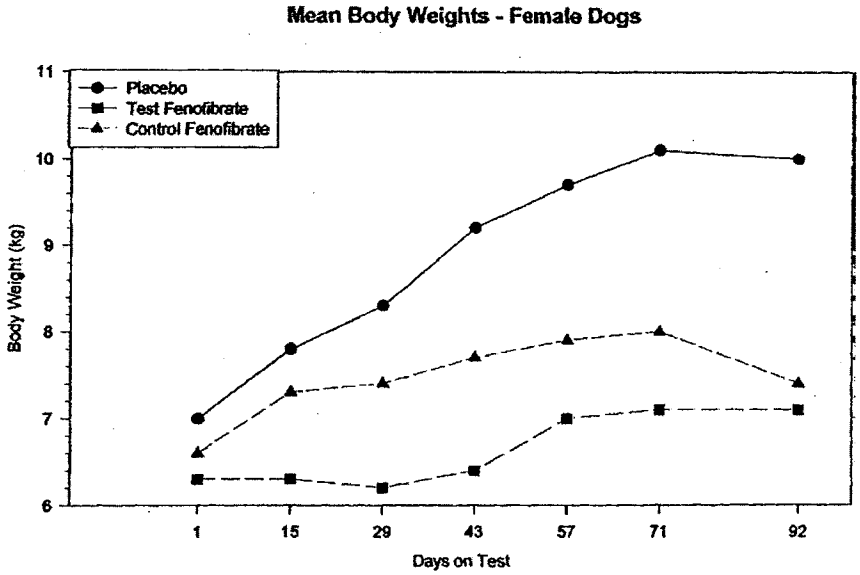


Figure. Mean body weights in females



Food consumption: No treatment related effects on food consumption were observed.

Ophthalmoscopy: No treatment related effects were observed

Electrocardiograms: No drug related effects on ECG were observed in weeks 6 or 13.

Table 5 ECG Measurements, Group Means + S.D. – Mid Study (week 13)

Group	HR [bpm]	P Dur [sec]	P Amp [mV]	PR Int [sec]	QRS Dur [sec]	R Amp [mV]	QT Interval [sec]	ST Seg [mV]	MEA of QRS [mV]
1. Placebo Control Male	152 ± 12	0.7 ± 1.1	2.3 ± 0.6	1.4 ± 2.3	0.09 ± 0.02	0.77 ± 0.5	0.2 ± 0.01	WNL	43 ± 12
2. Test Fenofibrate Male	105 ± 16	0.03 ± 0.01	0.13 ± 0.06	0.07 ± 0.01	0.11 ± 0.01	1.07 ± 0.32	0.2 ± 0.01	WNL	80 ± 17
3. Control Fenofibrate Male	116 ± 3	0.04 ± 0.0	0.17 ± 0.06	0.08 ± 0.0	0.11 ± 0.1	0.93 ± 0.49	0.2 ± 0.01	WNL	47 ± 21
1. Placebo Control Female	119 ± 21	0.04 ± 0.0	0.2 ± 0.0	0.08 ± 0.0	0.09 ± 0.02	0.87 ± 0.47	0.2 ± 0.02	WNL	40 ± 35
2. Test Fenofibrate Female	122 ± 35	0.03 ± 0.01	0.17 ± 0.06	0.1 ± 0.02	0.10 ± 0.0	0.67 ± 0.06	0.2 ± 0.01	WNL	50 ± 20
3. Control Fenofibrate Female	110 ± 33	0.03 ± 0.01	0.17 ± 0.06	0.09 ± 0.01	0.10 ± 0.0	0.4 ± 0.26	0.2 ± 0.01	WNL	58 ± 18
Normal Ranges	70 – 160	≤ 0.04	≤ 0.4	0.06 – 0.13	≤ 0.05	≤ 2.5	0.15 – 0.25	+0.1 to –0.2	+40 to +100

Note : WNL – within normal limits

Hematology: No drug related effects were observed.

Biochemistry: Cholesterol was lower in week 13 in both fenofibrate treated groups compared to controls (males 4.6, 2.6, 2.6 mmol/l in controls, CIP fenofibrate and micronized fenofibrate respectively). These values in females were 4.6, 2.6, 2.0 mmol/l respectively, however in both sexes these were not significantly different from controls. No changes in TG levels were observed.

Urine analysis: No treatment related effects were observed

Organ Weights: In males, absolute testicular (21.2, 15.2, 14.5 g with placebo, CIP-fenofibrate and control-fenofibrate respectively), heart (101.4, 95.4, 86.8 g), and thymus (22.3, 18.8, 10.3 g respectively) weights were lower with both fenofibrates. In females, absolute spleen (71.0, 31.3, 51.8 g respectively), heart (76.9, 65.2, 66.3 g), thymus (16.2, 5.4, 3.8 g respectively), and uterus (2.2, 0.81, 0.94 g) weights were lower. Relative mean body weights were not provided

Gross pathology: one of 3 females in the CIP-fenofibrate group had 8 ml of serous fluid in the pericardium. No other drug related changes were observed.

Histopathology: Histopath data were very poorly presented. No summary Table was initially provided. Narrative summary was provided showing some differences in animals but it was not stated which group had these differences. All the changes were considered incidental. Sponsor states that there were some differences in the liver of some female dogs like reduced cytoplasmic density in periportal area, and dilation of sinusoids in the perivenous area with increased prominence of sinusoidal endothelial nuclei. However, it was unclear how many animals had these findings in the initial submission. The data were submitted on 4/21/03. These data are presented below and suggest that in general findings with two fenofibrate drugs were similar. Liver of female dogs had increased prominence of sinusoidal endothelial nuclei with both fenofibrates (0/3, 3/3*, 3/3 with placebo, CIP-fenofibrate and control-fenofibrate respectively). Similar findings were also observed in thyroid, spleen, kidney, etc with minor differences. However there was a higher incidence of cervical lymph node hyperplasia in females with CIP-fenofibrate vs the control fenofibrate (0/3, 2/3, 0/3 respectively). Most findings were of minimal severity (except in thyroid* and liver*, where findings were of minimal to mild severity).

Table. Histopath changes with placebo, CIP-fenofibrate and control fenofibrate (0, 2000, 2000 mg/day respectively) in a 13-week study in dogs.

	Males	Females
Thyroid interstitial Cell hyperplasia (minimal)	0/3, 2/3, 2/3	2/3, 2/3*, 2/3*
Liver cytoplasm, decreased portal density (minimal)	0/3, 0/3, 2/3	0/3, 1/3, 2/3
Liver interstitium increased endothelial prom (minimal)	0/3, 2/3, 2/3	0/3, 3/3*, 3/3
Biliary ducts, periportal lymph cuffs (minimal)	1/3, 1/3, 2/3	0/3, 0/3, 3/3
Kidney tubules medulla Intranephronic calculosis (minimal)	0/3, 2/3, 2/3	0/3, 2/3, 1/3
Spleen folic atrophy (minimal)	0/3, 1/3, 0/3	1/3, 0/3, 0/3
Spleen folic hyperplasia (minimal)	0/3, 1/3, 1/3	0/3, 1/3, 1/3
Cervical spinal cord axonal degeneration (minimal)	0/3, 1/3, 0/3	1/3, 0/3, 0/3
Cervical lymph node medullary sclerosis in males or hyperplasia in females (minimal)	0/3, 1/3, 1/3	0/3, 2/3, 0/3

*= minimum to mild severity scores

Toxicokinetics. The plasma levels are shown in the Table. The number of animals was only 3/sex/group and values were variable. It is basically very difficult to pick up any differences between two fenofibrates (CIP-fenofibrate and micronized Apotex-fenofibrate). There is a definite gender effect, females had higher values than males with both fenofibrates (in males means were 6.2 ± 3.0 & 11.1 ± 13.2 with CIP fenofibrate and micronized fenofibrate respectively, in females these values were 28.6± 9.9 & 41.1±19.7 respectively).

Table: plasma concentration of the drug in 13 week study in dogs, values are shown in weeks 0, 28, 56, 84, 91

Table 6 **Plasma Concentrations of Fenofibric Acid (ug/mL) in Male Dog**

Group	Dog	Day				
		0	28	56	84	91*
Placebo	VOT-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Placebo	XHT-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Placebo	YDT-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Cipher	VPT-1	BLOQ	9.00	7.75	13.4	5.33
Cipher	XXT-1	BLOQ	10.6	9.36	9.30	9.59
Cipher	ZFT-1	BLOQ	6.58	8.80	9.46	3.69
Apotex	SST-1	BLOQ	12.6	12.4	13.5	26.2
Apotex	SXT-1	BLOQ	3.39	1.38	1.41	1.32
Apotex	TFT-1	BLOQ	9.18	4.78	9.60	5.91

Table 7 **Plasma Concentrations of Fenofibric Acid (µg/mL) in Female Dog**

Group	Dog	Day				
		0	28	56	84	91
Placebo	UCS-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Placebo	YLS-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Placebo	ZES-1	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Cipher	WOS-1	BLOQ	32.8	62.2	29.4	32.1
Cipher	XIS-1	BLOQ	32.8	73.1	19.2	17.4
Cipher	YHS-1	BLOQ	71.3	39.0	25.9	36.2
Apotex	XTS-1	BLOQ	59.0	31.4	39.3	33.6
Apotex	YKS-1	BLOQ	41.0	9.67	23.3	26.3
Apotex	YVS-1	BLOQ	29.8	24.1	25.5	63.5

BLOQ : Below the lower limit of quantitation (1.00 µg/mL)

Toxicology summary: In a 13 week toxicity study in dogs, 2000 mg/day of CIP-fenofibrate were compared to micronized fenofibrate (doses were ≈ 240 mg/kg/day in males, and 300 mg/kg/day in females, based on weights of animals) vs placebo. Both the CIP-fenofibrate and micronized fenofibrate produced decreases in BW in dogs (males by up to 16-20%, females by up to 28%) compared to controls. Both fenofibrates produced slight decreases in testicular, heart, thymus, spleen and uterine weights. The target organs of toxicity were liver (reduced cytoplasmic density and increased prominence of sinusoidal endothelial nuclei), which were present with higher incidences in the female dogs than in male dogs, but were similar with both fenofibrates. Similar toxicity was also noted with both fenofibrates in the kidney tubules (intranephrotic calculosis), and spleen (hyperplasia). However there was a higher incidence of cervical lymph node hyperplasia in females with CIP-fenofibrate vs the control fenofibrate (0/3, 2/3, 0/3 in placebo, CIP-fenofibrate and control-fenofibrate respectively). In summary, no significant differences between CIP-fenofibrate and marketed micronized fenofibrate were seen. Note that this study was limited, as there were only 3 dogs/sex/group, no AUC values in dogs were provided, and plasma levels were variable. Previous toxicity studies in dogs with marketed fenofibrate have not shown liver to be the target organ of toxicity (although liver has been identified as a target organ of toxicity in rats), but cholelithiasis, with some nephritis and weight loss has been observed in dogs in previous studies. **No overt toxicity could be established in this study, and higher doses could have been used here.**

V. GENETIC TOXICOLOGY:

1) In Vitro Chromosome Aberration in Cultured Chinese Hamster ovary (CHO) cells

Key findings: The test was negative

Study no: 11500
Volume #, and page #: 1.1, pg.1
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 11/13/01
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: CIP- fenofibrate 3E012 (in Gelucire 44/14, PEG 20,000, Hydroxypropylcellulose and sodium starch Glycolate), control fenofibrate- Sigma lot # 110K1645.

Formulation/vehicle: DMSO

Methods:

Strains/species/cell line: The clone CHO-WB_1 of the CHO cell line, obtained by [redacted] from the [redacted]. b(4)

Dose selection criteria:

Basis of dose selection: This was based on relative cell growth (RCG) compared to solvent control, and formation of precipitate in the medium. The solvent control was DMSO in HEPES.

Range finding studies: In the range finding study at 0.32 & 0.128 mg/ml, reduction in RCG of 38% and 70% was observed with S9 activation (3 hrs exposure and harvested 18 hrs after initiation of treatment) and without S9 activation (20-24 hrs incubation) respectively, see Table below. Also, slight precipitate was observed at ≥ 0.128 mg/ml and moderate at ≥ 2 mg/ml. Range of 2-80 µg/ml was selected for non-activated system, and 5.1-200 µg/ml for activated system.

Table. Chromosome aberration in CHO cells, Range finding study with CIP-fenofibrate

WITHOUT ACTIVATION					WITH ACTIVATION				
Test Article Conc.	No. of Cells Per Flask ($X 10^4$)	Mean No. Of Cells ($X 10^4$)	RCG	Precipitate Beginning/ End of Exposure	Test Article Conc.	No. of Cells Per Flask ($X 10^4$)	Mean No. Of Cells ($X 10^4$)	RCG	Precipitate Beginning/ End of Exposure
Solvent	0.50	0.50	100%	NP / NP	Solvent	0.40	0.40	100%	NP / NP
Negative Media Control	3.38	3.38	676%	NP/NP	Negative Media Control	2.35	2.35	588%	NP/NP
5 mg/mL	0.00	0.00	0%	MP / SP	5 mg/mL	0.00	0.00	0%	MP / SP
2 mg/mL	0.00	0.00	0%	MP / SP	2 mg/mL	0.00	0.00	0%	MP / SP
0.8 mg/mL	0.00	0.00	0%	SP / SP	0.8 mg/mL	0.00	0.00	0%	SP / SP
0.32 mg/mL	0.00	0.00	0%	SP / NP	0.32 mg/mL	0.15	0.15	37.5%	SP / SP
0.128 mg/mL	0.35	0.35	70%	SP / NP	0.128 mg/mL	1.60	1.60	400%	SP / NP
0.05 mg/mL	3.75	3.75	750%	NP / NP	0.05 mg/mL	2.10	2.10	525% *	NP / NP
0.02 mg/mL	2.55	2.55	510%	NP / NP	0.02 mg/mL	2.55	2.55	638%	NP / NP

LEGEND :

RCG = Relative Cell Growth = $\frac{\text{No. of Cells in the Test Flask}}{\text{No. of Cells in the Solvent Flask}} \times 100$

Precipitate :

NP : no precipitate
SP : slight precipitate
MP : moderate precipitate
EP : extreme precipitate

Note: The solvent controls and 5 mg/mL levels contained a large volume of DMSO (0.5mL) which caused toxicity. The standard volume of DMSO to add, that will cause minimal toxicity, is 0.1mL or less. Since the amount of DMSO is diluted 2.5 fold with each diluted test article level, we can conclude that any toxicity from 0.32 mg/mL and below was due to the test article and not the DMSO. Studies B1 and/or B2 will be performed using 50 µl DMSO in media.

Conclusion: The test article was toxic at a concentration of 0.32 mg/mL and above.
Perform chromosome aberration assay at the following concentrations:

- 0.2, 0.08, 0.032, 0.0128, and 0.0051 mg/mL for –S9
- 0.08, 0.032, 0.0128, 0.0051, and 0.002 mg/mL for +S9.

Test agent stability: not specified

Metabolic activation system: both the phenobarbitol-5, 6-benzoflavone or fenofibrate induced rat liver homogenate (S9) were used.

In the definitive assay phenobarbitol-5, 6-benzoflavone induced S9 was used, while in the confirmatory assay, fenofibrate induced rat liver homogenate (S9) was used. This is because fenofibrate is a potent inducer of drug metabolizing enzymes in the rat liver.

Controls:

Vehicle: DMSO

Positive controls: MMC (mitomycin C) in the absence of metabolic activation, CP (cyclophosphamide) in the presence of metabolic activation

Exposure conditions:

Incubation and sampling times: Exposure was 3 hrs and harvest time was 18 hrs after the initiation of treatment.

Doses used: 5.1, 12.8, 32, 80, 200 µg/ml with S9 activation.
2, 5, 12.8, 32, 80 µg/ml without S9.

Contents of 200 mg fenofibrate capsules were dissolved in DMSO by heating for 1 hr at 45° C with shaking at 400 rpm

Toxicity in cultures: This was determined by relative cell growth (RCG) and relative mitotic index (RMI). At 80 µg/ml, RCG was 50-57% with and without

S9. The RMI range at these doses was 50-79% & 51-101% respectively. At 200 µg/ml the cell division was severely inhibited, and few metaphases from each duplicated culture were observed.

Study design: Two assays (a definitive and confirmatory) were carried out. Duplicate cell cultures were exposed to various concentrations of the drug. Cells were incubated for 20-24 hrs, exposed to the agents for 3 hrs and harvested 18 hrs after initiation of treatment. Positive (MMC & CP) and negative (DMSO) controls were similarly treated. Also the positive fenofibrate control (0.8 mg/ml) was included in the confirmatory assay. It is unclear if cells were just exposed to one dose of the pure fenofibrate.

Analysis:
No. of replicates: duplicate
Counting method: cell counter. 100 metaphases from each of the duplicated cultures were observed

Criteria for positive results: If the percent of cells with aberrations with the test agent show positive dose-response trend and a statistical significant increase over the vehicle control, or if the increase is observed at one or more concentrations, the drug would be considered positive.

Results:
Study validity: Appropriate dose selection was made for this study, and positive control responses were acceptable.

Study Outcome: In both the definitive and confirmatory assays the drug CIP-fenofibrate did not show any increase in structural chromosome aberrations at doses ranging from 5-80 µg/ml in the presence or absence of metabolic activation. Note that relatively lower doses of the drug (5-80 ug/ml) were examined in this study, as higher doses of the drug produced toxicity. The positive controls (with or without S9 mix) showed a significant increase in aberrations. The positive control fenofibrate (0.8 mg/ml) also did not induce any increase in structural chromosome aberrations. In conclusion, the drug was not clastogenic in this assay.

Summary of individual study findings:
Study validity: It was a valid study
Study outcome: The drug was negative in this assay and did not induce chromosomal aberrations in cultured Chinese Hamster ovary cells.

2) **Study Title: Effects of CIP-fenofibrate on Salmonella/Escherichia Coli Reverse Mutation Test: (AMES TEST).**

Key findings: The drug was negative in this assay.

Study no: 11501
Volume #, and page #: 1.1, pg.1
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 1/30/02
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: CIP- fenofibrate 3E012 (in Gelucire 44/14, PEG 20,000, Hydroxypropylcellulose and sodium starch Glycolate), control fenofibrate- Sigma lot # 110K1645.

Formulation/vehicle: Acetone
Study Endpoint: Mutagenesis (in vitro, base substitution mutations)

Methodology
Strains Employed: Salmonella typhimurium tester strains TA1535, TA1537, TA1538, TA98, TA100 (histidine requiring strains which require both biotin as well as histidine for growth) and E. coli tester strain WP2 urvA. The plasmid derivatives TA98, TA100 and E. coli tester strain WP2 urvA have increased sensitivity to certain mutagens

Dose Selection Criteria: The dose selection was based on a preliminary dose-range finding study where no cytotoxic effect of the drug was observed at doses up to 5 mg/plate using strains TA100 and WP2urvA. The cytotoxicity was based on reversion frequency, viability, and integrity of the background lawn. At 5 mg/plate with or without S9, slight precipitate was observed. Therefore, in the main assay, doses of 0.05, 0.1, 0.5, 1 and 5 mg/plate were selected for all strains. Two independent assays were conducted in triplicates.

Metabolic Activation System: Rat liver homogenate S9 from Aroclor -1254 induced rats was used for the initial assay, and fenofibrate induced rat liver homogenate (S9) was used for the confirmatory assay. Fenofibrate-induced S9 seems to have a substrate specificity that is different from Arcolor induced S9.

CONTROLS:
Solvent or Negative Control: Acetone.
Positive Controls: sodium azide (50 ug/ml), 2-nitrofluorene (50 ug/ml), 2-aminoanthracene (10 ug/ml), 9-aminoacridine (1000 ug/ml), benzo (a) pyrene (50 ug/ml), cyclophosphamide (1000 ug/ml).
For E-coli, 2-aminoanthracene (100 ug/ml) & methyl methanesulfonate (1 % v/v) were used.

Exposure Conditions
Methods: Two independent mutation tests were performed. A 'plate incorporation' method was used. The tester strains in the plate were exposed to the vehicle, drug, or positive controls. The cells were incubated for 2-3 days at 37^0C on minimal agar, in both the presence and absence of S9. Colonies were counted (method of counting was not stated if it was manual or electronic).

Concentrations Employed: 0.05-5 mg/plate.

Analysis
Counting method: This was not provided

Criteria for Positive Genotoxic Results: If the drug induces an increase in revertant colonies in a dose dependent manner, or if it is statistically significant, and the increase is at least 2 times for strains TA98, TA100 and 3 times for strain TA1535, TA153, & WP2 urvA compared to vehicle controls, the drug would be considered positive.

Results:
Study validity: Appropriate dose selection was made for this study, and positive control responses were acceptable.
Study Outcome: The drug CIP-fenofibrate was not mutagenic in any of the tester strains at doses ranging from 50-5000 µg/plate in the presence or absence of metabolic activation. However, a significant increase in the number of revertant colonies was observed with positive controls (with or without S9 mix). In conclusion, the AMES test was negative.

SUMMARY:
Statement: The reviewer concurs with the sponsor that the AMES test was negative for CIP-fenofibrate.

Genetic toxicology summary: CIP-fenofibrate drug product (this formulation which also contained gelucire 44/14) was not mutagenic/cytogenic in the following 2 tests: Ames test, and in vitro chromosome aberration test in Cultured Chinese Hamster ovary (CHO) cells.

As indicated earlier, there was a concern about positive micronucleus assay with gelucire 44/14, in which the sponsor was unable to explain the mortality in animals initially assigned in the study, but in new set of mice the mortality was not observed. This, combined with the weight of evidence from the two additional geno-toxicity studies conducted with the current CIP fenofibrate drug product suggest the absence of genotoxic potential of CIP fenofibrate, as well as addresses the concern indicated in IND 62,780 for the potential positive micronucleus test with Gelucire 44/14, which has limited clinical relevance.

X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

CIP Fenofibrate is a new formulation of fenofibrate [redacted] b(4)

[redacted] This is why the CIP fenofibrate [redacted] b(4)

[redacted] and exhibits the bio-availability of the micronized fenofibrate Tricor. It is available in capsules in [redacted] strengths, each containing 50, 100, 150 [redacted] mg of the drug. b(4)

Fenofibrate is approved (NDA 19-304, Tricor) for oral use in US, Canada, and Europe for the treatment of hypertriglyceridemia, primary hypercholesterolemia or mixed dyslipidemia. Tricor is available in capsules in three strengths, each containing 67, 134, or 200 mg of micronized fenofibrate. As per labeling, recommended doses of Tricor are up to 200 mg/day.

Following pharm/tox studies are summarized from fenofibrate Tricor, NDA 19-304:

Pharmacology: Fenofibrate is a prodrug, after absorption it is hydrolyzed in the plasma and tissues to its major metabolite, fenofibric acid (FF) and FF is extensively bound to plasma albumin. Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacologic activity of the drug. The extent of absorption after administration of a conventional dosage form is only approximately 30-50%, although this increases if fenofibrate is administered with a meal. Fenofibrate given with food, leads to 60% absorption. Fenofibrate is eliminated with a half life of 20 hrs in humans. Tissue distribution studies in rats indicate that maximal tissue concentration are reached 8 hrs after drug dosing and higher than plasma levels of drug are observed in liver, kidney and gut after oral administration of the radiolabeled drug, while levels in the heart, lungs and adrenals were slightly lower than those in plasma. Plasma FF is excreted in urine as glucuronide conjugate.

Toxicity of Tricor: The drug produces proxisome proliferation at doses above 30 mg/kg in rats. In acute toxicity study, single doses up to 5000 mg/kg did not cause mortalities in mice, rats, hamsters and dogs over a 7-day period. In repeat dose toxicity studies, liver and kidneys were the target organs of toxicity. Liver toxicity was dose related in rats, but not observed in dogs or monkeys. In dogs (7-24 month tox studies), 25-100 mg/kg/day induced weight loss associated with cholelithiasis and some nephritis. In monkeys, doses up to 50 mg/kg/day did not produce any toxicity. As per label, the drug fenofibrate (Tricor) does not have a mutagenic potential, but in 24 month rat CAC study the drug produces liver and pancreas carcinomas, pancreatic adenomas, and benign testicular interstitial tumors (in male rats). In mice it produces liver carcinomas. These effects are noted at 0.3-6 times the maximum recommended human dose.

Fenofibrate (Tricor) produces embryocidal and teratogenic effects in rats and embryocidal effects in rabbits at 7-10 times the maximum recommended human dose, and is labeled as category 'C'.

Fenofibrate is approved (NDA 19-304, Tricor) for oral use in US, Canada, and Europe for the treatment of hypertriglyceridemia, primary hypercholesterolemia or mixed dyslipidemia. Tricor is available in capsules in three strengths, each containing 67, 134, or 200 mg of micronized fenofibrate. As per labeling, recommended doses of Tricor are up to 200 mg/day.

Safety Evaluation: Extensive non-clinical studies have been conducted with the approved fenofibrate Tricor (under NDA 19-304). One non-clinical 13-week bridging toxicity study has been conducted in dogs, where the plasma concentration and toxicity of the current drug were compared to the micronized fenofibrate. Also, two geno-toxicity studies have been conducted with the current drug product. The toxicity observed in the 13 week bridging study is similar between the approved and CIP fenofibrate.

Supportive information for CIP-fenofibrate excipients was provided in DMF [redacted] b(4)
[redacted], DMF [redacted] These excipients have been either used

at the recommended or higher doses in other approved products (in the FDA inactive ingredient guide, 1996) or their toxicity is known.

The sponsor is proposing [redacted] as an initial dose for primary hyper cholesterolemia and 50 to [redacted] for hypertriglyceridemia. Currently the recommended dose of Tricor is up to 200 mg/day in the label. The animal studies suggest comparable toxicity based on the 13 week dog bridging study although Cmax was quite variable in the study b(4)

The sponsor has provided the comparative bioavailability after administration of CIP-fenofibrate (160 mg capsule) vs Tricor (micronized fenofibrate, 160 mg tablets) under fed conditions in humans, and state that the plasma concentration are equivalent.

Labeling Review: In general, the preclinical sections of the label for CIP-fenofibrate are similar to the approved Tricor label, however some modifications have been made. The following changes in labeling are recommended:

Sponsor's suggested label:

[redacted]

b(4)

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✔ Draft Labeling (b4)

✔ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21612 (CIP-fenofibrate)

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/s/

Indra Antonipillai
10/7/03 09:56:32 AM
PHARMACOLOGIST
This appliacation is recommended for approval pending labeling changes. Please communicate the labeling changes to the sponsor

There are labeling changes that need to be communicated to the sponsor

Karen Davis-Bruno
10/7/03 10:02:00 AM
PHARMACOLOGIST

4/17/03

NDA 21-612/Filing

Review completed 4/15/03
Signed off in DFS on 4/17/03

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21-612: This NDA is a 505(b)(2) application.
Submission date: 12/26/02
Sponsor: Cipher pharmaceuticals Ltd., Barbados, WI
Drug: Cipher (CIP) Fenofibrate.
Introduction: CIP-Fenofibrate is a new formulation of fenofibrate [redacted] b(4)
[redacted] The micronization of the drug (like approved micronized fenofibrate Tricor, NDA 19-304) increases its absorption, but is supposedly more costly. The current new drug formulation (CIP fenofibrate) contains gelucire 44/14 (polyglycolyzed glycerides), [redacted] This HLB b(4)
[redacted] similar to Tricor micronized drug.

ITEM: NDA 21-350	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		The sponsor has provided a 13-week toxicity study of the drug in dogs where the toxicity & plasma concentration of the current drug vs the micronized fenofibrate have been compared. Additionally, two genotoxicity studies with new drug are provided, as recommended by us. **The histopath summary Table with severity scores has not been provided and has been requested from the sponsor through CSO/PM, but this information is presented in the individual animal data.**

4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical eview? No carcinogenicity or other preclinical studies were conducted with the current drug, except one 13-week toxicity study in dogs and two genotox studies, which were recommended by us. This is because non-clinical studies have already been conducted with the approved fenofibrate (Tricor under NDA 19-304), and are not considered necessary for CIP-fenofibrate.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			Not applicable. Since non-clinical studies have already been conducted with the approved fenofibrate Tricor under NDA 19-304
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		Sponsor has used new formulation in the current product, and has provided supportive information for CIP-fenofibrate excipients. The excipients such as PEG (8000 & 20000) have already been used in other NDAs (in the FDA inactive ingredient guide, 1996) and also DMF [redacted] has been provided for [redacted]. The sponsor had provided tox studies (in dogs) and genotox studies with [redacted] under IND 62,780 (in a DMF [redacted]

b(4)
b(4)
b(4)

7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration in a 13 week tox study conducted in dogs was oral, which is the intended route in humans
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is similar to the approved Tricor fenofibrate label, and data express human dose multiples in mg/m2.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		

10) Reasons for refusal to file: Not applicable

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Reviewing Pharmacologist: Indra Antonipillai, HFD-510

Supervisory Pharmacologist: Karen Davis-Bruno

File name: 21612-filing

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/s/

Indra Antonipillai
4/17/03 09:25:22 AM
PHARMACOLOGIST
The histopathology summary Table with severity scores on a 13-week toxicity study in dogs is requested from the sponsor through CSO
The inofrmation from the sponsor is requested through CSO, it is not required for filing but is needed

Karen Davis-Bruno
4/17/03 11:57:17 AM
PHARMACOLOGIST