

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-612

MEDICAL REVIEW

Medical Team Leader Memo

NDA#: 21-612
Sponsor: Cipher Pharm
Drug Name: Lipofen (fenofibrate capsules)
Dosage Strengths: 50, 100, 150 mg
Indications: Lipid-altering

This is a resubmission of a 505(b)(2) application originally submitted in February 2003. The reference listed product was Tricor 54 and 160 mg tablets under NDA 21-203. No clinical studies have been conducted with Lipofen (originally known as CIP-fenofibrate and Luxacor). Seven biopharm studies evaluating the relative bioavailability of Lipofen to Tricor tablets and the food effect of Lipofen were conducted in the original NDA. The application received an approvable letter pending resolution of CMC and dissolution deficiencies.

All CMC issues and biopharm deficiencies have been addressed with this submission. The applicant has also provided sufficient evidence to establish bioequivalence between the 150 mg dose of Lipofen and 160 mg of Tricor tablets.

Since submission of the original NDA, the manufacturer for the reference listed product has gained approval of another formulation of Tricor (under NDA 21-656) based on BA/BE studies to the formulation approved under NDA 21-203. Tricor is currently marketed in the US as 48 and 145 mg tablets; this formulation has no food effect. Although Tricor 54 and 160 mg tablets have been withdrawn from the market, it remains listed in the Orange Book and can be used as a referenced listed product for 505(b)(2) or 505j applications.

The approval of Lipofen is based on the agency's findings of safety and effectiveness of Tricor under NDA 21-203. No patent certifications were made against NDA 21-656. Consequently, language in the label for Lipofen should be consistent with the approved label under NDA 21-203. Several sections of this label will differ from the currently marketed Tricor label (NDA 21-656 for 48 and 145 mg tablets).

Under the CLINICAL PHARMACOLOGY; Drug-drug interactions subsection, the Lipofen label will NOT include the following two paragraphs:

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For pravastatin, the increase in Cmax and AUC is unlikely to pose any serious safety concerns. Abbott has contended that the effect of fenofibrate on pravastatin is not of clinical concern and

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The clinical reviewer also notes that a mean change in AUC of 36% for pravastatin is highly unlikely to increase the risk of myopathy.

Fenofibrate reduces the rate and extent of atorvastatin. These changes may result in reduced efficacy; however, as clinical use of atorvastatin requires routine monitoring of effect on lipid parameters to ensure that adequate goals of therapy are achieved, any diminution of atorvastatin efficacy can be managed with upward dose titration.

Furthermore, the results of both of these drug-drug interaction studies have not been cross-labeled in the Lipitor or Pravachol labels as their findings have not been considered critical for the safe and effective use of these two statins.

Under the INDICATIONS AND USAGE section, a correction is being made to the table summarizing the Fredrickson Classification of hyperlipoproteinemias. For Type V hyperlipoproteinemias there are minor increases or no change in cholesterol levels. Consequently, the Lipofen label will contain the letter "C" to denote cholesterol under the last column/last row of this table. This correction is not in the Tricor label approved under NDA 21-203 and will have to be corrected to accurately reflect the disease state.

Conclusions

This reviewer recommends approval of this application pending appropriate labeling changes.

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Mary Parks
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MEDICAL OFFICER

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MEDICAL TEAM LEADER'S MEMO OF NDA SUBMISSION

NDA #: 21-612 (IND 62,780)

Sponsor: Cipher Pharmaceuticals Limited

Drug Product: CIP-fenofibrate

Dosage Strength: 50, 100, 150, _____ mg hard gelatin capsules

Indications: Fredrickson Types IIa/IIb and Types IV and V dyslipidemia

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BACKGROUND

Fenofibrate, a fibric acid derivative, was approved by the FDA in 1993 for the treatment of hypertriglyceridemia due to increases in very low-density lipoprotein cholesterol (VLDL-C) alone or in conjunction with increased chylomicrons (Fredrickson Types IV and V) based on studies using the standard formulation of fenofibrate 100 mg administered three times daily. Although marketed widely throughout Europe and Canada for this indication, this formulation was never marketed in the United States. In 1998, a supplemental new drug application (NDA 19-304/S001) was approved, establishing bioequivalence between the standard formulation of fenofibrate 100 mg to a micronized capsule formulation of 67 mg. The micronized formulation was marketed in the U.S. under the tradename, Tricor® (Abbott Laboratories). This was followed by the approval of another supplemental NDA (NDA 19-304/S003) establishing bioequivalence between the daily dosing of micronized formulations of 200 mg to three 67 mg capsules. Tricor was approved in a subsequent application for the treatment of elevated low-density lipoprotein cholesterol (LDL-C), total-C, triglycerides, and apolipoprotein B in adults with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb) based on the review of the integrated efficacy data from 4 placebo-controlled trials involving daily doses of fenofibrate 300 mg (standard formulation) or the bioequivalent 200 mg micronized formulation (Tricor) of fenofibrate (NDA 19-304/S005). In July 2001, a more bioavailable tablet formulation of Tricor was approved at 54 and 160 mg dosage strengths. These tablets were equivalent under fed conditions to the 67 and 200 mg capsules, respectively. Currently, the manufacturer is marketing only Tricor tablets in the U.S. markets.

Fenofibrate at daily doses equivalent to 160 mg Tricor can achieve mean reductions in TG levels of -46 to -55% in patients with Types IV/V dyslipidemia with greater reductions achieved in those individuals whose baseline TGs levels are higher.¹ Tricor should be taken with meals as the absorption of fenofibrate in Tricor formulations is increased by 35% in the fed state (w/ low-fat meal) compared to fasting conditions.

Cipher Pharmaceuticals Limited has submitted a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for a new fenofibrate formulation, CIP-fenofibrate. The proposed dosage strengths for CIP-fenofibrate are 50, 100, 150, _____ mg. _____

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Seven biopharmaceutic studies were conducted to support the approval of this application. No clinical studies for safety and efficacy were conducted with this product as the approval of this product relies on the bridging studies of CIP-fenofibrate to Tricor

¹ from Tricor® package insert based on studies published in *Clinical Therapeutics*, 11, pp 69-83, 1989.

micronized capsules/tablets and the reliance on the safety and efficacy findings already established for Tricor®. These studies are summarized in the following table:

Table 1. Studies Conducted by CIPHER for NDA 21-612

Study No.	Treatment Group(s)	Duration	N
01-401 to evaluate pK profile of CIP-fenofibrate.	CIP-fenofibrate 200 mg	single dose (Day 1) and multiple dose (Days 4-10)	25 healthy volunteers (12 males; 13 females)
01-399 dose proportionality study	CIP-fenofibrate dosed as 1 x 50mg, 1 x 100 mg, and 1 x 200 mg	single dose after standard high- fat breakfast for each dose followed by a 1-week washout period	17 healthy male volunteers
01-400 food effect study	CIP-fenofibrate 200 mg dosed under fasting, low-fat, and high-fat conditions	single dose for each meal condition separated by a 1- week washout period	17 healthy male volunteers
02-481 food effect study	Tricor 160 mg tablets dosed under fasting, low-fat, and high-fat conditions	single dose for each meal condition separated by a 1- week washout period	12 healthy male volunteers
02-494 bioequivalence study	CIP-fenofibrate 160 mg capsule versus Tricor 160 mg tablets	single dose administered under fed conditions (standard high- fat breakfast)	23 healthy male volunteers
02-557 bioavailability study	CIP-fenofibrate 160 mg capsules versus Tricor 160 mg tablets	single dose administered under fasting conditions	36 healthy male and female volunteers
02-558 bioavailability study	CIP-fenofibrate 5 x 40 mg capsules versus CIP- fenofibrate 1 x 200 mg capsules	single administration of each dose regimen under fed conditions separated by a 1-wk washout period	18 healthy male and female volunteers

Note: The proprietary name discussed in the IND and the initial submission of the NDA was CIP-fenofibrate. This name was rejected by the Division of Medication Errors and Technical Support. This name is used throughout this memo and is representative of the accepted proprietary name, Luxacor® (see below).

SUMMARY OF CLINICAL BIOPHARMACEUTICAL STUDIES

Dr. Wei Qiu from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the seven studies submitted in this application. This medical team leader memo will summarize only her findings of Studies 01-400 and 02-481 (food effect studies) and Study 02-494 (BE study between CIP-fenofibrate and reference listed product, Tricor 160 mg tablet).

Studies 01-400 and 02-481

The rate and extent of absorption of CIP-fenofibrate is increased in the presence of food. From Study 01-400, a single dose study of CIP-fenofibrate 200 mg demonstrated a 125% and 226% increase in AUC and Cmax under low-fat conditions compared to fasting conditions. These values were further increased under high-fat conditions to 158% and 365%, respectively. Compared to a food effect study conducted on Tricor 160 mg tablets (Study 02-481), CIP-fenofibrate has a greater food effect than that observed with Tricor (See Dr. Qiu's review for data summary).

Reviewer comment: This finding requires that labeling for CIP-fenofibrate discuss the presence of a food-effect. The label should also recommend that CIP-fenofibrate be taken with meals under the Dosage and Administration section.

Study 02-494

This was a relative bioavailability study comparing CIP-fenofibrate 160 mg to Tricor 160 mg tablets under high-fat conditions. The objective of this study was to show bioequivalence between the two products thereby allowing the approval of CIP-fenofibrate under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The ratios of the least-square means for AUC and C_{max} (CIP-fenofibrate/Tricor) were 102.21% and 94.73%, respectively. The 90% confidence intervals for AUC and C_{max} ratios were within the 80 to 125% range. Therefore, the 160 mg dose of CIP-fenofibrate is bioequivalent to Tricor 160 mg tablets under high-fat conditions. A different study evaluated the relative bioavailability of both these products under fasting conditions. Under fasting conditions, the extent of absorption (AUC) was similar between CIP-fenofibrate and Tricor; however, the rate of absorption (C_{max}) was 35% lower with CIP-fenofibrate. This difference is not considered clinically significant as the pharmacodynamic effects are more likely associated with the AUC than C_{max} and this product will be labeled to be taken under a fed state.

Reviewer comment: This product, at the highest proposed dose for marketing, is bioequivalent to the reference listed product. Based on dose-equivalent and dissolution studies, bio-waivers can be granted for the lower doses of CIP-fenofibrate (50, 100, and 150 mg).

OTHER DISCIPLINE REVIEW ISSUES

Chemistry deficiencies have been identified in Dr. William Adams' review.

OTHER ADMINISTRATIVE ISSUES

Financial disclosure

The sponsor provided financial disclosure information from all of the investigators participating in their 7 biopharm studies under section 1.3.1.6 of their submission. There were no reports of the following:

- any financial arrangements between the Sponsor and investigators that might influence the conduct or outcome of the study
- any significant payments of other sorts from the Sponsor
- any proprietary interest in the product tested
- any significant equity interest in the sponsor company

Pediatric Requirements

The sponsor has submitted a pediatric waiver request for Types IV and V dyslipidemia stating that the product would be ineffective or unsafe in all pediatric age groups. This reviewer agrees that fenofibrate has limited use in the pediatric patient population and recommends that this waiver be granted.

Tradename

The proposed proprietary name, CIP-fenofibrate, was deemed unacceptable by the Division of Medication Errors and Technical Support (DMETS). Fenofibrate is a United States Adopted Name (USAN) and such names are considered non-proprietary and

should not be subject to proprietary trademark rights. These names are entirely in the public domain. DMETS also raised objections to the use of the prefix, CIP-, citing potential confusion with the medical abbreviations, "QID" or "QD", based on writing sample studies conducted by the DMETS.

The sponsor was informed that their proposed proprietary name was unacceptable during a teleconference with the Division of Metabolic and Endocrine Drug Products on August 7, 2003. They were advised to submit several names indicating the order of preference by early to mid-September. DMETS will conduct another review of the proposed tradename(s).

The sponsor submitted the proposed tradename Luxacor® in October 2003. This name was deemed acceptable by DMETS and the Division of Metabolic and Endocrine Drug Products.

LABELING

The sponsor has similar label to that of the reference listed product, Tricor®; however, fenofibrate or their proprietary name has replaced Tricor and certain sections under Description, Chemical Structure, and Clinical Pharmacology contain language specific to this product. FDA reviewers for CMC and clinical pharmacology will make their recommendations on labeling within these sections.

The is reviewer notes that the Dosage and Administration contains the following opening statement:

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This statement needs to be deleted as no clinical benefit of titration with these doses have been demonstrated. A general recommendation to dose-adjust according to lipid lowering responses as summarized in the reference listed product is adequate.

CONCLUSIONS

As a 505(b)(2) submission the sponsor was required to demonstrate relative bioequivalence to another FDA-approved product (reference listed product) such that the efficacy and safety data established with the reference listed product can be relied upon without requiring the 505(b)(2) applicant to conduct additional clinical studies.

The clinical pharmacology studies submitted with this application do not demonstrate any unique advantage of Luxacor over that of Tricor. There is no evidence of increased bioavailability of this product or decreased food effect compared to Tricor. Given the different dosage strengths and increased food effect, this product is not AB-rated and should not be considered pharmacologically equivalent to Tricor. However, Cipher Pharmaceuticals has demonstrated bioequivalence between their 160 mg capsules with the 160 mg tablets of the reference listed product, Tricor. As such, this application and the proposed marketed dosage strengths of Luxacor can be approved based on the Agency's findings of safety and efficacy for Tricor.

RECOMMENDATIONS

Pending labeling changes and adequate responses to the chemistry deficiencies, this application is approvable.

COMMENTS TO BE CONVEYED IN ACTION LETTER

Under the DOSAGE AND ADMINISTRATION section of the Luxacor® label, the following sentence must be deleted:

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David Orloff
12/15/03 06:21:51 PM
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Concur with Dr. Parks

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