CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-418

OTHER REVIEW(S)

6/17/09

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-418
APPLICANT	Mutual Pharmaceutical Company, Inc.
DRUG NAME	FIBRICOR (fenofibric acid)
SUBMISSION DATE	June 12, 2009 (Division's Version)
SEALD REVIEW DATE	June 17, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

10 Page(s) Withheld

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✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Jeanne Delasko
6/17/2009 04:58:47 PM
CSO
SEALD comments sent to division (DMEP) 06/17/09

Laurie Burke
6/17/2009 05:49:47 PM
INTERDISCIPLINARY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 16, 2009

TO: Mary H. Parks, M.D.
Director
Division of Metabolic and Endocrine Products

FROM: Gopa Biswas, Ph.D.
John Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D._____
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Supplement to DSI memorandum for NDA 22-418, Fenofibric Acid Tablets, 105 mg, Sponsored by Mutual Pharmaceutical Company, Inc.

The following information supplements DSI's memorandum dated 05/15/09 regarding NDA 22-418 (Fenofibric Acid Tablets) for the following bioequivalence study:

Study Number: MPC-028-07-1007: A Single-Dose, Bioequivalence Study of 105 mg Fenofibric Acid Tablets Versus 145 mg TriCor® (Fenofibrate) Tablets Under Fasting Conditions

From March 24 through 26, 2009, DSI audited the clinical portion of Study MPC-028-07-1007 at PRACS Institute-Cetero Research, Ltd., Fargo, ND. Following the inspection, Form-483 was issued. Recently, DSI received written responses (attachment 1) to the 483 items from PRACS Institute-Cetero Research, Ltd. Below is an evaluation of their written responses:

1. **The firm failed to report to the IRB all unanticipated problems involving risk to human subjects.**

Specifically, the firm failed to report subject #04's miscarriage to the IRB as a serious adverse event (SAE). The miscarriage occurred after subject #04 was discontinued from the study.

Cetero Research Response: Cetero Research has revised their SAE reporting method by incorporating detailed documentation of notifying the IRB on their SAE report form, and by retraining clinical staff on SAE reporting.

2. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.**

Specifically, the firm changed 50 of the 54 subjects' case report forms (CRFs) from meeting inclusion/exclusion criteria to not meeting inclusion/exclusion criteria without documented justification.

Cetero Research Response: Cetero Research has implemented a Data Clarification Form (DCF) for requested changes to the CRF or any additions to source documentation. The DCF will be completed and signed by the requestor. Based on that request, changes will be made followed by the clinical investigator and the QAU signing the DCF.

Conclusion:

DSI evaluated and found that the PRACS Institute-Cetero Research written responses to be adequate. The data from Study MPC-028-07-1007 are adequate for review if the medical officer of DMEP has decided that the abnormal clinical laboratory test results from the 50 subjects cited in Form-483 Item 2 above are not clinically significant.

After your review, please attach this memo to the original NDA submission.

Gopa Biswas, Ph.D.

John A. Kadavil, Ph.D.

cc: DFS
DSI/Viswanathan/Biswas/Kadavil
DSI/Rivera-Lopez/CF
OND/ODEII/DMEP/Johnson

cc: email
CDER DSI PM TRACK

Draft: JAK, GB 6/15/09
Edit: MKY 6/16/09
DSI: 5897; O:\BE\EIRCOVER\22418cetresp.doc
FACTS: 979552

Attachment 1

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/s/

John Kadavil
6/16/2009 04:09:06 PM
PHARMACOLOGIST
Dr. Martin Yau signed the paper copy on June 16, 2009. Hard copies available upon request.

5/15/09

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 15, 2009

TO: Mary H. Parks, M.D.
Director
Division of Metabolic and Endocrine Products

FROM: Gopa Biswas, Ph.D.
John Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 5/15/2009
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-418 Fenofibric Acid Tablets, 105 mg, Sponsored by Mutual Pharmaceutical Company, Inc.

At the request of Division of Metabolic and Endocrine Products, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study Number: MPC-028-07-1007: A Single-Dose, Bioequivalence Study of 105 mg Fenofibric Acid Tablets Versus 145 mg TriCor® (Fenofibrate) Tablets Under Fasting Conditions

The clinical portion of the study was conducted at PRACS Institute-Cetero Research, Ltd., Fargo, ND. — The analytical portion was conducted at [redacted] b(4)
[redacted] Following the inspection at [redacted] (December 15-17, 2008), no Form FDA-483 was issued. Following the inspection at PRACS Institute-Cetero Research (March 24-26, 2009), Form FDA-483 was issued. The firm's response to Form FDA-483 was not received as of the date of this review. Our evaluation of the significant findings is as follows:

PRACS Institute-Cetero Research, Ltd., Fargo, ND

1. **The firm failed to report to the IRB all unanticipated problems involving risk to human subjects.**

For study MPC-028-07-1007, source records showed that subject #04 had a positive pregnancy test on November 3, 2007 at period II check in, and was dropped from the study prior to the start of period II.

During a post-study follow-up with subject #04, the firm was notified that the subject had a miscarriage, at which time the firm documented this as a serious adverse event (SAE). However, this SAE was never reported to the PRACS Institute, Ltd. IRB.

It is objectionable that this SAE (subject #04's miscarriage) was not reported to the IRB. Subject #04's discontinuation and miscarriage was discussed in the study report.

It should be noted that subject #04 participated in period I, however she tested negative for pregnancy at screening and period I check in. Furthermore, the firm's SAE report indicates that subject #04 received the reference drug (TriCor®) during period I.

2. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.**

For study MPC-028-07-1007, the firm changed 50 of the 54 subjects' case report forms (CRFs) from meeting inclusion/exclusion criteria to not meeting inclusion/exclusion criteria for medical history, physical examinations, clinical laboratory test results, clinically significant vital sign measurements and ECG parameters. Changes to the CRFs were done on 7/25/08, more than 8 months after those 50 subjects completed the study.

Additionally, a protocol deviation log was created on 7/28/08 indicating that the 50 CRFs were changed due to "Misinterpretation of protocol". However, the firm's records do not indicate how this assessment was made. Furthermore, the firm's records do not indicate any correspondence with the sponsor regarding these changes.

As per the protocol, subjects not meeting health screening criteria can not be included in the study. Therefore, it is objectionable that:

- 50 out of 54 subjects not meeting the eligibility criteria were allowed to participate in the study
- The case report forms were modified more than 8 months after completion of the study without documented justification
- The site created a protocol deviation log for those 50 subjects citing "misinterpretation of protocol" without further clarification

It should be noted that the 50 subjects deviating from inclusion/exclusion criteria are listed in the final report.

Conclusion:

Following the above inspections, the Division of Scientific Investigations concludes the following:

- It is objectionable that PRACS Institute-Cetero Research failed to report subject #04's miscarriage to the IRB and failed to completely assure subject safety. As per the protocol, the IRB should be notified of all SAEs.[1] Furthermore, DSI plans to follow-up and determine if the firm has implemented corrective actions by reporting all SAEs to the IRB.
- It is objectionable that the firm changed 50 of the 54 subjects' CRFs from being study eligible to being study ineligible without clarification, more than 8 months after study completion. DSI recommends that the review division evaluate the extent of these subject deviations, and also consider the impact of enrolling these ineligible subjects.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

---

[1] MPC-028-07-1007/PRACS R07-1032 Protocol version 1.5, Page 23, Section 8.3 - Expedited Reporting

Gopa Biswas, Ph.D.

John Kadavil, Ph.D.

Final Classification:
NAI - [redacted]
VAI - PRACS Institute-Cetero Research, Ltd., Fargo, ND b(4)

cc: DFS
DSI/Viswanathan/Kadavil/Biswas
DSI/Patague/Rivera-Lopez/CF
OND/ODEII/DMEP/Marchick

cc: email
HFR-CE1505/Despins
HFR-CE300/Holaday
Draft: GB, JAK 5/1/09, 5/14/09
Edit: JAO 5/13/09, 5/14/09
DSI: 5897; O:\BE\eircover\22418mut.fen.doc
FACTS: 979552

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/s/

Gopa Biswas
5/15/2009 01:59:05 PM
UNKNOWN
Dr Martin K Yau signed the paper copy on behalf of Dr CT Viswanathan

5/8/09

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 8, 2009
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Through:	Melina Griffis, R.Ph., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Robin E. Duer, R.N., M.B.A., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Fibricor (Fenofibric Acid) Tablets, 35 mg and 105 mg
Application Type/Number:	NDA 22-418
Applicant:	Mutual Pharmaceutical Company, Inc.
OSE RCM #:	2009-410

CONTENTS

EXECUTIVE SUMMARY

Fibricor will be available in two strengths, 35 mg and 105 mg. Our evaluation of the container labels noted that when compared side by side they are difficult to distinguish. The container labels for both the 35 mg and 105 mg strengths incorporate similar trade dress and this visual similarity could lead to product selection errors and ultimately dispensing of an incorrect strength especially when both are stored next to one another on a pharmacy shelf. To minimize this risk the Applicant should revise the labels so that the two different strengths are adequately differentiated. Additionally, it is important to insure that the product sizes 30, 60 and 90 have a Child Resistant Closure since they can be considered a unit of use and be dispensed directly to the patient.

The Division of Medication Error Prevention and Analysis (DMEPA) believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 4 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Applicant to evaluate the proposed Fibricor container labels.

1.2 REGULATORY HISTORY

Fibricor (Fenofibric Acid) is a pending 505(b)(2) NDA application with an anticipated action date of June 15, 2009. The initial submission for this NDA did not include a proposed proprietary name. The proposed proprietary name Fibricor was submitted to the NDA on October 10, 2008 and is evaluated under a separate review (see OSE review 2008-1764). The referenced listed drug for Fibricor is Tricor (NDA 21-656).

1.3 PRODUCT INFORMATION

Fibricor (Fenofibric Acid) is indicated for the treatment of hypercholesterolemia and hypertriglyceridemia. Fibricor will be available as oral tablets in two dosage strengths, 35 mg and 105 mg. The recommended usual dose will be 35 mg to 105 mg given once daily. Fibricor will be supplied in bottles of 30, 60, 90, 100, 250, 500 and 1,000 count.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use

or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The package insert and patient package insert labeling is intended to communicate to practitioners and patients, all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

Mutual Pharmaceutical Company submitted the following Fibricor labeling for the Agency's review on September 30, 2008 (see Appendices):

- Proposed Fibricor container labels, 35 mg (30, 60, 90, 100, 250, 500 and 1,000 count) (see Appendix A)
- Proposed Fibricor container labels, 105 mg (30, 60, 90, 100, 250, 500 and 1,000 count) (see Appendix B)
- Proposed Fibricor package insert (no image)

DMEPA reviewed the proposed package insert labeling for Fibricor for the purpose of comparing it with the proposed container labeling.

3 DISCUSSION

The proposed container labels were reviewed for possible medication errors. The following observations were made:

The appearance of the 35 mg container label is almost identical to that of the 105 mg container label. The only differentiating feature is the font color of the drug strength. The 35 mg container label uses blue color font for the strength, and the 105 mg container label uses red color font for

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

the strength. However, this small presentation of strength, in conjunction with the use of same colors (pink vs. orange) and blue for both labels minimizes the potential differentiation.

Additionally, the bottle sizes of 30, 60 and 90 are considered unit of use based on the usual dosage of this product. Therefore these product sizes should contain a Child Resistant Closure (CRC).

4 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the colors used on the container labels contributes to the similar appearance of the bottles and does not provide for adequate differentiation which introduces vulnerability to confusion that could lead to medication errors. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and we provides recommendation in Section 4.2 that aim at reducing the risk of medication errors.

4.1 COMMENTS TO THE DIVISION

We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Millie Wright, OSE Project Manager, at 301-796-1027.

4.2 COMMENTS TO THE APPLICANT

A. Container Labels (35 mg and 105 mg)

As currently presented, both labels look almost identical when compared side by side because the same colors used for the trade dress are also used to differentiate the two strengths. This color scheme does not provide enough differentiation to distinguish between the two different strengths. Revise the labels to incorporate a more adequate means of differentiation (e.g., different contrast color schemes, boxing, etc.).

B. Child Resistant Closure

The bottle sizes of the 30, 60 and 90 count are considered unit of use based on the usual dosage of this product and could be dispensed directly to the patient. Therefore these product sizes should contain a Child Resistant Closure (CRC).

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/s/

Melina Griffis
5/8/2009 10:57:33 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/8/2009 11:18:01 AM
DRUG SAFETY OFFICE REVIEWER