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APPLICATION NUMBER:

22-418

SUMMARY REVIEW

8/14/09

Summary Review for Regulatory Action

Date	August 3, 2009
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA	22-418
Applicant Name	Mutual Pharmaceutical Company
Date of Submission	15 August 2008
PDUFA Goal Date	15 June 2008
Proprietary/Established Name	Fibricor/fenofibric acid
Dosage Forms/Strength	Tablets, 35 mg and 105 mg
Proposed Indication(s)	1. Severe Hypertriglyceridemia 2. Primary Hyperlipidemia and Mixed Dyslipidemia
Recommended Action:	Approval

Material Reviewed/Consulted	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Not Applicable
Pharmacology Toxicology Review	Lee Elmore, PhD
CMC Review/OBP Review	Xavier Ysern, PhD, and Houda Mahayni, PhD
Microbiology Review	Not Applicable
Clinical Pharmacology Review	Immo Zdrojewski, PhD
DDMAC	Not Applicable
DSI	Gopa Biswas, PhD
CDTL Review	Not Applicable
OSE/DMEPA	Robin Duer, RN, MBA
OSE/DDRE	Not Applicable
OSE/DSRCS	Not Applicable

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA= Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

Mutual Pharmaceutical Company submitted NDA 22-418 for Fibricor (fenofibric acid) as a 505b2 application with Tricor (fenofibrate) as the reference listed drug. Tricor was approved in the 1990s for the treatment of hypertriglyceridemia and primary hyperlipidemia and mixed dyslipidemia. Fenofibric acid, the active moiety of fenofibrate, is formed in-vivo following oral intake of fenofibrate. The proposed doses of Fibricor are 105 mg and 35 mg once-daily.

A number of fenofibrate compounds are currently approved for hypertriglyceridemia and primary hyperlipidemia and mixed dyslipidemia. The Division recently approved fenofibric acid (Trilipix) as monotherapy for hypertriglyceridemia, primary hyperlipidemia, mixed dyslipidemia, and for coadministration with a statin for patients with mixed dyslipidemia on an optimal dose of a statin to lower triglycerides (TG) and increase of high density lipoprotein (HDL) levels.

2. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable.

3. Nonclinical Pharmacology/Toxicology

I agree with the nonclinical pharmacology/toxicology reviewer that there are no outstanding issues that would preclude approval of this NDA.

4. Clinical Pharmacology/Biopharmaceutics

The pivotal data in support of this NDA come from a bioequivalency study in which the rate and extent of exposure to fenofibric acid from 105 mg of Fibricor were compared with the rate and extent of exposure to fenofibric acid from 145 mg of Tricor. The table below taken from Dr. Zdrojewski's review provides the relative bioequivalency of Fibricor under fasted conditions.

Parameter	Fibricor (105 mg)	Tricor (145 mg)	% Ratio	90% CI
$AUC_{0\text{-last}}$	148.59	158.70	93.63	91.3, 96.1
AUC_{inf}	162.96	173.93	93.69	91.7, 95.8
C_{max}	12.00	10.65	112.69	107.9, 117.6

The geometric mean ratios of AUC and C_{max} and their 90% confidence intervals for Fibricor vs. Tricor meet the standard bioequivalence criteria. Hence, one can conclude that Mutual's 105 mg fenofibric acid is bioequivalent to Abbott's 145 mg fenofibrate.

Under fed conditions, the rate and extent of absorption of 105 mg Fibricor were approximately 10% lower than the rate and extent of absorption of 145 mg Tricor; however, the values for the 90% confidence interval were within 80 to 125% and Fibricor is therefore considered bioequivalent to Tricor under fed conditions.

According to Dr. Zdrojewski, the rate of exposure to fenofibric acid from Fibricor is approximately 20% to 35% lower under fed vs. fasted conditions. I agree with Dr. Zdrojewski that this degree of reduction in C_{max} is unlikely to be of clinical significance. The extent of absorption of fenofibric acid from Fibricor is not affected by food.

Mutual has provided data indicating that the 35 mg tablets of Fibricor are dose proportional to the 105 mg tablets of Fibricor.

In her assessment of the requested biowaiver for the lower dose of Fibricor, Dr. Houda Mahayni, the Biopharmaceutics reviewer, concluded that the dissolution method submitted in support of the biowaiver was not acceptable because the speed was not discriminative. However, as noted above and by Dr. Mahayni, given that the sponsor provided evidence that 3 x 35 mg Fibricor tablets are bioequivalent to 1 x 105 mg Fibricor tablet and that the 35 mg Fibricor tablet is compositionally proportional to the 105 mg Fibricor tablet, a biowaiver can be granted for the lower Fibricor dose.

5. Clinical/Statistical-Efficacy

The assessment of Fibricor's efficacy for the proposed indications of the treatment of hypertriglyceridemia, primary hyperlipidemia, and mixed dyslipidemia is based on the Agency's finding of efficacy for the reference listed drug, Tricor. Since Mutual has provided data indicated that Fibricor is bioequivalent to Tricor, one can assume that Fibricor's efficacy is comparable to Tricor's.

6. Safety

The assessment of Fibricor's safety is based on the Agency's finding of safety for the reference listed drug, Tricor. In addition, Dr. Chowdhury, the clinical reviewer, has evaluated safety information from Mutual's 10 pharmacokinetics studies and the published literature. The adverse events reported from the pharmacokinetics studies were consistent with the adverse events provided in the Tricor labeling. Review of the published literature did not reveal any new safety information that merits inclusion in the Tricor or Fibricor labels.

7. Pediatrics

A full waiver for pediatric studies was granted for the Fibricor NDA. For the indication to treat hypertriglyceridemia, there are an insufficient number of pediatric patients with the condition to feasibly conduct an adequately-sized clinical trial. For the indications to treat primary hyperlipidemia and mixed dyslipidemia, fenofibric acid would not provide a meaningful

benefit relative to statin therapy and would not be used by a substantial number of pediatric patients. The PeRC agreed with granting Mutual a full waiver for pediatric studies.

8. Other Relevant Regulatory Issues

An audit of the pivotal bioequivalency study by the Division of Scientific Investigations (DSI) revealed that the case report forms for 50 of the 54 study participants were altered 8 months after the study was completed. Upon alteration, the 50 subjects were deemed ineligible per the study inclusion/exclusion criteria.

On 21 May 2009, the Division requested that Mutual clarify why the case report forms were changed after the study was completed. The company provided a response on 4 June 2009. Dr. Chowdhury's medical review provides a detailed assessment of Mutual's response. Briefly, most of the 50 case report forms were altered after the study was completed because one or more of the screening laboratory values were outside the reference range, but based on the judgment of the medical investigator the abnormalities were not considered clinically significant. Indeed, the laboratory values that were outside of the reference range at screening did not appear to be clinically significant. Thus, I agree with Dr. Chowdhury that the violations noted by DSI would not be expected to influence the efficacy or safety data from the pivotal bioequivalency study.

Mutual provided in the NDA submission a signed form FDA 3454 certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted in support of approval of the NDA.

In a letter dated 22 December 2008, Mutual requested confirmation that the three-year exclusivity granted to Trilipix (fenofibric acid) would not delay approval of their fenofibric acid NDA. In a memo of 29 July 2009, Janice Weiner, JD, MPH, FDA counsel from the Division of Regulatory Policy I, concluded that the three-year exclusivity granted to Trilipix would not preclude approval of Mutual's fenofibric acid NDA. The Trilipix exclusivity was granted because Abbott Pharmaceuticals was required to conduct clinical studies of their fenofibric acid coadministered with statins in order to gain approval of an indication specifically for the coadministration of Trilipix with a statin. This indication was not requested by Mutual. Therefore the Division's approval of Trilipix and the granting of three years of exclusivity will not block approval of Mutual's fenofibric acid NDA.

The Office of Surveillance and Epidemiology concluded that the proposed tradename, Fibricor, was acceptable. I agree with this assessment.

9. Decision/Action/Risk Benefit Assessment

I agree that this 505b2 application should be approved.

The CMC discipline is recommending that the [redacted] b(4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22418	ORIG 1	MUTUAL PHARM	FENOFIBRIC ACID TABS 35MG/105MG ORAL

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

/s/

ERIC C COLMAN
08/14/2009