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APPLICATION NUMBER:

21-695

MEDICAL REVIEW(S)

Medical Team Leader Memo

NDA #:	21-695
Sponsor:	Reliant Pharm
Drug product:	Fenofibrate (micronized capsules) 43 mg, 87 mg, and 130 mg
Date of Submission:	December 21, 2003
PDUFA goal date:	October 4, 2004

Background

Reliant Pharmaceuticals submitted a 505(b)(2) new drug application for fenofibrate, micronized capsules in dosage strengths of 43, 87, and 130 mg for the treatment of Types IIa/IIb, IV, and V dyslipidemia. The referenced listed product is Tricor® 200 mg capsules manufactured by Abbott Laboratories, approved under NDA 19-304, but withdrawn from US market for business reasons after the approval of Tricor® tablets under NDA 21-203.

No clinical studies of efficacy and safety were conducted for this application. The applicant conducted BE testing, food-effect studies, dose-proportionality, and dose-equivalence studies to bridge their formulation with the reference listed product. The results of these studies would then allow for the Agency to rely on the findings of safety and effectiveness of Tricor capsules.

The biopharm studies submitted to this NDA are:

- FF4C- Single dose BE study under fasting and fed condition
- FF3- Multiple-dose BE study under fed condition
- FF2- Food effect on RP-1824 capsules
- FF4B- Dose equivalence study
- FF4- Dose proportionality study

These studies were reviewed in detail by Dr. Jayabharathi Vaidyanathan from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

Summary of Biopharm Study Results

Bioequivalence Between Reliant Fenofibrate and Tricor Capsules

Reliant's 130 mg capsule was compared to Tricor 200 mg capsules under low fat and fasting conditions in a single-dose study and under steady-state conditions. The single dose relative BA study under low-fat conditions failed to demonstrate bioequivalence between the two capsules. The least square means of AUC_{inf} and C_{max} of fenofibric acid were 83.51% and 105.98%, respectively. The 90% confidence interval of AUC_{inf} was lower than the 80-125% range.

The applicant conducted a multiple-dose relative BA study comparing Reliant's 130 mg capsule to Tricor 200 mg capsules. After 7 days of dosing under low-fat fed conditions,

the ratio of least square means of (RP 1824 130 mg fed/Tricor® 200 mg fed) for $AUC_{\square ss}$ and $C_{max\ ss}$ and C_{min} were 88.4%, 91.7% and 88.4% respectively. Because the 90% confidence interval for the $AUC_{\square ss}$ and $C_{max\ ss}$ were in the 80-125% range, the RP 1824 130 mg capsules and Tricor® 200 mg capsules were concluded to be bioequivalent after multiple dosing under low fat meal conditions.

Establishment of BE to the reference listed product after multiple dosing versus a single dose study is acceptable as fenofibrate should be chronically administered for the effective treatment of dyslipidemia. Furthermore, this product will not be labeled as AB-rated to Tricor®.

Food Effect
Similar to Tricor® capsules, a food effect was observed with Reliant's product. The AUC was increased by 24% and the Cmax increased 2-fold under high-fat conditions compared to fasting conditions.

Dose-Equivalence
Dosage form equivalency was evaluated using two 43 mg RP 1824 versus one 87 mg RP 1824 capsule and three 43 mg RP 1824 versus one 130 mg RP 1824 capsule under fasting conditions. The rate and extent of absorption of RP 1824 capsules were similar when administered either as single 87 or 130 mg or multiple 43 mg capsules under fasting conditions. Therefore, dosage form equivalence between the three strengths was established.

Dose-Proportionality
The 43, 87, and 130 mg dosage strengths was less than dose-proportional; however, this study was conducted under fasting conditions.

Audits
Clinical audits of the site where the multiple-dose relative BA study was conducted did not reveal and concerns regarding the reliability of the data supporting approval of this application.

CMC
No CMC deficiencies were identified

Financial Disclosure
The sponsor provided a signed form FDA 3454 under item 19, certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies submitted for approval of this application.

Labeling
Labeling comments have been conveyed to the sponsor in a separate correspondence. Recommendations based on the BPH review include that the dosing of this product be with meals as there is evidence of a food effect.

Proprietary Names
Two proprietary names were submitted for review by Division of Medical Errors and Technical Support (DMETS). Both were found to be acceptable. The applicant has selected Antara® as the tradename for their fenofibrate product. This reviewer has no objection to this proposal.

Pediatric Study Requirements

Pediatric study requirements should be waived for this product. The indications for this product include treatment of hypercholesterolemia (primary or mixed dyslipidemia in Types IIa and IIb) and hypertriglyceridemia (Types IV and V dyslipidemia). The treatment of hypercholesterolemia in pediatric patients is more effectively managed with HMG-CoA reductase inhibitors. Hypertriglyceridemia in Types IV and V dyslipidemia are generally not seen pediatric patients.

Recommendations

The applicant has conducted adequate studies bridging their formulation of fenofibrate to the reference listed product, Tricor® capsules. Consequently, this 505b2 application should be approved.

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/s/

Mary Parks
9/29/04 10:39:56 AM
MEDICAL OFFICER

David Orloff
9/29/04 11:21:02 AM
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Concur with Dr. Parks. BE established in multiple dosing protocol. Approved, relying in part on previous findings of safety and efficacy for Tricor. No clinical or preclinical investigations required.