CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-656

MEDICAL REVIEW

8/25/04

Medical Team Leader Memo

NDA #:	21-656
Sponsor:	Abbott Laboratories
Drug Product:	Tricor ~~®~~ (fenofibrate) 48 and 145 mg tablets
Date of Submission:	October 29, 2003 (letter date)
Date Review Completed:	August 20, 2004

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 a non-micronized formulation of fenofibrate 100 mg administered three times daily. This formulation was never marketed in the United States and in 1998, a supplemental new drug application (NDA 19-304/S001) was submitted for the micronized formulation of fenofibrate. The 67 mg capsule of this formulation was found to be bioequivalent to the 100 mg dose of the non-micronized formulation. The micronized formulation was approved and subsequently marketed in the U.S. as 67 and 200 mg capsules under the trade name, Tricor®.

The absorption of fenofibrate is markedly increased with food. Under high-fat conditions, bioavailability can increase ~35% from that observed under the fasting state. Consequently, the dosing recommendations for fenofibrate include administration with meals. In an attempt to increase bioavailability and decrease the food effect of fenofibrate, Abbott Laboratories has reformulated Tricor and data have been submitted to the Agency under separate NDAs. In 1999, NDA 21-203 was submitted for the approval of Tricor tablets at doses of 54, 107, and 160 mg. This product was found to be bioequivalent to the capsule formulation; however, a food effect was still observed and the recommendation to take with meals remained in the package insert.

The applicant now submits NDA 21-656 which contains another reformulation of fenofibrate that does not have a food effect. This product is available in two dosage strengths: 48 and 145 mg tablets. The increased bioavailability and absence of food effect is attributed to a manufacturing process which decreases the mean particle size of the drug substance to < ~~—~~ This process is described as ~~—~~ which results in a NanoCrystal® colloidal dispersion (NCD) which undergoes additional steps before being compressed into tablet cores that are film-coated.

Clinical studies conducted to support the approval of this application included a food effect study evaluating Tricor ~~—~~ under fasting, low-fat, and high-fat condictions and a relative BA study comparing Tricor ~~—~~ 145 mg tablets, 48 mg tablets x 3, and Tricor 200 mg capsules under low-fat conditions. In addition, the applicant conducted two drug interaction studies to evaluate the effect of fenofibrate 200 mg capsules on the pharmacokinetics of pravastatin and atorvastatin. Effects of atorvastatin on pharmacokinetics of fenofibrate were also evaluated. The design, conduct, and results

of these studies have been thoroughly reviewed by Dr. Wei Qiu for the Office of Biopharmaceutics and Clinical Pharmacology.

No clinical efficacy studies were conducted. Demonstration of bioequivalence between Tricor ' and the reference listed product, Tricor capsules, would allow NDA 21-656 to rely on the Agency's findings of safety and effectiveness of the reference listed product.

Food Effect Study
The bioavailability of Tricor 145 mg tablets was evaluated under high-fat fed, low-fat fed, and fasting states. The ratios of least square means for AUC_∞ and Cmax of fenofibric acid were 105.2% and 100.7%, respectively, for the comparison of high-fat fed to fasting state. These ratios were 101.2% and 100.9%, respectively, for the comparison of low-fat fed to fasting state. The 90% confidence intervals of AUC and Cmax ratios were within the range of 80 to 125%.

In summary, no food effect was observed with this formulation of fenofibrate.

Relative BA Study
This study compared one tablet of Tricor 145 mg and three tablets of Tricor 48 mg to Tricor 200 mg capsules. The ratios of least square means for AUC_∞ and Cmax of fenofibric acid were 86.2% and 100.8%, respectively, for the comparison between Tricor 145 mg and Tricor 200 mg capsules. The ratios of least square means for AUC_∞ and Cmax of fenofibric acid were 101.2% and 100.9%, respectively, for the comparison between Tricor 48 mg x 3 tablets to Tricor 200 mg capsules. The 90% confidence intervals for the AUC and Cmax ratios for both comparison were within the range of 80 to 125%.

In summary, Tricor 145 mg and Tricor 48 mg x 3 were found to be relatively bioavailable to the reference listed product, Tricor 200 mg capsules.

Drug Interaction Study w/ Pravastatin
Co-administration of 160 mg fenofibrate tablet once daily for 10 days increased pravastatin steady state Cmax and AUC values by 36% and 28%, respectively.

Drug Interaction Study w/ Atorvastatin
Co-administration of 160 mg fenofibrate tablet once daily for 10 days decreased steady-state atorvastatin AUC values 17% but did not affect the Cmax values. Steady-state AUC or Cmax values of fenofibric acid were not affected upon co-administration of 20 mg atorvastatin once daily for 10 days.

Financial Disclosure
The applicant submitted financial disclosure documents for the clinical pharmacology studies submitted for review under NDA 21-656. No clinical investigators had financial holdings or interests that would otherwise affect the integrity of the data supporting approval of this NDA.

DSI Inspections
A DSI audit was performed of the clinical and analytical portions of Protocol M02-558 (relative BA study of Tricor and Tricor capsules) and raised concerns regarding the accuracy of data from diluted study samples. Dr. Qiu re-analyzed the study results excluding subjects with questionable data and no difference in BE results was noted

from the overall dataset. In conclusion, the concerns raised during the DSI audit do not appear to affect the final results of the study.

CMC

The chemistry reviewer has identified several deficiencies including the type II DMF and proposed manufacturing process and in-process controls. These and other deficiencies noted in Dr. William Adams review are to be conveyed to the applicant in an approvable letter.

Labeling

Proposed labeling for Tricor 48 and 145 mg tablets is similar to the approved labeling for the reference listed product with the following exceptions:

- dosage strengths have been changed to reflect either the 48 and 145 mg tablets, whichever is relevant
- the CLINICAL PHARMACOLOGY section discusses the results of the relative bioavailability study between the two products and the food-effect study of Tricor 145 mg tablets under the Pharmacokinetics/Metabolism subsection
- the WARNINGS section discusses the results of the drug-drug interaction studies between fenofibrate and the 2 statins, pravastatin and atorvastatin
- the DOSAGE AND ADMINISTRATION section discusses the absence of food effect with this formulation and that Tricor tablets can be given without regard to meals

In her review, Dr. Qiu has recommended changes to the proposed label. These changes should be conveyed to the sponsor in the action letter.

Proprietary Name

The proposed proprietary names were not found acceptable the by the Division of Medical Errors and Technical Support (DMETS). The Division of Drug Marketing, Advertisement, and Communications (DDMAC) rejected the trade name, from a promotional perspective. The applicant was notified during a teleconference on May 10, 2004, that neither of the proposed proprietary names was acceptable to the Agency. The applicant stated that they plan to discontinue marketing of Tricor tablets after approval of the new formulation and that based on a similar approach with the transition from Tricor capsules to tablets, such a 'phase-out' of a product lasts approximately 5 months. Consequently, the applicant requests to retain the trade name Tricor®. This was found acceptable by the review division however, in a separate teleconference on August 3, 2004, the applicant was informed that DMETs recommended a descriptor for this new formulation that would accompany but not be a part of the trade and established names. The importance of this descriptor was to allow distinction between this formulation and generic brands which was developed using the Tricor capsule formulation. As the technology was under patent protection, the applicant was told to submit several proposals that would appropriately describe the new formulation without infringing on any such patents.

On August 16, 2004, a meeting was held between members of the review division, labeling and nomenclature committee (LNC) and DMETS. It was concluded that no descriptor regarding the change in formulation was necessary for this product and that differences in tablet strengths would be sufficient for distinguishing the to-be-marketed fenofibrate formulation under NDA 21-656 from previous formulations of fenofibrate.

In a submission dated July 30, 2002, the applicant gave general plans for informing healthcare professional about the new formulation to reduce the confusion between currently marketed Tricor 54 and 160 mg tablets and the new formulation for Tricor 48 and 145 mg tablets. The applicant states that a clinical letter describing this new formulation will be distributed to physician offices and faxed to the top 10,000 prescribers in 2 waves. No draft version of this letter or educational materials were provided with this submission.

Conclusions and Recommendations

The clinical biopharm studies have demonstrated bioequivalence between this formulation of Tricor (48 and 145 mg tablets) and the reference listed product, Tricor® 200 mg capsules. In addition, this formulation has no evidence of food effect hence dosing instructions can include recommendations to take regardless of meals.

Several deficiencies were identified in the CMC review of this application. Pending adequate responses from the applicant to these deficiencies, this application is approvable.

In addition to the CMC deficiencies, the following items should be conveyed in the AE letter:

- recommended labeling changes based on Dr. Wei Qiu's review of NDA 21-656
- a request that the applicant submit a draft version of the "clinical letter" and any other educational materials that Abbott is proposing to distribute to physicians regarding this new formulation based on their submission dated July 30, 2002 to NDA 21-656

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/s/

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