

021203 \_ ORIGINAL APPROVAL \_

PACKAGE

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number** 21-203

**Trade Name** Tricor

**Generic Name** fenofibrate

**Sponsor** Abbott Laboratories

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION 21-203**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-203**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-203

Abbott Laboratories  
Attention: Marilou Reed  
Associate Director, Regulatory Affairs  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

Dear Ms. Reed:

Please refer to your new drug application (NDA) dated November 10, 1999, received November 12, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tricor (fenofibrate) Tablets 54, 160 mg.

We acknowledge receipt of your submissions dated February 19, March 2, April 20, May 14, and August 13, 2001. Your submission dated March 2, 2001, received March 5, 2001, constituted a complete response to our September 12, 2000, action letter.

This new drug application provides for the use of a tablet formulation of Tricor, for adjunctive therapy to diet to reduce elevated LDL-C, Total-C, triglycerides and Apo-B and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed lipidemia (Fredrickson Types IIa and IIb), and as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia), indications previously approved for the capsule formulation.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

We note that in your submission dated June 5, 2000, received June 6, 2000,

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The final printed labeling (FPL) must be identical to the submitted labeling (including packaging) submitted August 13, 2001, immediate container and carton labels submitted November 10, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-203." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until September 5, 2003. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic  
and Endocrine Drug Products, HFD-510  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-203**

**APPROVABLE LETTER**



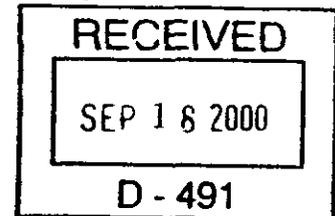
DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-203

Food and Drug Administration  
Rockville MD 20857

Abbott Laboratories  
Attention: Marilou Reed  
Associate Director, Regulatory Affairs  
D-491/AP6B-1  
100 Abbott Park Road  
Abbott Park, IL 60064-6108

SEP 12 2000



Dear Ms. Reed:

Please refer to your new drug application (NDA) dated November 10, 1999, received November 12, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tricor (fenofibrate ) tablets.

We acknowledge receipt of your submissions dated June 1, 5, and 13, July 12, and August 2, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

**1. Concentration-Response Model**

A PK/PD relationship for fenofibrate has not been established. Drug dosing times and sampling times for determination of plasma drug levels were not recorded in study CFEN-8802. Thus, the precise relationship between plasma fenofibric acid levels and the lipid altering endpoints examined (triglycerides [TG] and cholesterol lowering) cannot be determined. Furthermore, because only one dosage level of fenofibrate (3 X 100 mg of standard or 200 mg of micronized, which are equivalent) was studied in the trial, this precludes use of a model that assumes that the observed lipid-altering response is, in fact, the E<sub>max</sub> (maximum pharmacological effect). Taken together these facts undermine any conclusions about the relationship of plasma fenofibric acid levels to the therapeutic lipid altering effect for fenofibrate.

Further exploration of this path for approval is not recommended given the nature of the available data.

**2. Bioequivalence**

Bioequivalence has not been established between TRICOR micronized capsules and TRICOR tablets. The data submitted are from a study conducted in the fed state.

Submit the results of a 2-way crossover bioequivalence study that compares the 160 mg TRICOR tablet with the 200 mg TRICOR capsule conducted under fasting conditions.

### **3. Dissolution**

The dissolution method that was submitted in this application is incomplete, thereby preventing the evaluation of the method and specifications.

Submit alternative dissolution methods for fenofibrate tablets over the range of physiologic pH values, with and without sodium lauryl sulfate, as appropriate, for each of the to-be-marketed formulations.

### **4. Effects of fenofibrate on HDL-C**

The pooled lipid-altering data from the fenofibrate clinical trials submitted in the application are sufficient to support language in the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections of the package insert for TRICOR describing the expected effect of TRICOR on HDL-C levels in patients with Fredrickson Types IIa and IIb hyperlipoproteinemia. However, the data submitted are insufficient to support the removal from the CLINICAL PHARMACOLOGY section of the disclaimer to the effect that no independent effect of raising HDL-C or of lowering TG on cardiovascular morbidity or mortality has been established.

Because the biopharmaceutics aspects of this application do not support approval at this time, final negotiations on labeling will be deferred pending your satisfactorily addressing the aforementioned deficiencies.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6418.

Sincerely,

*/s/*

David G. Orloff, M.D.  
Director  
Division of Metabolic and  
Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**