CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-656

APPROVABLE LETTER

8/30/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-656

Abbott Laboratories
Attention Ernesto J. Rivera, Pharm D.
Regulatory Affairs Manager
200 Abbott Park Road, D-491/AP30-1E
Abbott Park, IL 60064

Dear Dr. Rivera:

Please refer to your new drug application (NDA) dated October 29, 2003, received October 30, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tricor (fenofibrate) Tablets, 48 mg and 145 mg.

We acknowledge receipt of your submissions dated December 9 and 11, 2003, January 16(2), April 19 and 20, May 14, June 1, July 7, 9, and 29, and August 5, 2004.

We completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

CHEMISTRY, MANUFACTURING, and CONTROLS

1. Regarding the proposed manufacturing process and in-process controls, provide the following information:
   a. Identify the equipment to be used in the compression and coating steps.
   b. Specify the acceptable ranges for % yield in each manufacturing step.
   c. Specify the maximum hold time for compression blend and un-coated cores.
   d. Provide a brief description of the tablet dies.
   e. Specify whether step [redacted] is performed in one or more parts.
   f. Identify the documentation that will be received from [redacted] with each bulk lot of coated tablets. This documentation should include the date of manufacture for each in-process material.
   g. Describe the calculation of % yield in step [redacted]
   h. Specify the acceptable range for coating weight.

2. Regarding stage [redacted] in documents S05.06122 and S05.06123, revise these documents to indicate the date of manufacture of the [redacted] ? as the start of the drug product expiration date. Alternatively, you may provide data to demonstrate that the proposed extended storage of intermediates does not affect the stability of packaged tablets through the end of their proposed drug product shelf-life.

3. Regarding the proposed regulatory analytical method descriptions:
   a. Since fenofibrate has low water solubility, revise the submitted Abbott and [redacted] analytical methods to use the same procedures for preparation of each solution (delete references to "example" procedures in the [redacted] methods).
   b. Revise the submitted Abbott and [redacted] dissolution methods to identify the maximum time and condition for storage of each solution.

4. Provide a copy of the method validation study, the method transfer study, and [redacted] methods referenced in [redacted] Technical Report TRP-R&D-05-019/2.

5. For the proposed blister package, identify the moisture protection class provided by the formed package and provide the results of USP <671> testing to support the claim.

6. Revise the Postapproval Stability Protocol to include a commitment to add an annual drug product lot to the protocol.

7. Based on our review of the submitted 12 month stability data:
   a. Confirm that the term "Unspecified Impurities" is in accordance with the ICH guidance Q3B(R) and Q6A.
   b. There is an observed increase in Impurity [redacted] over time, therefore a separate release and shelf-life specification should be established for this impurity.
   c. Identify the source of the continuously increasing residual moisture.
   d. Provide the results of dissolution testing on each of the primary and full scale studies in commercial, physician sample, and bulk package configurations using the method and criterion proposed in item 8 below.
   e. We acknowledge "NMT [redacted]" as an interim release and stability criterion for Moisture Content and agree with your proposal to revise this criterion appropriately when the further stability data becomes available.

8. The dissolution method and criterion should be revised as follows:
   medium: 1000 mL of 25mM sodium lauryl sulfate at 37°C
   apparatus: USP apparatus II ([redacted]) at [redacted]
   criterion: Q= [redacted] in 30 minutes
   The proposed drug product and shelf-life specifications and method descriptions should be revised to use this method and criterion.

9. We have identified deficiencies in DMF [redacted] and the DMF holder submitted a response on August 18, 2004, which was not reviewed in this cycle.

LABELING

10. Regarding the labeling:
    a. Submit revised draft labeling for the package insert. The labeling should be identical in content to the enclosed labeling (text for the package insert). (Additions to your draft labeling submitted June 1, 2004, are indicated by underlining and deletions by strikethrough.)

b. Revise the list of excipients to indicate the actual ingredients in the film-coatings instead of the trade names for the coating materials.
c. Revise the label storage statement to use the USP definition for controlled room temperature.
d. Provide mock-ups of labeling for cartons (for bottles).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format-NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format-Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format.

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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendments, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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 Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

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

Enclosure

14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

8 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Mary Parks
8/30/04 04:30:37 PM
for Dr. Orloff