CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-224

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-224

NDA APPROVAL

Abbott Laboratories
Attention: Natalie Tolli
Associate Director, Dyslipidemia
Dept. RA76, Building AP30-1NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Tolli:

Please refer to your new drug application (NDA) dated December 7, 2007, received December 7, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trilipix (fenofibric acid) Delayed Release Capsules, 45 mg, 135 mg.

We acknowledge receipt of your submissions dated March 20, April 7 and 10, May 7, June 6, 9, 13 and 23, August 7, 21 and 25, September 9 and 30 (2 submissions), October 2, 8 and 15, November 5, 2008.

This new drug application provides for the use of Trilipix (fenofibric acid) Delayed Release Capsules for the following indications:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
- As monotherapy to reduce TG in patients with severe hypertriglyceridemia.
- As monotherapy to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the

National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-224."

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-224."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) will not be sufficient to assess the signal of a serious risk of rhabdomyolysis in patients with mixed dyslipidemia who are receiving Trilipix (fenofibric acid) Delayed Release Capsules in combination with an HMG-CoA reductase inhibitor (statin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess this signal of serious risk or to identify unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

1. An observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis in patients treated with a fibrate in combination with a statin, versus statin or fibrate monotherapy. This study will be conducted using a large, independent database that allows access to medical records to validate diagnoses. A recommended algorithm for identification of the inception cohorts of statin and fibrate users, estimation of person-time on drug, and identification of cases of rhabdomyolysis is provided in "Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid-Lowering Drugs" by Graham and Staffa, published in JAMA December 1, 2004.

Your submission of September 30, 2008 states that you will conduct this study according to the following timetable:

Protocol Submission:	no later than January 31, 2009
Study Initiation:	no later than April 30, 2009
Final Report Submission:	no later than January 31, 2010

Submit protocols to your IND 70,345 with a cross-reference letter to this NDA 22-224. Submit all final reports to your NDA 22-224. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise unertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the following indications for the reasons stated:

A. As monotherapy to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.

We are waiving the pediatric study requirement because statins are considered first-line treatment for primary hypercholesterolemia and mixed dyslipidemia.

B. As monotherapy to reduce TG in patients with severe hypertriglyceridemia.

We are waiving the pediatric study requirement because necessary studies are impossible or highly impracticable. This is because severe hypertriglyceridemia in children is rare.

For the following indication, we are waiving the pediatric study requirement for ages 0-11 years, and deferring the requirement for ages 12-17:

C. In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because statins are first-line therapy, and the incidence of high TG and/or low HDL requiring additional therapy in this age range is very rare.

We are deferring submission of your pediatric study requirement for ages 12-17 years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

2. Deferred pediatric clinical trial under PREA for use in combination with a statin to reduce TG and increase HDL-C in pediatric patients ages 12 to 17 years with mixed dyslipidemia who are on optimal statin therapy to achieve their LDL-C goal.

   Final Study Submission: No later than **March 31, 2009**
   Study Initiation: No later than **July 31, 2009**
   Final Report Submission: No later than **February 28, 2013**

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study requirement must be clearly designated **"Required Pediatric Assessment."**

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your submission dated October 15, 2008. These commitments are listed below.

3. Conduct a dose equivalence study of Trilipix (fenofibric acid) Delayed Release Capsules, to compare the pharmacokinetics of 3 x 45 mg Trilipix capsules against 1 x 135 mg Trilipix (fenofibric acid) Delayed Release Capsules.

Protocol Submission:	by December 31, 2008
Study Start:	by February 28, 2009
Final Report Submission:	by September 30, 2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **"Postmarketing Study Commitment Protocol," "Postmarketing Study Commitment Final Report,"** or **"Postmarketing Study Commitment Correspondence."**

RISK EVALUTION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that a REMS is necessary for Trilipix (fenofibric acid) Delayed Release Capsules to ensure the benefits of the drug outweigh the risk of rhabdomyolysis when Trilipix (fenofibric acid) Delayed Release Capsules are co-administered with a statin.

Your proposed REMS, appended to this letter, submitted on November 5, 2008, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Trilipix (fenofibric acid) Delayed Release Capsules
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-224 REMS ASSESSMENT

NEW SUPPLEMENT for NDA 22-224
PROPOSED REMS MODIFICATION
REMS ASSESSMENT (if included)

Prominently identify other REMS-related submissions, such as the detailed plan to evaluate patients' understanding about the safe use of and risks associated with Trilipix (fenofibric acid) Delayed Release Capsules described below, with the following wording in bold capital letters at the top of the first page of the submission:

REMS - OTHER

If you do not submit electronically, please send 5 copies of submissions related to your REMS

Please note that:

- This Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18)] or 21 CFR 201.80(f)(2)];

- You are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];

- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)].

Additionally, you are responsible for submitting for review a detailed plan to evaluate the patients' understanding about the safe use of and risks associated with Trilipix (fenofibric acid) Delayed Release Capsules. The submission should include:

- All methodology and instruments that will be used to evaluate the patient's understanding about the safe use of Trilipix (fenofibric acid) Delayed Release Capsules. This should include, but not be limited to:

    - Sample size and confidence associated with that sample size
    - How the sample will be determined (selection criteria)
    - The expected number of patients surveyed
    - How the participants will be recruited

- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with their methodology
- Explain what will be done with the resulting data from the surveys.

- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and the correlation to the messages in the Medication Guide.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Package Insert, Medication Guide, REMS
45 mg, 90-count bottle label
135 mg. 90-count bottle label

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

/s/

Eric Colman
12/15/2008 01:32:48 PM
Eric Colman for Mary Parks