DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022224/S-005, 006

**SUPPLEMENT APPROVAL**
**RELEASE REMS REQUIREMENT**

Abbott Laboratories
Attention: Kelly Kaleck-Schlinsog
Associate Director, Dyslipidemia & Metabolism
Dept. PA76, Building AP-30-1NE
200 Abbott Park Road
Abbott Park, IL 60064

Dear Ms. Kaleck-Schlinsog:

Please refer to your Supplemental New Drug Applications (sNDAs) dated August 3, 2011, received August 4, 2011 (S-005), and dated August 4, 2011, received August 5, 2011 (S-006) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trilipix (fenofibric acid) Delayed Release Capsules, 45 mg, 135 mg.

We acknowledge receipt of your amendments to your sNDA (S-005) dated September 23 and 29, 2011 and your risk evaluation and mitigation strategy (REMS) assessment dated August 31, 2011.

We also refer to our letter dated July 6, 2011, notifying you of new safety information that we believe should be included in the labeling for Trilipix (fenofibric acid) under Section 505(o)(4) of the FDCA, notifying you that you must submit a proposed REMS modification under Section 505-1, and notifying you of a requirement for a postmarketing clinical trial under Section 505(o)(3). You were instructed to submit timetables for the final protocol submission, trial completion, and final report submission within 30 days from the date of our July 6, 2011 letter. The new safety information as defined in section 505-1(b)(3) of the FDCA pertains to the Agency's review of the ACCORD-Lipid clinical trial data which confirmed that individuals treated with the combination of a fibrate and a statin did not experience a statistically significant reduction in major adverse cardiovascular events (MACE) compared to individuals treated with a statin alone. Furthermore, subgroup analysis suggested an increased risk of MACE in women as compared to men treated with the combination of a fibrate and a statin versus treatment with a statin alone.

Supplemental new drug application S-005 provides for revisions to the labeling for Trilipix (fenofibric acid). Supplemental NDA S-006 provides for a proposed REMS modification to eliminate the requirement for the approved Trilipix (fenofibric acid) REMS. We also refer to your submission dated September 23, 2011 which contained your proposed milestone dates.

The agreed upon changes to the language included in our July 6, 2011, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

In the **FULL PRESCRIBING INFORMATION**, under **INDICATIONS AND USAGE,** the following heading was re-inserted:

1.5 General Considerations for Treatment

In the **FULL PRESCRIBING INFORMATION**, under **WARNINGS AND PRECAUTIONS, 5.9 Mortality and Coronary Heart Disease Morbidity**:

The Action to Control Cardiovascular Risk in Diabetes-Lipid (ACCORD-Lipid) trial was a ~~4.7 year~~ randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, (b) (4) -the hazard ratio for MACE in men receiving the combination therapy versus statin monotherapy was 0.82 (95% CI 0.69-0.99) and (b) (4) -the hazard ratio for MACE in women receiving the combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.'

To the **Medication Guide**, under **What is Trilipix?**

**Trilipix (b) (4) has not been shown to lower your risk of having heart problems or a stroke (b) (4)**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling

[21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Trilipix (fenofibric acid) was originally approved on December 15, 2008, and the most recent REMS modification was approved on September 14, 2010. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Trilipix (fenofibric acid) outweigh its risks.

Therefore, we agree with your proposal, and a REMS for Trilipix (fenofibric acid) is no longer required.

We remind you that the Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Our letter dated July 6, 2011, notified you of a requirement for a postmarketing clinical trial under Section 505(o)(3) of the FDCA, based on the new safety information described above.

You were required to conduct the following trial

1796-1 A randomized, double-blind, placebo-controlled trial evaluating the effect of Trilipix (fenofibric acid) on the incidence of major adverse cardiovascular events in high-risk men and women at LDL-C goal on statin therapy, but with residually high triglycerides and low HDL-C.

You were also required to submit timetables for the final protocol submission, trial completion, and final report submission within 30 days from the date of our July 6, 2011 letter.

The timetable you submitted on September 23, 2011 states that you will conduct this trial according to the following schedule:

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|---|---|
| Final Protocol Submission: | December 31, 2012 |
| Trial Completion: | January 31, 2020 |
| Final Report Submission: | January 31, 2021 |

Submit the protocol to your IND 070345, with a cross-reference letter to this NDA. Submit the final report to your NDA. Prominently identify the submission with the following wording in bold capital

letters at the top of the first page of the submission, 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 undertaken 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.

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

Sincerely,

*{See appended electronic signature page}*

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

ENCLOSURE:
Content of Labeling

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

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/s/

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AMY G EGAN
09/30/2011