DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18631/S-039

SUPPLEMENT APPROVAL

sanofi aventis US
Attention: Nancy Dougherty
US Regulatory Affairs Marketed Products
55 Corporate Drive
MailStop: 55A-430A
Bridgewater, NJ 08807

Dear Ms. Dougherty:

Please refer to your Supplemental New Drug Application (sNDA) dated August 19, 2010, received August 19, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRENTAL (pentoxifylline) 400 mg Extended-Release Tablets.

This Changes Being Effected supplemental new drug application provides for changes to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections to include more information regarding anaphylaxis and particular drug interactions with antihypertensive drugs.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. The changes to the label are as follows:

- To the **PRECAUTIONS-General** section, the following was added:

  "At the first sign of anaphylactic/anaphylactoid reaction, TRENTAL must be discontinued."

- Under the **PRECAUTIONS-Drug Interactions**, the term "antihypertensive drugs" and deleted and "plus nifedipine or captopril" was added.

- The following was also added to **PRECAUTIONS-Drug Interactions**:

  "Postmarketing cases of increased anticoagulant activity have been reported in patients concomitantly treated with pentoxifylline and vitamin K antagonists. Monitoring of anticoagulant activity in these patients is recommended when pentoxifylline is introduced or the dose is changed."

- In the section **ADVERSE REACTIONS**. "Anaphylactoid reactions" was deleted and "cholestasis" and "Immune system disorders - anaphylactic reaction, anaphylactoid reaction, anaphylactic shock" added.

- Other minor editorial changes were also made to the label.

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, 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with

21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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, please call:

Alison Blaus
Regulatory Health Project Manager
301-796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

NORMAN L STOCKBRIDGE
07/05/2012