DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18631/S-036

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Cristina Di Ramio, PharmD, RPh
Manager, US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Di Ramio:

Please refer to your Supplemental New Drug Application (sNDA) originally submitted 13 November 2008, and resubmitted 22 July 2010 and 26 April 2013under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRENTAL (pentoxifylline) extended-release tablets, 400 mg.

We also acknowledge receipt of your amendment dated 16 April 2014.

The 26 April 2013, submission constituted a complete response to our 26 February 2013 action letter.

This Prior Approval supplemental new drug application proposes changes to the Clinical Pharmacology, Precautions, and Dosage and Administration sections as well as a clarification of the dosage form. These changes are proposed in response to four submitted publications describing pentoxifylline use in patients with cirrhosis, with renal impairment and on its effects on glucose production in diabetics and healthy subjects. This supplemental new drug application provides for the following revisions to the labeling:

- In the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Metabolism** subsection, the following sentence was changed to show the change in C_{max} and AUC in fold change instead of a percentage:

    - "Coadministration of TRENTAL extended-release tablets with meals resulted in an increase in mean Cmax and AUC by about 28 % and 13% for pentoxifylline, respectively."

      Was changed to

      "Coadministration of TRENTAL extended-release tablets with meals resulted in an increase in mean AUC and Cmax of about 1.1 and 1.3-fold for pentoxifylline, respectively."

    - "C_{max} for Metabolite I also increased by about 20%."

      Was changed to read

      "C_{max} for Metabolite I also increased about 1.2-fold."

- In the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Metabolism** subsection, the following language was added:

  "Patients with Hepatic Impairment
  In patients with mild to moderate liver impairment AUC and C_{max} of pentoxifylline increased 6.5- and 7.5-fold, respectively, after a single 400 mg dose of TRENTAL. AUC and C_{max} of the active Metabolite I also increased 6.9- and 8.2-fold, respectively, in hepatic impaired subjects. TRENTAL has not been studied in patients with severe hepatic failure.

  Patients with Renal Impairment
  In patients with mild, moderate, or severe renal impairment the exposure to pentoxifylline and its active Metabolite I are not increased. In contrast, $AUC_{0\text{-}tss}$ and C_{max} of the active Metabolite V in patients with mild to moderate renal impairment increased 2.4- and 2.1-fold, respectively, with a 400 mg three times daily regimen of TRENTAL. In severe renal impairment $AUC_{0\text{-}tss}$ and C_{max} of the active Metabolite V increased 12.9- and 10.6-fold, respectively, with a 400 mg TRENTAL three times daily regimen. The increase in exposure to Metabolite V is only slightly smaller in both renal impairment groups if TRENTAL is administered twice daily."

- In the **PRECAUTIONS** section, **General** subsection, the following was added:

  "In patients with hepatic or renal impairment, the exposure to pentoxifylline and/or active metabolites is increased. The consequences of the increase in drug exposure are not known (please see Pharmacokinetics and Metabolism and DOSAGE AND ADMINISTRATION)."

- In the **Drug Interactions** subsection of **PRECAUTIONS,** the following underlined text was added:

  "TRENTAL has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, and antiarrhythmics, without observed problems."

- In the **DOSAGE AND ADMINISTRATION** section, the following language was added:

  "In patients with severe renal impairment (creatinine clearance below 30 ml/min) reduce dose to 400 mg once a day. Dosing information cannot be provided for patients with hepatic impairment."

- Throughout the label the dosage form was amended from "Tablets" to "Extended-release Tablets".

- Lastly, there were other minor editorial changes.

APPROVAL & LABELING

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

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) 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 via 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 with the revisions 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate-container labels submitted on 14 September 2012, 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 *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. 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 18631/S-036**." Approval of this submission by FDA is not required before the labeling is used.

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

REQUIRED PEDIATRIC ASSESSMENTS

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

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, RAC
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Safety Deputy Director
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

ALISON L BLAUS
04/17/2014

MARY R SOUTHWORTH
04/17/2014