



NDA 20839/S-058

SUPPLEMENT APPROVAL

sanofi aventis
Attention: Cristina Di Ramio, PharmD
Manager US Regulatory Affairs
55 Corporate Drive
Mail Stop: 55C-205A
Bridgewater, NJ 08807

Dear Dr. Di Ramio:

Please refer to your Supplemental New Drug Application (sNDA) dated July 19, 2013, received July 19, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We acknowledge receipt of your amendments dated October 3 and December 11, 2013.

This Prior Approval supplemental new drug application provides for changes to an existing warning for allergic cross-reactivity among thienopyridines, new adverse reaction information that has been observed in post-marketing experience, and new drug interaction information regarding selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

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. These changes are as follows:

FULL PRESCRIBING INFORMATION (FPI) CHANGES

- Under **WARNINGS AND PRECAUTIONS**, the following warning was deleted:

5.6 Allergic Cross-Reactivity among Thienopyridines

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since allergic cross-reactivity among thienopyridines has been reported

And replaced with:

5.6 Cross-Reactivity among Thienopyridines

Hypersensitivity including rash, angioedema or hematologic reaction have been reported in patients receiving Plavix, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines [*see Contraindications (4.2) and Adverse Reactions (6.2)*].

- Under section 6, **ADVERSE REACTIONS**, sub-section 6.2 **Postmarketing Experience**, the following changes were made:
 - To “*Blood and lymphatic system disorders*”, “acquired hemophilia A” was added
 - To “*Skin and subcutaneous tissue disorders*”, “erythematous rash” was updated to “erythematous or exfoliative rash”
- Under section 7, **DRUG INTERACTIONS**, the following sub-section was added:

7.4 SSRIs and SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

- The **HIGHLIGHTS** were changed to reflect the above changes in the FPI.

MEDICATION GUIDE CHANGES

- Under the section, “**What should I tell my doctor before taking Plavix?**”, subsection “**Especially tell your doctor if you take:**”, the following bullet was added:

“selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Ask your doctor or pharmacist for a list of SSRI or SNRI medicines if you are not sure.”

We note that your December 11, 2013, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 that includes labeling changes 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(1)(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).

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
Deputy Director for Safety
Division of Cardiovascular & 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/

ALISON L BLAUS
12/12/2013

MARY R SOUTHWORTH
12/12/2013