



NDA 020839/S-070

SUPPLEMENT APPROVAL

Sanofi-Aventis U.S. LLC
C/o Sanofi US Services Inc.
Attention: John Cook
Senior Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop: 55C-300
Bridgewater, NJ 08807

Dear Mr. Cook:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 25, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg and 300 mg Tablets.

We also refer to our letter dated January 9, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for oral P2Y12 inhibitors. This information pertains to the risk of decreased exposure to clopidogrel's metabolites when clopidogrel and opioids are used concomitantly.

We also refer to our Safety Labeling Change Order Letter dated, March 9, 2018.

We further refer to our Dispute Appeal Denied letter, dated May 11, 2018.

This supplemental new drug application provides for revisions to the labeling for Plavix, consistent with the revisions in our May 11, 2018 Dispute Appeal Denied letter as follows:

1. In **HIGHLIGHTS/DRUG INTERACTIONS**, a bullet was added:
 - Opioids: Decreased exposure to clopidogrel. Consider use of parenteral anti-platelet agent (7.2)

2. Under **DRUG INTERACTIONS**, the following section was added:

7.2 Opioids

As with other oral P2Y12 inhibitors, co-administration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites [see Clinical Pharmacology (12.3)]. Consider the use of a parenteral antiplatelet agent in acute

coronary syndrome patients requiring co-administration of morphine or other opioid agonists. .

3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added to the section titled Drug Interactions:

Opioids

Co-administration of 5 mg intravenous morphine with 600 mg loading dose of clopidogrel in healthy adults decreased the AUC and Cmax of clopidogrel's thiol metabolites by 34%. Mean platelet aggregation was higher up to 2 to 4 hours with morphine co-administration.

4. The **DRUG INTERACTIONS** section was renumbered, and some of the cross-references were updated to reflect these changes.
5. The table of Contents and the revision date were updated.
6. There were no changes made to the Medication Guide.

There are no other changes from the last approved package insert and patient package insert.

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.

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, 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 include 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(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).

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:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

MARY R SOUTHWORTH
05/25/2018