DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020839

LABELING ORDER

Sanofi-aventis US, LLC
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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel) 75 mg and 300 mg Tablets.

On January 9, 2018, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of clopidogrel to address the risk of decreased absorption of clopidogrel with concomitant use of morphine. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

In your February 8, 2018 submission, FDA received your notification detailing the reasons why you believe a labeling change to address the risk of decreased absorption of clopidogrel with concomitant use of morphine is not warranted for clopidogrel.

Section 505(o) requires FDA to promptly review your submission and initiate discussions if necessary. We also refer to modified labeling language that we forwarded to you by e-mail on February 28, 2018, and to your response received on March 7, 2018.

We have completed the review of your submission dated March 7, 2018, initiated discussions of your submission and did not reach agreement, and find that your proposed labeling changes do not adequately address the new safety information described above.

Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the January 19, 2018, SLC Notification letter (attached), as modified in accordance with our e-mail dated February 28, 2018 (attached).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

We will consider your submission of the CBE supplement a request to withdraw your prior approval supplement submitted on March 7, 2018, under 21 CFR 314.65.

Alternatively, by March 14, 2018, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 22, Room 6300
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Lori Anne Wachter, RN, BSN, RAC
Safety Regulatory Project Manager
Food and Drug Administration
Division of Cardiovascular and Renal Products
Building 22, Room 4158
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Khushboo Sharma, CDER Formal Dispute Resolution Project Manager, at (301) 796-1270. Appeals received by the Agency later than March 14, 2018, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject

you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES: Safety Labeling Change Notification Letter
Emails/letters

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020839

SAFETY LABELING CHANGE NOTIFICATION

Sanofi-aventis U.S. LLC
Attention: Frances Polizzano, PharmD.
Senior Manager, Global Regulatory Affairs, North America
55 Corporate Drive
MailStop: 55C-205A
Bridgewater, NJ 08807

Dear Dr. Polizzano:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel) 75 mg and 300 mg Tablets.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since clopidogrel was approved on November 17, 1997, we have become aware of a drug-drug interaction resulting in decreased exposure to clopidogrel's active metabolite when clopidogrel and morphine are used concomitantly. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for $P2Y_{12}$ inhibitors as follows:

1. Under **DRUG INTERACTIONS**, add the following text to Section 7.2:

   Co-administration of opioid agonists delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying [*see Clinical Pharmacology (12.3*)]. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

2. Under **CLINICAL PHARMACOLOGY**, add the following text to Section 12.3:

   Drug Interactions/Effect of other drugs on Plavix
   Co-administration of 5 mg intravenous morphine with 600 mg loading dose of clopidogrel in healthy adults decreased the AUC and C_{max} of clopidogrel's active

metabolite by 34%. Inhibition of platelet aggregation was also delayed and reduced.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT 070
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

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
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
01/09/2018

Wachter, Lori

To: john.cook@sanofi.com
Subject: Plavix (clopidogrel) NDA 020839

Importance: High

Dear John,

We have received and considered your response to our safety labeling change notification letter (submitted 02/08/2018) and have the following comments:

We believe that the decrease in exposure demonstrated in the cited studies is clinically relevant because the clinical effectiveness of Plavix is a result of its antiplatelet activity which is dependent on exposure to its active metabolite.

While we acknowledge the inconsistency in the reported PK measures of clopidogrel active metabolite in Hobl et al. (2014) compared to other publications, we do not expect it to have an impact on the assessment of relative change in PK when co-administered with morphine. Moreover, the decrease in plasma exposures with clopidogrel active metabolite when co-administered with morphine is consistent with a decrease and delay in platelet inhibition activity as measured by various platelet function assays. Although the more commonly used light transmittance aggregometry platelet function assay was not used in the healthy adult study by Hobl et al. (2014), multiple P2Y12 platelet function assays (MEA, VASP and P2Y-Innovance) show a delay in clopidogrel's antiplatelet activity when co-administered with morphine. Lastly, we believe such an interaction between clopidogrel and morphine is expected when taken together with the abundance of reports that exists which show a clinically significant interaction for morphine with other oral P2Y12 inhibitors having similar PK properties.

Alerting prescribers about the potential for an interaction with opioid agonists, as well as offering a practical option for managing the drug interaction ("consider use of a parenteral anti-platelet") is appropriate.

After further review we believe the new portion of Section 7, 12 and highlights should appear as follows:

7.2 Opioids

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying [*see Clinical Pharmacology 12.3)].* Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

12.3 Drug Interactions/Effects of other drugs on Plavix

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 active metabolite by 34%. Mean platelet aggregation was higher up to 2 to 4 hours with morphine co-administration.

Highlights/Drug interactions

- Opioids: Opioids: Decreased exposure to clopidogrel. Consider use of parenteral anti-platelet agent

If you do not submit a labeling supplement with this language by March 7th, we will proceed with next regulatory steps to ensure this language appears in labeling.

Feel free to contact me with any questions.

Regards,

Lori

Lori Anne Wachter, RN, BSN, RAC
Regulatory Health Project Manager for Safety

Center for Drug Evaluation and Research
Office of New Drugs
U.S. Food and Drug Administration
Tel: 301-796-3975
Lori.wachter@fda.hhs.gov

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

/s/

ROBERT TEMPLE
03/09/2018