DEC 2 1 2018

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Public Citizen
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Washington, DC 20009

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The Johns Hopkins University School of Medicine
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Re: Docket No. FDA-2013-P-1056

Dear Drs. Wolfe and Holtzman:

This letter responds to your citizen petition dated August 21, 2013, (Petition) requesting that the Food and Drug Administration (FDA or the Agency) require the addition of a boxed warning[1] to the labeling for clopidogrel[2] tablets addressing the "increased risks of major and minor bleeding with use beyond 12 months following implantation of drug-eluting coronary artery stents."[3] You further request that FDA require an updated Medication Guide containing the information in the proposed boxed warning to be dispensed to all patients when their clopidogrel prescriptions are filled. Finally, your Petition asks FDA to ask application holders to send "Dear Doctor" letters warning physicians of the potential adverse events identified in the proposed boxed warning.[4] In support of your Petition, you assert that there is little evidence of additional benefit from use of clopidogrel beyond 12 months after percutaneous insertion of a drug-eluting stent

[1] While the Petition requests a "black-box warning," the regulation that describes specific requirements on content and format of labeling for most human prescription drug and biological products, including clopidogrel tablets, 21 CFR 201.57, refers to such a warning simply as a "boxed warning." *See* 21 CFR 201.57(c)(1). We will, therefore, use the term "boxed warning" throughout this response.

[2] Although the active ingredient for the drug that is the subject of this petition is clopidogrel bisulfate, we use the term "clopidogrel" in this response as was done in the Petition.

[3] Petition at 2, 9-10.

[4] Petition at 2, 10.

(DES), while the risk of major and minor bleeding persists as long as patients are on clopidogrel.

We have carefully considered the information submitted in the Petition, as well as important new information that has become available concerning the effects of clopidogrel one year after stent insertion. Based on our review of this information, and for the reasons described below, the Petition is denied.

Background

FDA approved Plavix (clopidogrel bisulfate) tablets, for oral use, on November 17, 1997, under new drug application 020839. Numerous abbreviated new drug applications for clopidogrel have also been approved.[5] Clopidogrel is a $P2Y_{12}$ platelet inhibitor used in the treatment of acute coronary syndrome, recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. The complete approved indications for clopidogrel are as follows:

1.1 Acute Coronary Syndrome (ACS)

- Plavix is indicated to reduce the rate of myocardial infarction (MI) and stroke in patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization. Plavix should be administered in conjunction with aspirin.
- Plavix is indicated to reduce the rate of myocardial infarction and stroke in patients with acute ST-elevation myocardial infarction (STEMI) who are to be managed medically. Plavix should be administered in conjunction with aspirin.

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

- In patients with established peripheral arterial disease or with a history of recent myocardial infarction (MI) or recent stroke Plavix is indicated to reduce the rate of MI and stroke.[6]

Clopidogrel, an inhibitor of platelet function, reduces the rate of MI and stroke by preventing the formation of coronary artery blood clots. Given this mode of action, some increased risk of bleeding is to be expected. The Highlights of Prescribing Information (Highlights) section of the Plavix Prescribing Information (PI) states: "[b]leeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction."[7] In addition, the following warning is included in the WARNINGS AND

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[5] Information about clopidogrel abbreviated new drug applications can be found on FDA's website referred to as Drugs@fda, which is available at https://www.accessdata.fda.gov/scripts/cder/daf/.

[6] Plavix (clopidogrel bisulfate) tablets Prescribing Information, revised May 2018 (2018 Prescribing Information), INDICATIONS AND USAGE section, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020839s070lbl.pdf. The INDICATIONS AND USAGE section of the 2018 Prescribing Information reflects changes made since the Petition was submitted, which more accurately reflect currently available data. We note that these changes, however, are not directly relevant to the Petition or this response.

PRECAUTIONS section of Plavix's PI : "Thienopyridines, including Plavix [clopidogrel], increase the risk of bleeding."[8] Information about bleeding is also included in the Patient Counseling Information section of the PI.[9] Finally, Plavix's Medication Guide[10] also warns that "Plavix [clopidogrel] can cause bleeding which can be serious and can sometimes lead to death."[11]

Discussion

As you indicated in your Petition, there once was little evidence of a useful effect of clopidogrel for stented patients after one year at the time the Petition was submitted, which raised important questions about the value of long-term use in such patients. Since that time, however, findings from the Dual Antiplatelet Therapy (DAPT)[12] trial have become available that have shed new light on the benefits of taking clopidogrel for more than one year after stent insertion.

The overall results of the large DAPT trial demonstrated that use of DAPT for up to 30 months in patients who received a DES, compared to use of DAPT for 12 months after receiving a DES, reduced the rate of ischemic (i.e., thrombotic) events, although the benefit of extended therapy was accompanied by an increase in bleeding events. Further analyses of the data from the DAPT trial, along with data from other clinical investigations, have suggested that the benefit/risk profile of extended DAPT compared to 12 months of DAPT is considerably more favorable in some patients than in others.[13, 14, 15] Each of these publications has recommended a scoring algorithm based on patient characteristics to guide physicians in selecting patients for extended DAPT. These algorithms vary in their inputs, but use aspects of the patient's medical history, stent-

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[7] 2018 Prescribing Information.

[8] Id. at section 5.2.

[9] Id. at section 17.

[10] Plavix Medication Guide, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020839s070lbl.pdf, p. 23.

[11] Id. at p. 26.

[12] Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155-2166. *Dual antiplatelet therapy* or DAPT is the treatment of patients with coronary artery disease with aspirin plus a $P2Y_{12}$ inhibitor such as clopidogrel, prasugrel, or ticagrelor. In this letter, "DAPT" refers either to the DAPT trial cited here or to dual antiplatelet therapy.

[13] Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016;315(16):1735-1749.

[14] Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389(10073):1025-1034.

[15] Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol. 2016;67(19):2224-2234.

related factors, and/or results of common diagnostic procedures to assess an individual's thrombotic risk and/or bleeding risk. In general, higher levels of thrombotic risk and lower levels of bleeding risk are each associated with better outcomes with a longer duration of DAPT, while lower levels of thrombotic risk and higher levels of bleeding risk are each associated with better outcomes with a shorter duration of DAPT compared to extended DAPT. These publications provide physicians with ways to identify patients who have received a DES for whom the antithrombotic benefits of extended DAPT would be expected to outweigh the added risk of both major and minor bleeding.

Citing the results of the DAPT trial and many other publications, the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease (2016 ACC/AHA DAPT Guidelines) explains that decisions about the prolongation of DAPT necessitate a tradeoff between decreasing ischemic risk and increasing bleeding risk. These guidelines recommend that use of DAPT for longer than 12 months "may be considered" in patients who have received a coronary stent for treatment of an acute coronary syndrome (who have a greater risk of thrombotic events than those treated for stable coronary disease) and who have tolerated DAPT without bleeding complications for 12 months and are otherwise not at high bleeding risk.[16]

We agree with the 2016 ACC/AHA DAPT Guidelines' recommendation that decisions regarding the duration of DAPT in patients who have received a DES should be made on a case-by-case basis by clinicians familiar with the individual characteristics of the patient to best address the needs of each patient. An unqualified statement advising physicians that continuation of clopidogrel for longer than 12 months following percutaneous insertion of a DES is of "questionable additional benefit" in a boxed warning—or indeed in any section of labeling—would be inconsistent with available data. These data, from both randomized and non-randomized studies, indicate that in selected patients the added benefits of extended DAPT outweigh the added risks such as increased risk of bleeding.

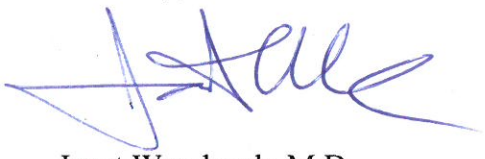
and

[16] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1082-1115.

Conclusion

For the reasons stated above, the Petition is denied. Please be assured, however, that FDA remains committed to ensuring the safety and effectiveness of all approved drugs. As with all FDA-approved drugs, we will continue to monitor and review available safety information related to clopidogrel and seek labeling changes or take other actions within our authority as appropriate.

Sincerely,



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