AUG 0 7 2017

Sammy Almashat, MD, MPH
Researcher
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

Re: FDA-2016-P-4584

Dear Dr. Almashat:

This letter responds to your citizen petition received on December 28, 2016 (Petition), on behalf of Public Citizen's Health Research Group (Public Citizen). In the Petition, you request that the Food and Drug Administration (FDA or Agency) take immediate action with respect to the labeling of repaglinide-containing medications (i.e., Prandin, PrandiMet) and clopidogrel (Plavix). More specifically, the Petition asks FDA to require that:

(1) "The label of repaglinide-containing medications (PRANDIN, PRANDIMET) include information on a serious drug-drug interaction with clopidogrel (PLAVIX) that could result in severe hypoglycemia"; and

(2) "The labels of both repaglinide-containing medications and clopidogrel include a contraindication to the use of the two drugs together due to this interaction."

We have carefully considered the Petition, and for the reasons described below, the Petition is granted in part and denied in part.

## I. SUMMARY OF THE PETITION

Prandin (repaglinide) tablets were first approved on December 22, 1997 (new drug application (NDA) 020741, originally held by Novo Nordisk, Inc.).[1] As described in the labeling in effect at the time of the Petition, Prandin is "an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM)."[2] The drug is indicated "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."[3] Repaglinide has also been

[1] NDA 020741 was transferred to Gemini Laboratories LLC on February 15, 2017.
[2] Drugs@FDA, Prandin Approved Labeling, July 29, 2010, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020741s038lbl.pdf.
[3] Id. at 10.

approved in eight abbreviated new drug applications (ANDAs).[4]

As described in the labeling in effect at the time of the Petition, PrandiMet (repaglinide and metformin hydrochloride (HCl)) tablets are "a meglitinide and biguanide combination product" indicated as an "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin HCl or who have inadequate glycemic control on a meglitinide alone or metformin HCl alone."[5] PrandiMet was first approved on June 23, 2008 (NDA 022386, held by Novo Nordisk, Inc.).

Clopidogrel was first approved as Plavix (clopidogrel bisulfate) tablets on November 17, 1997 (NDA 020839, held by Sanofi Aventis US). The product is a P2Y12 platelet inhibitor indicated for acute coronary syndrome, recent myocardial infarction, recent stroke, or established peripheral arterial disease.[6] There are currently 20 approved ANDA products with clopidogrel as their active ingredient.[7] The product is approved in 75 milligram (mg) and 300mg doses.

According to the Petition, dangerously low blood sugar levels can result when repaglinide and clopidogrel are taken together.[8] Public Citizen cites a 2014 study conducted in Finland and a 2016 study conducted in Japan as evidence that increased blood levels of repaglinide resulted in a significant drop in blood glucose levels when subjects were given clopidogrel concomitantly.[9] The Petition states that "[o]n July 31, 2015, Health Canada issued an alert to health care professionals warning about the risk of dangerously low blood sugar levels when repaglinide and clopidogrel are taken together."[10] The Petition notes that FDA had not taken similar action.[11]

## II. RESPONSE TO THE PETITION

FDA's regulation of drug safety is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et. seq.) and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations). After an approved drug enters the marketplace, FDA may have cause to reassess its safety and take regulatory action if warranted and appropriate.

Prescription drug labeling must contain a summary of the essential scientific information needed for the safe and effective use of a drug, including a description of clinically significant interactions with other drugs.[12] FDA agrees that there is a clinically relevant drug interaction between repaglinide and clopidogrel. Mean repaglinide exposure may increase up to 5.1-fold

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[4] ANDAs 077571, 078555, 090008, 090252, 091517, 201189, 203820, and 200624.
[5] Drugs @ FDA, PrandiMet Approved Labeling, April 4, 2012, at 1, available at: http://www.accessdata.fda.gov/dru gsatfda_docs/label/2012/022386s000lbl.pdf.
[6] Drugs@FDA, Plavix Labeling, September 6, 2016 at 1, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020839s062s064lbl.pdf.
[7] ANDAs 076273, 076274, 076999, 077665, 078004, 078133, 090307, 090494, 090540, 090625, 090844, 091023, 091216, 201686, 202266, 202925, 202928, 203751, 204165 and 204359.
[8] Petition at 3.
[9] Id. at 2-3.
[10] Id. at 3.
[11] Id.
[12] 21 CFR §§ 201.56 and 201.57.

with a 300 mg dose of clopidogrel, and there is substantial individual variability in the increase.[13]

On February 8, 2017, FDA approved two labeling supplements for Prandin (repaglinide). Supplement 041 converted the prescribing information of the labeling to Physician Labeling Rule format, and Supplement 042 added information regarding the risk of hypoglycemia and drug-drug interaction information regarding concomitant use of repaglinide and clopidogrel.

Approval of Supplement 042 added cautionary language regarding the risk of hypoglycemia to the WARNINGS AND PRECAUTIONS section of the labeling for Prandin as follows:

> "Hypoglycemia: PRANDIN may cause hypoglycemia. Skip the scheduled dose of PRANDIN if a meal is skipped to reduce the risk of hypoglycemia. Reduce the dose of PRANDIN if hypoglycemia occurs."

Supplement 042 also added language concerning concomitant use of repaglinide and clopidogrel. The revised DRUG INTERACTIONS section explains that clopidogrel was found to increase repaglinide exposures by 3.9- to 5.1-fold.[14] The HIGHLIGHTS OF PRESCRIBING INFORMATION recommend avoiding concomitant use of repaglinide with clopidogrel, but that if concomitant use cannot be avoided, to initiate dosing at 0.5 mg before each meal and to not exceed a total daily dose of 4 mg: "Clopidogrel: Avoid concomitant use; if used concomitantly initiate at 0.5 mg before each meal and limit total daily dose to 4 mg."

In addition, the revised labeling notifies the prescriber that increased frequency of glucose monitoring may be required if repaglinide and clopidogrel are used concomitantly. FDA would support similar changes to labeling for PrandiMet (repaglinide and metformin HCl) tablets.

FDA has approved revisions adding information to the DRUG INTERACTIONS section of the labeling for Plavix (clopidogrel). The revised labeling similarly recommends avoiding concomitant use of repaglinide and clopidogrel and the need for dose restrictions and glucose monitoring if concomitant use cannot be avoided. The following text has been approved (additions are shown below as underlined text and deletions are shown as strikethrough text):

> **7.5 Repaglinide (CYP2C8 Substrates)**
>
> The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Plavix can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose-adjustment and~~/or~~ appropriate monitoring.
>
> ~~Concomitant administration of Plavix with repaglinide significantly increases systemic exposures to repaglinide~~ Plavix increased repaglinide exposures by 3.9-5.1-fold *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of repaglinide with Plavix. ~~When~~ If concomitant use ~~is required in a patient maintained on clopidogrel,~~ cannot be avoided, initiate repaglinide at 0.5 mg ~~with~~ before each meal and ~~titrate based on blood glucose~~

[13] Tornio A, Filppula AM, Kailari O, et al. Glucuronidation converts clopidogrel to a strong time-dependent inhibitor of CYP2C8: A phase II metabolite as a perpetrator of drug-drug interactions. Clin Pharmacol Ther. 2014;96(4):498-507.
[14] See id.

~~levels. D~~ do not exceed a total daily dose of 4 mg. ~~If concomitant use of clopidogrel is required in a patient stabilized on higher doses of repaglinide, down titrate the dose of repaglinide based on blood glucose levels to not exceed a total daily dose of 4 mg.~~ Increased frequency of glucose monitoring may be required during concomitant use.

Accordingly, your request that the labeling for products with repaglinide include information on a drug-drug interaction with clopidogrel is granted.

However, the Petition is denied to the extent that it requests a contraindication to the use of repaglinide and clopidogrel together. The contraindication section of the labeling must describe situations in which the drug "should not be used because the risk of use… clearly outweighs any possible therapeutic benefit."[15] Although we agree that the additional language discussed above for the repaglinide and clopidogrel labeling is appropriate, we disagree that a contraindication is required. FDA believes that the risks associated with a drug-drug interaction occur when repaglinide is taken with the 300 mg dose of clopidogrel. The 300 mg dose is indicated only for acute coronary syndrome. Affected patients typically are under intense monitoring in a hospital and would receive a 300 mg dose under these conditions.

FDA is not aware of any significant postmarketing safety signals that the drug-drug interaction has caused serious hypoglycemia. With dose reduction and increased frequency of monitoring as specified in the revised labeling, the risk of hypoglycemia is reduced, and we do not believe that the risks of using these two drugs concomitantly outweigh the benefits.[16] The Agency believes that dose adjustment for repaglinide is adequate to address the drug-drug interaction and the associated risks described in the Petition.[17]

## III. CONCLUSION

For the reasons described in this response, the Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[15] 21 CFR §§201.56 and 201.57

[16] *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format*, at 8, available at: https://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf .

[17] Petition at 2 (citing Tornio A, Filppula AM, Kailari O, et al., Glucuronidation converts clopidogrel to a strong time-dependent inhibitor of CYP2C8: A phase II metabolite as a perpetrator of drug-drug interactions. Clin Pharmacol Ther. 2014;96(4):498-507).