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Citizen Petition

Date: December 21, 2016

On behalf of Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, the undersigned submits this petition under Section 352 the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. §§ 10.30 and 201.56 to request the Commissioner of Food and Drugs to immediately 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.

A. ACTION REQUESTED

Immediately 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.

B. STATEMENT OF GROUNDS

1. Background: Repaglinide and clopidogrel

Repaglinide is marketed, both on its own (PRANDIN) and in combination with the diabetes medication metformin (PRANDIMET), for the treatment of Type 2 diabetes.[1] It is a member of the family of diabetes drugs known as meglitinides, which stimulate the release of insulin from cells in the pancreas.[2]

[1] In the remainder of this petition, repaglinide-containing medications will be referred to collectively as "repaglinide."
[2] Carilion Materials Management. Label: PRANDIN (repaglinide) tablets. August 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2a07020-a596-4282-bb7c-c9ebe6edcd61&audience=consumer. Accessed December 20, 2016.

Clopidogrel (PLAVIX) is a widely used drug that decreases blood clot formation by interfering with platelet activation and aggregation.[3] It was approved by the FDA to reduce the long-term risk of a new heart attack or stroke in patients who have suffered a recent heart attack or stroke or have established peripheral vascular disease (for example, evidence of narrowed or blocked arteries in the legs or neck). The drug also is approved for the immediate treatment of acute coronary syndrome to reduce the chance of subsequent heart attack or stroke.

2. Studies showing risk of dangerous drug interaction

In October 2014, a study (Tornio et al.) demonstrating a significant interaction between clopidogrel and repaglinide was published in the journal *Clinical Pharmacology & Therapeutics*.[4] Researchers in Finland studied 9 healthy subjects who were given repaglinide with and without clopidogrel over separate three-day periods, using a crossover design. Repaglinide at a 0.25 milligram (mg) dose was given to subjects one hour after either a placebo or clopidogrel on the first and third days of each study period. During the clopidogrel administration period, a dose of 300 mg of clopidogrel was given on the first day of treatment, with 75 mg given on the second and third days. The researchers then measured blood levels of both repaglinide and glucose at 5 minutes before and 15, 30, 45, 60, 80, and 100 minutes after and at 2, 2.5, 3, 4, 5, 7, and 9 hours after the administration of repaglinide.

Clopidogrel increased the geometric mean area under the concentration-time curve of repaglinide by 5.1-fold on day 1 of clopidogrel administration (300 mg dose), and by 3.9-fold on day 3 of administration (75 mg dose), compared to levels of repaglinide when given alone ($P < 0.001$). The elimination half-life of repaglinide was lengthened by 42% after the 300 mg dose of clopidogrel on the first day and by 22% after a 75 mg dose on the third day ($P < 0.005$).

The increased blood levels of repaglinide resulted in a significant drop in blood glucose levels when subjects were given clopidogrel concomitantly, as seen in the following table:

Table. Blood glucose levels in nine healthy volunteers after a single oral dose of 0.25 mg repaglinide (taken from Table 2, of the same title, from Tornio et al.).

Variable (all in mg/dL)*	**Placebo (control)**	**Clopidogrel 300 mg (day 1)**	**Clopidogrel 75 mg (day 3)**
Baseline concentration	101 ± 9	97 ± 7	99 ± 7
Minimum concentration	79 ± 9	59 ± 11***	70 ± 11†
Mean concentration from 0 to 3 hours	103 ± 9	83 ± 11****	92 ± 11**†
Mean concentration from 0 to 9 hours	101 ± 7	83 ± 7***	90 ± 7††

* All values converted into units of mg/dL from the mmol/L presented in the article.
**P < 0.05 vs. control, ***P < 0.005 vs. control, ****P < 0.001 vs. control, †P < 0.005 vs. clopidogrel 300 mg, ††P < 0.001 vs. clopidogrel 300 mg.

[3] Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Label: PLAVIX (clopidogrel bisulfate) tablet. September 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=01b14603-8f29-4fa3-8d7e-9d523f802e0b&audience=consumer. Accessed December 20, 2016.

[4] 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.

The combination of repaglinide and a 300 mg dose of clopidogrel caused the minimum glucose concentration to decrease by a clinically significant average of 39% from baseline by day 1 (the decrease was statistically significant compared with placebo).

Based on an *in vitro* study, the authors identified the metabolite clopidogrel acyl-β-D-glucuronide as the likely culprit acting as a strong inhibitor of the CYP2C8 hepatic enzyme responsible for the metabolic clearance of repaglinide.

A 2016 Japanese study confirmed both the degree of and the probable mechanism behind the clopidogrel-repaglinide interaction.[5] The researchers tested various drug interactions, including clopidogrel and repaglinide, in 24 healthy male volunteers. In the initial phase, subjects received 0.1 mg of repaglinide, followed by water; in the second, drug interaction phase, subjects received 0.1 mg of repaglinide, along with 300 mg of clopidogrel. Blood samples were taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

The concentration of repaglinide, as measured by the area under the curve up to 8 hours after dosing, increased by 3.1-fold when co-administered with clopidogrel, compared to repaglinide given alone ($P < 0.05$). Similar to the 2014 study, the researchers' tests concluded that clopidogrel acyl-β-D-glucuronide, inhibiting CYP2C8, was most likely responsible for the interaction with repaglinide.

3. Health Canada and FDA actions thus far

On 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.[6] Health Canada also required that the Canadian product labels for both drugs be updated to reflect information about this dangerous drug interaction and to include a contraindication that warns against taking the two drugs together under any circumstances. The Canadian warning for patients explains, "Severe hypoglycemia [low blood sugar] can cause loss of consciousness, seizure, brain damage and even death."[7]

The FDA has not taken similar actions. Regarding the U.S. product labels, only the label for clopidogrel includes information on the interaction with repaglinide, within the Drug Interactions section.[8] Inexplicably, the FDA has not required the same information to be inserted into the

[5] Kim SJ, Yoshikado T, Ieiri I, et al. Clarification of the mechanism of clopidogrel-mediated drug-drug interaction in a clinical cassette small-dose study and its prediction based on in vitro information. *Drug Metab Dispos*. 2016;44(10):1622-1632.
[6] Health Canada. Gluconorm (repaglinide) - New contraindication for concomitant use with clopidogrel. July 31, 2015. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/54454a-eng.php. Accessed December 20, 2016.
[7] Health Canada. Drug Product Database online query. Repaglinide label, updated April 2016. Clopidogrel label, updated June 2016. https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed December 20, 2016.
[8] Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Label: PLAVIX (clopidogrel bisulfate) tablet. September 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=01b14603-8f29-4fa3-8d7e-9d523f802e0b&audience=consumer. Accessed December 20, 2016.

label for repaglinide.[9] Moreover, there is no contraindication to the use of the two drugs together in either label,[10,11] as was put in place in Canada.

4. Reasons to include a contraindication, in both labels, in addition to information in the Drug Interactions section

In addition to adding information on the clopidogrel-repaglinide interaction to the repaglinide label, there are several compelling reasons to add a contraindication to both labels.

First, the degree of hypoglycemia seen in the 2014 study (Tornio et al.) that served as the basis for the 2015 Health Canada risk communication was clinically significant (see Table) and poses a substantial danger for certain diabetic patients who are already at risk for hypoglycemic episodes. Second, clopidogrel is very widely used, including in the diabetes population (which has a higher rate of cardiovascular disease than the general population) for whom repaglinide is indicated. And third, because there are many alternatives to repaglinide for diabetes treatment, the risks of using these two drugs concomitantly outweigh any benefits.

C. ENVIRONMENTAL IMPACT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

[9] Carilion Materials Management. Label: PRANDIN (repaglinide) tablets. August 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2a07020-a596-4282-bb7c-c9ebe6edcd61&audience=consumer. Accessed December 20, 2016.

[10] Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Label: PLAVIX (clopidogrel bisulfate) tablet. September 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=01b14603-8f29-4fa3-8d7e-9d523f802e0b&audience=consumer. Accessed December 20, 2016.

[11] Carilion Materials Management. Label: PRANDIN (repaglinide) tablets. August 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2a07020-a596-4282-bb7c-c9ebe6edcd61&audience=consumer. Accessed December 20, 2016.

E. CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,

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