DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

OCT 3 1 2014

Eric Nellis
Sammy Almashat, M.D., M.P.H.
Michael Carome, M.D.
Sidney M. Wolfe, M.D.
Public Citizen
1600 20th Street, N.W.
Washington, D.C. 20009

Helge L. Waldum, M.D., Ph.D.
Trondheim University Hospital
Trondheim, Norway
c/o Public Citizen
1600 20th Street, N.W.
Washington, D.C. 20009

Re: Docket No. FDA-2011-P-0741

Dear Mr. Nellis and Drs. Almashat, Carome, Wolfe, and Waldum:

This letter responds to your citizen petition (Petition) dated August 23, 2011, and received by the Food and Drug Administration (FDA or the Agency) on October 11, 2011.[1] In your Petition, you request that FDA immediately add boxed warnings and other safety information to the labels for all proton pump inhibitors (PPIs) marketed in the United States, specifically: (1) Nexium (esomeprazole magnesium); (2) Dexilant (dexlansoprazole); (3) Prilosec (omeprazole); (4) Zegerid (omeprazole and sodium bicarbonate); (5) Prevacid (lansoprazole); (6) Protonix (pantoprazole sodium); (7) Aciphex (rabeprazole sodium); (8) Vimovo (esomeprazole magnesium and naproxen); (9) Prilosec OTC (omeprazole); (10) Zegerid OTC (omeprazole and sodium bicarbonate); (11) Prevacid 24HR (lansoprazole); and (12) "all generic counterparts of these products."[2] You also request that FDA require distribution of Medication Guides for these products and ask sponsors to send "Dear Doctor" letters to physicians regarding these matters.

FDA has carefully considered the information submitted in your Petition, the comments submitted to the docket, and other relevant data identified by the Agency. For the reasons

[1] The Petition was postmarked on October 6, 2011.

[2] To the extent new PPI products have been approved subsequent to the filing of your Petition, we interpret your Petition as applying to those products as well. We have also interpreted your Petition as applying to combination products that include a PPI component.

explained below, your Petition is granted in part and denied in part. Your Petition is granted to the extent that it requests the following:

- In the labeling of all PPI products, addition of information regarding the risk of *Clostridium difficile*-associated diarrhea and the risk of drug-drug interactions between PPIs and mycophenolate mofetil and methotrexate;
- In the labeling of certain PPI products (omeprazole and esomeprazole), addition of information regarding the risk of drug-drug interactions with clopidogrel;
- In the labeling of certain prescription PPI products, addition of information regarding the risks of vitamin B12 deficiency and acute interstitial nephritis and certain information regarding treatment length for gastroesophageal reflux disease (GERD); and
- Issuance of Medication Guides for certain prescription PPI products regarding certain safety risks.

With regard to your other requests, your petition is denied.

I. BACKGROUND

A. PPIs

PPIs are inhibitors of the gastric H^+,K^+-ATPase (proton pump) and can diminish the daily production of acid (basal and stimulated) by 80% to 95%. Several PPIs are approved for clinical use in the United States, including: omeprazole and its S-isomer esomeprazole, lansoprazole and its R-isomer dexlansoprazole, rabeprazole, and pantoprazole. Maximal suppression of acid secretion requires several doses of a PPI because it can only inactivate an activated proton pump, and not all pumps are active simultaneously. PPIs are approved for a number of indications, which vary to some extent from product to product. Those indications include treating GERD, treating duodenal ulcer, eradicating *H. pylori*, and reducing non-steroidal anti-inflammatory drug-associated gastric ulcer.

Prilosec (omeprazole), the first PPI product, was approved by FDA on September 14, 1989, as a prescription-only product. Several other PPI products were subsequently approved, including Prevacid (lansoprazole) in 1995, Aciphex (rabeprazole) in 1999, Protonix (pantoprazole) in 2000, Nexium (esomeprazole) in 2001, Dexilant (dexlansoprazole) in 2009, and esomeprazole strontium in 2013. Additionally, FDA has approved several PPI fixed-combination prescription drugs, including Prevpac (lansoprazole, clarithromycin, and amoxicillin) in 1997, Zegerid (omeprazole and sodium bicarbonate) in 2004, Vimovo (esomeprazole and naproxen) in 2010, and Omeclamox-Pak (omeprazole, clarithromycin, and amoxicillin) in 2011. FDA has also approved PPI products for nonprescription (often referred to as over-the-counter or OTC) use: Prilosec OTC (omeprazole) in 2003, Prevacid 24HR (lansoprazole) in 2009, Zegerid OTC (omeprazole and sodium bicarbonate) in 2009, Zegerid OTC powder (omeprazole and sodium bicarbonate) in 2013, and Nexium 24HR (esomeprazole) in 2014.

B. Warnings in Drug Labeling

1. Labeling for Prescription Drug Products

Labeling for prescription drug products is generally governed by 21 CFR 201.50, *et seq.*, with specific requirements for content and format set forth in 21 CFR 201.57. Under section 201.57, drug product labeling must describe clinically significant adverse reactions,[3] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these occur. (21 CFR 201.57(c)(6)(i).) Labeling for prescription drugs must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug. (*Id.*) The "Drug Interactions" section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs. (21 CFR 201.57(c)(8)(i).) Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), FDA is authorized to require holders of approved drug applications to make labeling changes based on new safety information that becomes available after the approval of the drug that FDA believes should be included in the labeling of the drug. (Section 505(o)(4) of the FD&C Act; 21 U.S.C. 355(o)(4).) [4]

A boxed warning is the most serious warning placed in the labeling of a prescription medication. A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and other words that convey the general focus of information in the box. As stated in 21 CFR 201.57(c)(1):

> Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

As explained in FDA's Warnings Guidance, a boxed warning may be required when: [5]

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug;

---

[3] Section 201.57(c)(7) defines "adverse reaction" as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." *See also* FDA Guidance for Industry on *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,* October 2011 (Warnings Guidance), at 3-5. Guidances are available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The Warnings Guidance represents FDA's current thinking on this topic.

[4] As defined in the FD&C Act, "new safety information" is information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved. (Section 505-1(b)(3) of the FD&C Act; 21 U.S.C. § 355-1(b)(3).)

[5] Warnings Guidance at 11.

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.

Infrequently, a boxed warning may be appropriate to highlight information that is especially important to a prescriber.[6] Whether to require a boxed warning is within FDA's discretion, and the Agency exercises this discretion judiciously to preserve the impact and significance of boxed warnings.

2. *Labeling for Nonprescription Drugs*

Labeling for nonprescription products is generally governed by 21 CFR 201.60, *et seq.* Unlike labeling for prescription products, nonprescription labeling is directed at consumers. The format and content requirements for nonprescription product labeling, also known as the "Drug Facts" label, are set forth in 21 CFR 201.66. Although there are no detailed sections in nonprescription labeling comparable to boxed warnings or "Warnings and Precautions" that appear on prescription labeling, labeling for nonprescription products must bear adequate directions for use. (Section 502(f)(1) of the FD&C Act; 21 U.S.C. 352(f)(1).) Additionally, a drug product is misbranded if any word, statement, or other information required by or under authority of the FD&C Act to appear on the label or labeling is not "placed thereon with such conspicuousness . . . and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use." (Section 502(c) of the FD&C Act; 21 U.S.C. 352(c).)

C. Medication Guides

A Medication Guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. The Agency will require a manufacturer of a prescription drug product to distribute a Medication Guide when it determines that the drug product poses a serious and significant public health concern and that patient labeling is necessary to ensure the safe and effective use of the product (21 CFR 208.1(a) and (b).) Under 21 CFR 208.1(c), FDA will require a Medication Guide when it determines that one or more of the following circumstances exist:

- The drug product is one for which patient labeling could help prevent serious adverse effects;

- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product; or

---

[6] *Id.*

- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

D. Dear Healthcare Provider Letters

Dear Healthcare Provider Letters (DHCP Letters, also known as Dear Doctor Letters) are correspondence from the manufacturer or distributor of a drug (or, in some cases, from FDA) intended to alert physicians and other health care providers responsible for patient care about important new or updated information regarding a drug product.[7] DHCP Letters can be issued when it is important to communicate information to health care practitioners involved in prescribing or dispensing a drug or in caring for patients who receive a drug. FDA can require a sponsor to issue a DHCP letter or other communication that is approved as part of a communication plan of a Risk Evaluation and Mitigation Strategy.[8]

II. DISCUSSION

Your Petition asserts that a number of risks are associated with PPI use, including those of rebound acid hypersecretion, bone fracture, bacterial overgrowth, magnesium deficiency, drug-drug interactions, vitamin B12 deficiency, and acute interstitial nephritis. You request that FDA take certain actions to notify consumers and physicians about these risks. Specifically, you request that FDA require boxed warnings for prescription PPIs and "equivalent, prominent warnings" for nonprescription PPIs, as well as certain labeling changes for all PPIs. You also request that all PPIs approved for the treatment of GERD include in the "Indications" section of their labels specific recommendations for treatment length. Finally, you request that FDA require the distribution of Medication Guides to patients taking PPIs and ask that sponsors send "Dear Doctor" letters to healthcare providers. The requests set forth in the Petition are discussed in turn below.

A. Boxed Warnings and Other Requested Labeling Changes

1. Rebound Acid Hypersecretion

Your Petition states that "[t]here is increasing evidence that after using PPIs for a month or more . . . upon withdrawal of PPIs, there is a rebound hypersecretion of acid (RAHS), accompanied by symptoms, as the drug-increased, acid-secreting activity in the stomach is no longer being suppressed by the PPIs." (Petition at 4.) Your Petition reviews editorials and studies addressing RAHS and PPIs and requests that the Agency require a boxed warning addressing this risk. Specifically, you suggest that the Agency require sponsors to include the following language in a

---

[7] See 21 CFR 200.5; FDA Guidance for Industry and FDA Staff on *Dear Health Care Provider Letters: Improving Communication of Important Safety Information*, January 2014, at 1. Guidances are available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The guidance represents FDA's current thinking on this topic.

[8] FDA Draft Guidance on *Drug Safety Information – FDA's Communication to the Public*, March 2012, at 10. Guidances are available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

boxed warning on all prescription PPI labeling and "equivalent, prominent warnings" on nonprescription PPI labeling:

> Recent evidence shows that treatment with proton pump inhibitors (PPIs) for as little as 4 weeks can cause patients to become dependent on the medication, resulting in symptoms coming back after discontinuation of these drugs. This is caused by an increase in the level of acid production in the stomach that occurs after stopping PPIs in what is known as 'rebound acid hypersecretion' or RAHS. Prior to starting PPI therapy for symptoms such as heartburn or indigestion, talk to your doctor about alternative therapies that may be safer. If therapy is needed, use should be limited to periods of 1-2 weeks or on-demand use. If you feel that your heartburn or indigestion symptoms have worsened after finishing a trial of PPI therapy, do not restart the medication before talking to your doctor.

(*Id.* at 27.)

FDA Response

We have carefully reviewed the studies and other information cited in the Petition, as well as additional studies regarding RAHS that we identified in medical literature.[9] Although some of those studies showed that RAHS occurs after the cessation of several weeks of PPI therapy, there is insufficient data to warrant labeling changes for any PPI products at this time as there is no scientifically sound evidence that directly associates the occurrence of RAHS with the occurrence of clinically significant symptoms. This is important because symptoms do not always correlate to the amount of acid in the stomach and may be brought on by other conditions. Therefore, there is not sufficient evidence to establish that RAHS leads to clinically relevant symptoms.

For example, although some studies found a correlation between gastric pH levels following the cessation of PPI therapy and gastrin or chromogranin A levels, which can indicate the presence of cells that stimulate the production of stomach acid,[10] those studies did not examine the correlation between discontinuance of long-term PPI therapy and the symptoms associated with RAHS. Other studies examined this correlation but were lacking in other regards, by failing to include gastric acid measurements, or exclude confounders or bias.[11] Furthermore, studies of actual patient populations found no significant evidence of RAHS accompanied by symptoms.[12]

---

[9] E.g., Lødrup, A.B., Reimer, C., & Bytzer, P. (2013). Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scandinavian journal of gastroenterology*, 48(5), 515-522.

[10] Waldum, HL, Arnestad, JS, Brenna E, et.al. (1996). Marked increase in gastric acid secretory capacity after omeprazole treatment. *Gut*; 39: 649-653; Gillen, D, Wirz, A, McColl, K.E.L. (2004) *Helicobacter pylori* eradication releases prolonged increased acid secretion following omeprazole treatment. *Gastroenterology* 126(4): 980-988.

[11] Niklasson A, Lindstrom L, et al. Dyspeptic symptom development after discontinuation of a PPI: a double-blind placebo-controlled trial. (2010) *Am J Gastroenterol.* 105(7) 1531-1537; Reimer C, Sondergaard B, et al. Proton pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. (2009) *Gastroenterology* 137(1); 80-87 e81.

[12] Lodrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. (2013) *Scandinavian journal of gastroenterology*. 48(5), 515-522.

In sum, we have concluded that there is insufficient evidence of a casual association between the cessation of PPI therapy with the emergence of clinically significant symptoms of RAHS in patients. Therefore, warnings regarding RAHS in the labeling of PPI products, including boxed warnings, are not warranted at this time for either prescription or nonprescription products. With regard to this request, your petition is denied.

2. *Fracture*

Your Petition discusses multiple studies describing an association between PPI therapy and an increased risk for osteoporosis-related fractures of the hip, wrist, and spine. (Petition at 7.) The Petition also describes FDA's May 25, 2010, announcement that it was revising PPI labeling to include safety information about this risk. (*Id.*) Your Petition asserts that, due to the severity of the risk of bone fracture, the Agency should require a boxed warning in the labeling of prescription PPI products and an "equivalent, prominent warning" on nonprescription PPI products. (*Id.* at 7-8.) Specifically, you suggest that the Agency require sponsors of both prescription and nonprescription PPIs to include the following language in prominent warnings on all PPI labeling: "Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine." (*Id.*at 28.)

FDA Response

As you note, FDA assessed whether the risk of bone fracture is associated with the use of PPIs after the safety concern was identified in a December 27, 2006, article, "Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture."[13] Starting in 2007, the Agency undertook an extensive review of this matter, which resulted in a Drug Safety Communication regarding bone fracture risk,[14] as well as the addition of risk information to the "Warnings and Precautions" section in the labels of all prescription PPIs.[15] These labeling changes were approved in 2010. At that time, however, the available data was uncertain regarding the magnitude of the risk of bone fractures associated with PPI use and did not warrant a boxed warning.

---

[13] Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296:2947-53, Dec. 27, 2006.

[14] FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors, available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm (issued May 25, 2010, updated Mar. 23, 2011).

[15] For example, the "Warnings and Precautions" section of the Dexilant label states:

> Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Available at http://general.takedapharm.com/content/file/PI.pdf?applicationCode=9EFB34B3-FB69-4190-A2BE-A90B8CB94E25&fileTypeCode=DEXILANTPI.

In addition to the Agency's prior review, we have carefully reviewed the studies and the other information cited in the Petition. We have also reviewed the relevant medical literature for any epidemiologic studies published subsequent to FDA's prior review. We found no information altering our prior conclusions regarding the risk of bone fracture. Overall, although the studies showed evidence of a causal association between long-term PPI use and fracture risk, we did not find, in our judgment, that those potential reactions warrant a boxed warning at this time, particularly given the lack of data on fatal outcomes related to PPI use and bone fractures and the relatively low magnitude of risk. This risk is already described in detail in the "Warnings and Precautions" section of the prescription labeling where appropriate, and that warning provides the essential scientific information needed for the safe and effective use of the drug. Based on this updated review, your request for a boxed warning on labeling of prescription PPI products is denied.

Regarding your request for a prominent warning regarding the risk of fractures on nonprescription PPI labeling, we note, and you acknowledge, that studies indicate that the risk of fracture is increased in patients who received high-dose or long-term PPI therapy. In contrast to most prescription PPIs, nonprescription PPIs are labeled for use once daily for up to 14 days, a short-term use. According to the labeling for nonprescription PPIs, after that 14-day period, consumers are directed to stop use and consult a doctor.[16] This treatment course may be repeated every 4 months, up to 3 times per year, if necessary. Further, nonprescription PPIs are only available at low doses.

We acknowledge that consumers, either on their own, or based on a physician's recommendation, may take these products for periods of time that exceed the directions on the nonprescription label. We are also aware, however, that consumers are less likely to read a product's labeling if it has little white space and a large amount of text. Additional information about risks associated with long-term, high-dose uses of PPI products may detract from other, more important information on the nonprescription labeling. Thus, because bone fracture is not associated with short-term use of PPIs, no labeling changes regarding this risk are warranted for nonprescription PPIs at this time.[17]

3. *Bacterial Overgrowth*

Your Petition states that the decrease in gastric acidity resulting from PPI use may increase the likelihood for bacteria to thrive in the gastrointestinal (GI) tract. (Petition at 8.) The Petition

---

[16] For example, in the "Warnings" section, the Prilosec OTC label states, "**Stop use and ask a doctor if** . . .

- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months."

In the "Directions" section, the Prilosec OTC label states, "[D]o not use for more than 14 days unless directed by your doctor . . . . **[D]o not take for more than 14 days or more often than every 4 months unless directed by a doctor.**" Available at http://www.prilosecotc.com/LocaleData/enUS/Assets/Documents/prilosec_label_image.pdf .

[17] Certain fixed-combination prescription PPI products are indicated only for *H. pylori* eradication and are indicated for 10 or 14 day use. To the extent the labeling for these products currently includes information about risks associated with long-term use, we are working with the sponsors of those products to have that information removed from the labeling.

discusses two risks that arise from this bacterial overgrowth. First, the Petition discusses the risk of *Clostridium difficile* (*C. difficile*) infections, in which a toxin produced by bacteria is associated with the development of severe diarrhea. (*Id.* at 9.) Second, the Petition discusses the risk of community-acquired pneumonia (CAP), which the Petition explains can develop when infected secretions from the upper GI tract are aspirated. (*Id.*) The Petition also asserts that CAP can develop when PPIs inhibit the function of enzymes that ordinarily prevent bacterial growth in the respiratory tract. (*Id.*)

The Petition reviews various studies and explains that the risks of *C. difficile* infection and CAP are increased as a result of PPI use and requests that FDA require a boxed warning notifying patients and physicians of these risks. (*Id.* at 9-10.) Specifically, you suggest that the Agency require sponsors to include the following language in a boxed warning in all prescription PPI labeling and "equivalent, prominent warnings" on nonprescription PPI labeling: "An increased likelihood of certain serious infections, such as *C. difficile* diarrhea and community-acquired pneumonia, has been associated with long-term PPI use." (*Id.* at 28.)

FDA Response

Changes were made to the labeling of all prescription PPI products in 2012 and a Drug Safety Communication was issued on February 8, 2012, regarding *C. difficile*-associated diarrhea linked with PPI use.[18] These communications were based on a review of the medical literature and adverse event reports on the risk of infection. In the course of that review, the Agency found that the majority of relevant studies (23 of 28 reviewed) demonstrate a statistically significant increased risk of *C. difficile* infection or disease with PPI exposure. In addition, the data indicate that symptoms of *C. difficile* may begin with any duration of use. All prescription PPI labeling has been updated to include warning language related to this risk.[19] Similarly, as a result of this review, all nonprescription PPI labeling was revised to include language in the "Warnings" section of the Drug Facts Label directing consumers to stop use and consult a doctor if they experience diarrhea.

---

[18] FDA Drug Safety Communication: clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs), available at http://www.fda.gov/drugs/drugsafety/ucm290510.htm.

[19] For example, the Prilosec label was changed to include the following:

> **WARNINGS AND PRECAUTIONS**
>
> **5.3 *Clostridium Difficile* Associated Diarrhea**
>
> Published observational studies suggest that PPI therapy like PRILOSEC may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see *Adverse Reactions (6.2)*].
>
> Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
>
> *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with PRILOSEC, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

Available at http://www1.astrazeneca-us.com/pi/Prilosec.pdf.

In light of the discussion above, we agree that safety information regarding the risk of *C. difficile*-associated diarrhea should appear on the labeling of PPI products in light of the studies showing an increased risk of *C. difficile* infection after PPI use. To the extent your Petition requests the addition of this safety information to the labeling of PPI products generally, that request is granted.

While adverse reactions related to *C. difficile* infection are a risk associated with taking these products, in our judgment, the risk of *C. difficile* does not warrant a boxed warning at this time, in part because *C. difficile*-associated diarrhea resolves if treated, and it would be exceptionally rare for the condition to go untreated. This risk is already described in detail in the "Warnings and Precautions" section of the prescription labeling and that discussion provides the essential scientific information needed for the safe and effective use of the drug. Likewise, an "equivalent, prominent warning" in the labeling of nonprescription PPI products is not warranted at this time. With regard to this request, your petition is denied.

Regarding the risk of developing CAP,[20] we have carefully reviewed the studies referenced in the Petition, other relevant medical literature, and reports of adverse events related to CAP and PPI use. The studies reviewed generally found that, while an association between CAP and PPI use may exist, the data showing any causal association between CAP and PPI exposure was lacking.[21] The data showing such a causal association was reported from only a few studies, and the evidence for a dose response from exploratory analysis was weak. In some cases, a potential causal association was shown more often in populations with other risk factors for CAP, such as in elderly patients with comorbidities. Also, it is possible that unmeasured or residual confounders may play a role in explaining the apparent association given the low magnitude of reported risk.[22]

Because the risk and causal association are not well established, no changes to the labeling of PPI products regarding the potential of developing CAP are warranted at this time. Accordingly, we are denying your request that the risk of CAP be reflected in a boxed warning on the labeling of prescription PPIs and "equivalent, prominent warnings" on the labeling of nonprescription PPI products.

---

[20] We note that three PPI products, Prevacid (lansoprazole), Aciphex (rabeprazole), and Zegerid (omeprazole and sodium bicarbonate), mention pneumonia in the Adverse Reactions sections of their labeling. These Adverse Reaction sections include a list of many of the adverse events reported for the drugs, but a reported adverse event by itself does not always indicate reasonable evidence of a causal association between the drug and the adverse event. As noted in FDA's Warnings and Precautions Guidance, and discussed above, "to include an adverse event in [the Warnings and Precautions section], there should be reasonable evidence of a causal association between the drug and the adverse event," which is not the case here. Warnings Guidance at 3.

[21] *E.g.*, Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. *Aliment Pharmacol Ther.* 2010 Jun; 31(11):1165-1177. Epub 2010 Mar 4; Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: A systematic review and meta-analysis of clinical trials. *Can J Gastroenterol.* 2008 Sept; 22(9):761-766.

[22] Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Jackson LA. Use of proton pump inhibitors and H2 blockers and risk of pneumonia in older adults: a population-based case-control study. Pharmacoepidemiol Drug Saf 2010; 19:792–802; Laheij RJ, Sturkenboom MC, Hassing RJ, Deileman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004; 292:1955–1960.

4. Magnesium Deficiency

Your Petition asserts that severe hypomagnesemia is "another serious problem associated with long-term PPI use." (Petition at 10.) The Petition describes FDA's March 2, 2011, Drug Safety Communication regarding the association between long-term PPI use and low magnesium levels.[23] (*Id.* at 11.) Your Petition reviews the available data and asserts that, due to the severity of the risk of magnesium deficiency, the Agency should require a boxed warning on prescription PPI products and an "equivalent, prominent warning" on nonprescription PPI products. (*Id.*) Specifically, you suggest that the Agency require sponsors to include the following language in a boxed warning on all prescription PPI labeling and "equivalent, prominent warnings" on nonprescription PPI labeling:

> Hypomagnesemia (magnesium deficiency), symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, heart arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals should consider monitoring magnesium levels prior to initiation of PPI treatment and periodically while the patient is on the drug.

(*Id.* at 28.)

FDA Response

As your Petition notes, independent of this Petition, FDA has reviewed the medical literature and adverse event reports to assess the risk of hypomagnesemia in patients undergoing prolonged PPI treatment.[24] That review showed that clinically symptomatic hypomagnesemia and hypomagnesemia resulting in serious outcomes were reported in patients with long-term PPI exposure. As a result, in mid-2011, the Agency required sponsors to include information regarding the risk of hypomagnesemia in the labeling of prescription PPIs.[25]

---

[23] FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs), available at http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm (issued Mar. 2, 2011).

[24] *E.g.*, Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *NEJM* (Oct. 26, 2006). 355(17); 1,834-1,836; Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW. Hypomagnesium induced by several proton-pump inhibitors. *Ann Intern Med* (Nov. 17, 2009). 151(10); 755-756.

[25] The following language now appears in the "Warnings and Precautions" sections of prescription PPI products (other than those indicated solely for 10 or 14 day use):

> Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
>
> For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

We have updated our prior review of this matter and continue to agree that safety information regarding the risk of magnesium deficiency associated with the long-term use (three months or greater) of PPIs should appear on the labeling of prescription PPI products (other than those indicated solely for 10 or 14 day use) given the evidence of a causal association between duration of PPI use and hypomagnesemia. While adverse reactions related to hypomagnesemia are a risk associated with long-term use of these products, in our judgment those potential reactions do not warrant a boxed warning at this time, in part because our review indicates that hypomagnesemia is a rarely reported adverse event that resolves if treated.[26] In addition, this risk is already described in detail in the "Warnings and Precautions" section of the prescription labeling and that discussion provides the essential scientific information needed for the safe and effective use of the drug.

Thus, a boxed warning regarding the risk of magnesium deficiency is not warranted at this time, and no changes to the labeling of prescription PPI products indicated for long-term use are necessary. With regard to this request, your Petition is denied.

Regarding your request for a prominent warning regarding the risk of magnesium deficiency on nonprescription PPI labeling, we note that studies indicate that the risk of magnesium deficiency is increased in patients who received long-term PPI therapy. As discussed above, nonprescription PPIs are labeled for use once daily for up to 14 days. According to the labeling for nonprescription PPIs, after that 14-day period, consumers are directed to stop use and consult a doctor. For the reasons noted above, additional information about risks associated with long-term use of PPI products may detract from other, more important information on the nonprescription labeling. Thus, because magnesium deficiency is not associated with less than 14-day use of PPIs, no labeling changes are warranted for the nonprescription PPI products at this time. Accordingly, your petition is also denied with regard to this request.

5. Drug-Drug Interactions

Your Petition states that PPIs have a wide array of potential interactions with metabolic systems and other drugs, many caused by the increased gastric pH induced by PPIs. (Petition at 11.) In particular, the Petition asserts that the anti-coagulant effect of clopidogrel, a drug indicated for the prevention of heart attacks and other cardiovascular events, may be significantly diminished by concomitant use of PPIs. (*Id.* at 12.) The Petition notes that FDA has required a warning regarding interactions between clopidogrel and omeprazole on clopidogrel's labeling. (*Id.* at 13.) The Petition also asserts that all PPI products, not just omeprazole, might interact with clopidogrel, and patients should be alerted to that possibility. (*Id.*) Your Petition requests that FDA require that the "Highlights" section of labeling for all PPI products mention the potential for an interaction between the PPI product and clopidogrel. (*Id.* at 29.)

The Petition additionally describes potential interactions between PPIs and drugs that may be impacted by the decreased acid secretion induced by PPIs. (*Id.* at 14.) Specifically, you describe potential interactions between PPIs and mycophenolate mofetil, an immunosuppressant given to organ transplant recipients, and methotrexate, a drug used in the treatment of cancer. (*Id.*) Your

[26] Warnings Guidance at 11.

Petition requests that FDA require that the labeling for PPI products include information about these potential interactions. (*Id.* at 29.)

FDA Response

Regarding clopidogrel, several pharmacokinetic and pharmacodynamic studies have been submitted to the Agency by PPI sponsors, as well as the sponsor of clopidogrel, regarding the extent of the interaction between the two products.[27] We have reviewed these studies and the studies referenced in the Petition, and determined that they do not show a class-wide drug-drug interaction between clopidogrel and PPIs. Rather, the studies have shown that only omeprazole and esomeprazole products (including Prilosec, Zegerid, and Nexium, and the drugs approved under abbreviated new drug applications that reference them) strongly inhibit the conversion of clopidogrel to its active moiety, potentially lessening its clinical effect. The lesser effect seen in other PPIs, which do not have a clinically significant effect on exposure to the active metabolite of clopidogrel, does not warrant a warning at this time.

Independent of this Petition, the Agency has required that the labeling for both prescription and nonprescription omeprazole and esomeprazole products contain a warning regarding the potential drug interaction.[28] To the extent your Petition requests warnings regarding interactions between clopidogrel and omeprazole and esomeprazole products, that request is granted. We have found insufficient evidence, however, to indicate that a broader warning of potential interactions with all PPIs is warranted at this time. Thus, no labeling changes regarding this matter are required for the other PPI products, and your request that PPI products other than omeprazole and esomeprazole carry a warning regarding interactions with clopidogrel is denied.

Regarding mycophenolate mofetil, we have reviewed the studies referenced in the Petition and additional studies evaluating interactions between PPI drugs and mycophenolate mofetil.[29] Although the results of those studies varied to some extent, several demonstrated a clinically significant drug-drug interaction between mycophenolate mofetil and certain PPIs, which we

---

[27] These studies are described in the relevant product labels. For example, see the "Pharmacokinetics" section of the Prilosec label, available at http://www1.astrazeneca-us.com/pi/Prilosec.pdf.

[28] For example, the Prilosec label states the following:

> **5.4 Interaction with Clopidogrel**
>
> Avoid concomitant use of PRILOSEC with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as omeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using PRILOSEC, consider alternative anti-platelet therapy [*see Drug Interactions (7.3) and Pharmacokinetics (12.3)*].

Available at http://www1.astrazeneca-us.com/pi/Prilosec.pdf.

[29] *E.g.*, The role of proton pump inhibitors on early mycophenolic acid exposure in kidney transplantation: evidence from the CLEAR study. Kiberd BA, Wrobel M, Danavino R, Keown P, Gourishankar S. *Ther Drug Monit.* 2011 Feb; 33(1):120-3; Proton pump inhibitors reduce mycophenolate exposure in heart transplant recipients – a prospective case controlled study. Kofler S, Shvets N, Bigdeli AK, König MA, Kaczmarek P, Deutsch MA, Vogeser M, Steinbeck G, Reichart B, Kaczmarek I. *Amer J. Transplant.* 2009 Jul; 9(7):1650-6. Epub 2009 Jun 10.

believe could indicate the existence of a class-wide interaction between PPIs and mycophenolate mofetil.[30] As a result of this interaction, PPIs can result in altered absorption of immediate-release mycophenolate mofetil formulations, possibly due to gastric acid suppression leading to incomplete dissolution of the drug. Thus, we agree that the potential drug-drug interaction between mycophenolate mofetil and PPI products should be reflected in the labeling of all PPI products. With respect to this request, your Petition is granted. We are working with application holders for the prescription and nonprescription PPI products to add this information to the products' labeling.

Regarding methotrexate, independent of your Petition, we reviewed studies[31] and adverse event reports for evidence of an interaction with PPI products. We have updated that prior review and have also examined the studies referenced in the Petition. The materials reviewed demonstrate evidence of a possible drug-drug interaction between the two and that PPIs may be linked to decreased elimination of methotrexate, leading to methotrexate toxicity. Specifically, studies have identified multiple mechanisms through which PPIs interact with methotrexate. For example, studies have indicated that H^+/K^+-ATPase inhibitors (such as PPIs) inhibit hydrogen ion elimination and block the active tubular secretion of methotrexate, resulting in an increase in the elimination half-life of methotrexate.[32] Additionally, our review of adverse event reports identified cases of renal toxicity, hematologic events, mucositis, and myalgia resulting from decreased elimination of methotrexate, possibly leading to accumulation of methotrexate and its metabolite due to an interaction with a PPI. In light of this review of literature and adverse event reports, we agree that the potential drug-drug interaction between methotrexate and PPI drugs poses a safety risk and should be reflected in the labeling of all PPI products. With respect to this request, your petition is granted. This information has been added to the labeling for prescription PPI products,[33] and we are working with application holders for the nonprescription PPI products to add this information to the nonprescription labeling.

---

[30] Based on the gastric acid suppression effects of PPIs and drug interactions caused by gastric acid reducing agents, we consider that the observed interaction of immediate release mycophenolate mofetil with that of PPIs could be class-wide. *E.g.*, pH-Dependent Drug–Drug Interactions for Weak Base Drugs: Potential Implications for New Drug Development. L Zhang, F Wu, SC Lee, H Zhao, L Zhang. Clin Pharmacol Ther. 2014 Aug;96(2):266-77. Epub 2014 Apr 14; Rohss K, Lind T, Wilder-Smith C. Eur J Clin Pharmacol. 2004; 60:531–539;

[31] *E.g.*, Bauters TGM, Verlooy J, Robays H, et al. Interaction between methotrexate and omeprazole in an adolescent with leukemia: A case report. *Pharm World Sci* 2008; 30: 316-18; Troger U. Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. *BMJ* 2002; 324: 1497.

[32] *E.g.*, Reuben MA, Starr FL, Birmingham S, et al. Characterization of a renal H,K ATPase alpha subunit mRNA found to be identical with gastric H,K ATPase mRNA. Gastroenterology 1993; 104 (suppl): 177.

[33] For example, the Vimovo label states the following:

> **5.23 Concomitant use of VIMOVO with Methotrexate**
>
> Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [see *Drug Interactions (7.8)*].

* * * *

6. *Vitamin B12 Deficiency*

Your Petition states that PPI use may lead to deficiencies of substances dependent on gastric acid for absorption and metabolism, including vitamin B12. (Petition at 15.) The Petition requests that the information currently available be included in the labeling for PPI products, noting that FDA has deemed the evidence sufficient to place a warning of the potential for vitamin B12 deficiency on the Protonix label. (*Id.* at 29.)

FDA Response

We have reviewed the studies and the other information cited in the Petition, as well as additional studies regarding vitamin B12 deficiency that we identified in the medical literature.[34] Based on this review, we agree that there may be a causal association between duration of PPI use and malabsorption of cyanocobalamin resulting in vitamin B12 deficiency, and safety information regarding this risk should appear on the labeling of all prescription PPI products indicated for long-term use. In this respect, your petition is granted. We are working with application holders for prescription PPI products, other than those indicated for 10 or 14 day use, to have information on the risk of vitamin B12 deficiency added to their labeling if it is not already included.[35]

Regarding nonprescription PPI labeling, we note that studies indicate that the risk of deficiency, if any, is associated with long-term PPI therapy (e.g., in excess of three years). As discussed above, nonprescription PPIs are labeled for use once daily for up to 14 days. According to the labeling for nonprescription PPIs, after that 14-day period, consumers are directed to stop use and consult a doctor. For the reasons noted above, additional information about risks associated with long-term use of PPI products may detract from other, more important information on the nonprescription labeling. Thus, because vitamin B12 deficiency is not associated with short-term use of PPIs, no labeling changes are warranted for the nonprescription PPI products at this time.

> **7.8 Methotrexate**
>
> NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Available at http://www.vimovo.com/pi/.

[34] *E.g.*, Baluck, RJ, Ruscin JM. (2004) A case-control study on adverse effects:H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. (2004) *J Clin Epidemiol*: 57(4)422-428.; Sheen E. and G. Triadafiopoulos. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci.* 2011; 56:931-950; Lam JR, Schneider JL, Zhao, Wei, Corley D.A. (2013) Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B12 Deficiency. *JAMA*. 310(22):2435-2442. Doi.10.1001/jama.2-13.280490.

[35] Because the risk is not relevant for prescription products that are indicated for use of only 10 or 14 days, such as Prevpac, this risk will not be added to the labeling for those products.

7. *Acute Interstitial Nephritis*

Your Petition describes a 2007 study that examined published case reports of acute interstitial nephritis (AIN) associated with PPI therapy. (Petition at 15.) The Petition states "the potential for severe sequelae following AIN possibly induced by PPI use necessitates proper alerting of patients and providers to this serious adverse effect. More evidence is needed to firmly establish a cause-and-effect relationship, but until further studies are undertaken, the existing evidence should be placed in the label." (*Id.* at 15-16.)

FDA Response

Independent of this Petition, the Agency reviewed studies[36] and adverse event reports to determine whether PPI use leads to an increased risk of AIN, and that prior review was updated in response to this Petition. The materials reviewed, including the materials referenced in the Petition, demonstrate evidence of a possible increased risk of AIN associated with PPI use. In the course of our review, we found that it is thought to be an idiosyncratic, hypersensitivity reaction. AIN is most often induced by allergic reactions to drug products, including to PPIs, and the symptoms, if exhibited, can include fever, rash, nausea, vomiting and malaise.[37] Drug-associated AIN can lead to renal failure if left untreated; however, it is frequently reversible if treated early and adequately. The development of AIN with PPI use appears to be rarely reported. Estimates of the incidence of PPI-associated AIN in the general population are not available; however, they have been estimated in New Zealand as 1 in 12,500 patient years.[38] Although nearly all prescription PPI products mention the risk of AIN in their labeling, those warnings do not currently appear class-wide and vary to some extent between products. Because we agree that the prescription PPI labeling should be consistent with regard to this risk and because there is reasonable evidence of a causal association, your Petition is granted with respect to this request, and we are working with sponsors of prescription PPI products to make this information consistent in product labeling throughout the class.

Nonprescription PPI labeling, however, presents somewhat different considerations given that the labeling is directed at consumers. The symptoms of AIN (e.g., rash, fever, fatigue, nausea, vomiting, and anorexia) are indistinguishable from relatively minor viral episodes that would not otherwise require discontinuation of nonprescription PPI products, and thus, inclusion of these symptoms on the labeling of nonprescription products may confuse consumers rather than facilitating their safe use of the product. We expect that consumers would consult a healthcare provider if symptoms of AIN were persistent. The prescription labeling changes for PPIs, which are written for healthcare providers, will appropriately inform healthcare providers of the possibility of interstitial nephritis. Additionally, as noted above, AIN appears to be typically linked with an allergic reaction to PPIs. All nonprescription PPI labeling already includes a

---

[36] *E.g.*, Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther* 2007; 26(4): 545-53; Ni N, Moeckel GW, Kumar C. Late-onset omeprazole-associated acute interstitial nephritis. *J Am Geriatric Soc.* 2010 Dec; 58(12): 2443-2444.

[37] *E.g.*, Kodner C, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. *Am Fam Physician.* 2003; 67(12): 2527-34.

[38] *See* Simpson IJ, Marshall MR, Pilmore H, Manley P, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology 2006; 11: 381-5.

warning not to take the product if allergic to the respective ingredients. In our judgment, the current labeling is sufficient. Thus, your request that information regarding AIN be included in nonprescription PPI labeling is denied.

8. GERD-Treatment Length

Your Petition states that some PPI products do not include sufficient information regarding recommendations for length of treatment for GERD in their labeling. (Petition at 28-29.) Specifically, you note that the Aciphex labeling includes information regarding length of treatment for GERD in its "Dosages and Administration" section but not in the "Indications and Usage" section. Additionally, you raise a question as to whether Protonix is indicated for non-erosive GERD, and assert that, if so, its labeling does not include information about treatment length for that indication. (*Id.*) You request that the labeling for these two PPI products include information regarding the indicated length of treatment of GERD in the appropriate sections. (*Id.* at 29.)

FDA Response

The "Indications and Usage" section is described in 21 CFR 201.57(c)(2)(i)(D), which sets forth a list of information that must be included in certain circumstances. That list includes the following:

> If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information [must be included in the "Indications and Usage" section,] with reference to the more detailed information in the "Dosage and Administration" section.

In light of the requirements set forth in 21 CFR 201.57(c)(2)(i)(D), we agree that prescription PPI labeling should include information regarding treatment length for GERD in both the "Indications and Usage" and "Dosage and Administration" sections for PPIs indicated to treat GERD. We are working with sponsors to include information regarding treatment length for GERD in both the "Indications and Usage" and Dosage and Administration" sections of prescription PPI labeling for PPIs indicated to treat GERD. With regard to this request, your Petition is granted.

Regarding Protonix, that product is labeled for the maintenance of healing of and symptomatic relief for erosive esophagitis, a type of GERD, and information about treatment length for that condition appears in the product's labeling in both the "Indications and Usage" and "Dosage and Administration" sections. Protonix is not indicated for non-erosive GERD, however. Thus, no changes to its labeling are necessary, and your request to that effect is denied.

B. Medication Guides

Your Petition requests that FDA require that patients prescribed[39] PPIs be provided with a Medication Guide to inform them of the risks associated with use of the products. (Petition at 28.) In addition to informing patients of the risks described elsewhere in the Petition, you request that the Medication Guide include information related to "step-up therapy, including lifestyle changes, antacids, and H2As [H2-receptor antagonists]." (*Id.*)

FDA Response

As stated above, the Agency requires distribution of a Medication Guide when the drug product poses a serious and significant public health concern, and patient labeling is necessary to ensure the safe and effective use of the product (21 CFR 208.1(a) and (b)). Under 21 CFR 208.1(c), FDA will require a Medication Guide in certain circumstances, including where patient labeling could help prevent serious adverse effects and where awareness of serious risks could impact patients' decisions to use a drug product. Both of those circumstances are present here,[40] considering the serious risks that will be described in the labeling, as discussed above. The information to be addressed in a Medication Guide — for example, information on the risks related to long durations of use, such as Vitamin B12 deficiency— could help prevent serious adverse effects and could impact patients' decisions to use the products.

Thus, regarding certain prescription PPI products, your request that the Agency require that sponsors distribute a Medication Guide regarding safety risks as described in the labeling is granted. FDA believes, however, that given the Drug Safety Communications issued regarding these products, the labeling changes described above, and the issuance of the Medication Guide as described, further information regarding "step-up therapy, lifestyle changes, antacids, and H2As," is not necessary for the safe and effective use of prescription PPI products. Accordingly, your request that FDA require that information be included in a Medication Guide is denied.

C. DHCP Letters

Your Petition requests that FDA ask sponsors of prescription PPI products to send a Dear Doctor Letter to physicians and other health care providers notifying them of the safety concerns with PPIs set forth in the Petition, as well as "detailed information on the efficacy of step-up therapy, including lifestyle changes, antacids, and H2As." (Petition at 28-29.) You also request that the letter include "guidelines on appropriate prescribing of PPIs in the inpatient setting, including a reminder that PPI therapy should be discontinued on discharge if not indicated." (*Id.* at 29.)

---

[39] On page 1 of the Petition, you request that Medication Guides be required for "all of these drugs." However, on pages 3 and 28 of the Petition, you request that Medication Guides be required for all *prescription* PPIs. Because 21 CFR part 208 does not apply to nonprescription products, we interpret your request as applying only to prescription PPI products. To the extent you are requesting Medication Guides for nonprescription products, that request is denied.

[40] We note, however, that the fixed-combination prescription drugs indicated for use for only 10 or 14 days present different considerations. FDA has determined that Medication Guides are not necessary for patients' safe and effective use of these products, and Medication Guides will not be distributed for these products at this time.

FDA Response

The Agency has posted Drug Safety Communications with information about several of the recent labeling changes, as referenced above.[41] FDA believes that these Drug Safety Communications, in conjunction with the labeling changes described above, are sufficient to address your concerns. We also note that the current prescription PPI prescribing information notes in several places that "[p]atients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated," as does the Medication Guide. Further, as described above, guidelines for physicians regarding appropriate prescribing of PPIs would not generally be included in a DHCP Letter. Thus, we deny your request to ask sponsors to issue a Dear Doctor Letter.

D. Information About PPIs Unrelated to Requested Actions

In addition to the requested actions addressed above, the Petition includes a discussion of various issues related to PPI use. For example, the Petition states that there may be a potential link between PPI use and gastric cancer. (Petition at 16-18.) It also describes prescribing practices related to PPIs at length, including recommendations to mitigate overuse of the products. (*Id.* at 18-24.)

Although you have not requested that FDA take action related to these matters, we have reviewed and considered the information presented in the Petition. Regarding the potential risk of cancer linked to PPI use, as you noted in the Petition, there is insufficient evidence to show such a link. We will continue to monitor this matter, and if data becomes available establishing causal association between PPIs and gastric cancer, we will consider whether a labeling change or other regulatory actions are warranted at that time. Regarding recommendations to mitigate over-prescribing of PPIs, we believe that the labeling changes described above, the availability of the Medication Guide, and the Drug Safety Communications described throughout the Petition are sufficient to address your concerns regarding safe and effective use of PPIs at this time.

III. CONCLUSION

For the reasons described above, the Petition is granted in part and denied in part. Your Petition is granted to the extent that it requests the following:

- In the labeling of all PPI products, addition of information regarding the risk of *C. difficile*-associated diarrhea and the risk of drug-drug interactions between PPIs and certain products (mycophenolate mofetil and methotrexate);

[41] FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors, available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm (issued on May 25, 2010 and updated on Mar. 23, 2011); FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs), available at http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm (issued on Mar. 2, 2011); FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs), available at http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm (issued on Feb. 8, 2012).

- In the labeling of certain PPI products (omeprazole and esomeprazole), addition of information regarding the risk of drug-drug interactions with clopidogrel;

- In the labeling of certain prescription PPI products, addition of information regarding the risks of vitamin B12 deficiency and acute interstitial nephritis and certain information regarding treatment length for GERD; and

- Issuance of Medication Guides for certain prescription PPI products regarding certain safety risks.

Your petition is denied to the extent that it requests the following:

- The addition of boxed warnings to labeling for prescription products and "equivalent, prominent warnings" for nonprescription labeling regarding the risk of RAHS, bone fracture, *C. difficile* infection, community-acquired pneumonia, and magnesium deficiency related to PPI use;

- For both prescription and nonprescription products, other than omeprazole and esomeprazole, addition of warnings in the labeling regarding drug-drug interactions with clopidogrel;

- For prescription products indicated for 10 or 14-day use and nonprescription products, addition of statements in the labeling regarding the risk of vitamin B12 deficiency;

- For nonprescription products, addition of statements in the labeling regarding the risk of AIN;

- Addition of information regarding treatment length for GERD in the Protonix labeling; and

- That FDA ask sponsors to issue DHCP Letters discussing safety issues related to PPIs.

FDA will continue to monitor and review available safety information related to PPIs and take any further action as appropriate.

Sincerely,

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