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August 23, 2011

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg:

Public Citizen, a research-based advocacy group representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352, and 21 C.F.R. §§ 10.30 and 201.56, **to immediately add black box warnings and other safety information concerning several severe risks** to the product labels of all proton pump inhibitors (PPIs) presently on the market in the United States (U.S.) (Nexium, Dexilant, Prilosec, Zegerid, Prevacid, Protonix, Aciphex, Vimovo, Prilosec OTC, Zegerid OTC, Prevacid 24-Hr, and all generic counterparts). In addition, the serious nature of so many of these adverse reactions also mandates the requirement for FDA-approved patient Medication Guides, none of which exist now, for all of these drugs.

For the past 20 years, PPIs have become increasingly popular, partly because of their ability to relieve acid-related symptoms, and are now one of the most widely used classes of drugs in the U.S., with 119 million prescriptions dispensed in 2009.[1] Some of the approved uses for prescription PPIs are treatment of gastroesophageal reflux disease (GERD), gastric ulcers and erosive esophagitis, and upper-gastrointestinal (GI) bleeding prophylaxis with nonsteroidal anti-inflammatory drug (NSAID) use. However, PPIs are often prescribed outside of their approved uses, for purposes such as stress ulcer prophylaxis in noncritical hospitalized patients[2] and long-term treatment of conditions such as GERD past the approved time frame.[3] It has been estimated that up to two-thirds of all people on PPIs do not have a verified indication for the drug.[4] In addition, even in many people with presumed GERD on PPI therapy, less intense acid-suppressive therapies are effective in relieving symptoms,[5] and in other cases, the medical problem does not even involve acid reflux.[6]

Compounding the problem of massive inappropriate use, recent evidence has documented several serious new safety problems with long-term PPI use. For some of these risks, current FDA-approved PPI labels do not mention the adverse effect at all, including the potential for developing dependence on the drugs, which results in rebound hypersecretion of stomach acid

and recurrence of symptoms after stopping PPI use. For other risks, even if mentioned, the label does not adequately explain or emphasize them. There are currently no black box warnings in the label of any PPI.

This petition outlines the current state of evidence of the risks involved with short- and long-term use of PPIs and asks that the FDA make prescribers and consumers aware of these risks through the following labeling changes.

We petition the FDA to require the inclusion of black box warnings identifying the following risks for all prescription PPIs (and equivalent, prominent warnings for over-the-counter [OTC] PPIs):

- *Rebound acid hypersecretion risk*: This is a form of dependence on PPIs that can be seen after as little as four weeks of use. Patients and providers need to be made aware of the possibility of dependence on PPIs and alerted not to take or prescribe PPIs beyond indicated uses and time frames. (Currently, this serious adverse effect is entirely missing from all PPI labels.)

- *Fracture risk*: Long-term and multiple daily-dose PPI therapy has been associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Due to its potential severity, this adverse effect also needs to be placed in a black box warning on all prescription PPIs and in an equivalent, prominent warning on OTC PPIs, in addition to its current place in the "Highlights" section of the prescription label.

- *Infection risk*: An increased likelihood of serious infections, such as *C. difficile*-caused diarrhea and community-acquired pneumonia has been seen with both short- and long-term PPI use. Pneumonia risk is currently entirely missing from all PPI labels, while information on *C. difficile* infections — although attributed to *all* PPIs in the label — is only present on three (Nexium, Prilosec, and Vimovo). Given the potentially fatal nature of these two conditions, particularly in elderly and other vulnerable populations, information about both conditions needs to be placed in a black box warning.

- *Magnesium deficiency risk*: Information on the risk of severe magnesium deficiency with long-term PPI use needs to be placed as a black box warning due to its potentially fatal course. This adverse effect is particularly concerning, given the possibility of concomitant use with many medications that prolong the QTc interval on an electrocardiogram, which in the presence of low magnesium would increase the likelihood of life-threatening heart rhythm disruptions, or arrhythmias. (The FDA has recently placed this information in the "Highlights" section of all prescription — but not OTC — PPI labels but has decided not to insert a black box warning.)

In addition to the black box warnings, we petition the FDA to require the following label changes for all PPIs:

- *Drug-drug interactions*: Taking PPIs may reduce the effectiveness of the heart-protective drug clopidogrel, leading to an increased rate of serious cardiovascular adverse events,

such as a heart attack. Some PPIs (e.g., omeprazole) have been shown to have a higher likelihood of interaction than others (e.g., pantoprazole); however, several PPIs have been implicated. Although a version of this warning is already on the omeprazole label, mention should be made in the "Highlights" section **of all PPIs** that the potential for a classwide interaction cannot be ruled out at this time.

Appropriate risk information on a potential interaction with at least two other medications used to treat serious conditions — methotrexate and mycophenolate mofetil — needs to be listed in the label.

- *Vitamin B12 deficiency*: The available evidence on the potential for vitamin B12 deficiency with long-term PPI use needs to be placed in the appropriate section of the label. Although the label states that this can occur with "any acid-suppressing medication," the warning has only been placed on the label for one PPI (Dexilant).

- *Acute interstitial nephritis*: Information regarding the potential for drug-induced acute interstitial nephritis, seen in at least 60 case reports, should be included in the appropriate section. There is currently no detailed risk information on any PPI for this adverse effect.

- *GERD-treatment length consistency*: All PPIs approved for the treatment of GERD should have specific recommendations for length of treatment in the "Indications" section of the label.

Finally, we urge the FDA to:

- Require the distribution of FDA-approved Medication Guides for patients — containing these adverse effect warnings and describing alternatives to PPI use for all patients — to be dispensed when prescriptions are filled.

- Ask the sponsors of all PPI medications to send a "Dear Doctor" letter alerting physicians to these adverse effects and to include information on appropriate prescribing of PPIs in inpatient and outpatient settings.

It is critical that these potentially dangerous adverse effects be made known to the public since they pose a serious threat to the general well-being of PPI users. The added risk information, and provider and patient awareness of appropriate PPI use, should help to limit the massive amount of needless overprescribing.

I. STATEMENT OF GROUNDS

A. Basic physiology in the stomach: gastrin, gastric acid release, and inhibition[7]

The production and release of gastric acid into the stomach is a crucial component of digestive function in humans, responsible for breaking down many foods that enter the stomach, thus making absorption possible further down the GI tract. Parietal cells carry out the final step in the physiologic pathway responsible for acid secretion in the stomach. Two hormones, gastrin and

somatostatin, are primarily responsible for the regulation of acid secretion. Gastrin is a hormone stored by G cells in the stomach that is responsible for initiating gastric acid release by acting on enterochromaffin-like (ECL) cells and, to a lesser extent, parietal cells. In the predominant pathway, gastrin stimulates histamine release from ECL cells. This histamine then binds to parietal cell histamine-2 (H2) receptors, causing the parietal cells to secrete gastric acid. Somatostatin, a hormone released by oxyntic D cells in the stomach, is the main inhibitor of histamine release from ECL cells and also inhibits the release of gastrin from G cells.

Negative feedback loops, primarily involving the opposing actions of gastrin and somatostatin, keep the level of acidity in the stomach within a certain range. When gastric acidity increases (pH decrease), somatostatin levels rise to inhibit gastrin secretion and ECL cell histamine release, thus making the stomach more alkaline. Conversely, when stomach acidity decreases (pH increase), somatostatin levels decrease, causing gastrin levels to rise, making the stomach more acidic. Thus, acid release in the stomach relies on a delicate hormonal balance involving gastrin and somatostatin, an interaction that is described as "… a cornerstone in the physiology of meal-stimulated acid secretion."[8] Any disruption to this balance, as clearly seen with PPIs, may potentially lead to long-term complications.

B. Hypergastrinemia and symptomatic rebound acid hypersecretion: a form of dependence on PPIs

There is increasing evidence that after using PPIs for a month or more — whether they are being used for approved indications or by otherwise healthy people — upon withdrawal of PPIs, there is a rebound hypersecretion of acid, accompanied by symptoms, as the drug-increased, acid-secreting activity in the stomach is no longer being suppressed by the PPIs. This creates a long-term dependence on these drugs. Given the millions of people on PPIs for mild and often vague symptoms, a large number of people are being exposed to a dependence-inducing substance without their knowledge. A recent editorial about PPI rebound acid hypersecretion (RAHS) stated: **"The current finding that these drugs induce symptoms means that such liberal [mis-] prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment."[9]**

The RAHS phenomenon is thought to be caused by the indirect PPI-induced effects on gastrin.[10] Treatment with acid-suppressive agents significantly decreases the amount of acid in the stomach. As a result, gastrin is subsequently produced at a much higher rate in order to compensate for the acid deficiency in the stomach. These high levels of gastrin in turn stimulate the growth and proliferation of ECL cells, which cannot stimulate acid production because of inhibition of this function in parietal cells by PPIs. After the discontinuation of the acid-suppressant, these ECL cells, now increased in number as a result of PPI therapy, appear to stimulate parietal cells to release a greater amount of acid than prior to therapy.

Previously, it has been shown that this phenomenon occurs with another class of acid-suppressing agents, H2-receptor antagonists (H2As).[11,12,13] However, two studies, including one randomized controlled trial, of patients on H2A therapy showed much shorter durations of RAHS (median of 2 days in one, and less than 10 days in another) than found in studies of

RAHS with PPI discontinuation,[14,15] while another study showed only a nocturnal RAHS effect after H2A therapy, with daytime acid output unaffected.[16] This milder RAHS effect seen after H2A therapy is likely due to the fact that H2As are less potent inhibitors of gastric acid release than PPIs, and that tolerance to H2As, but not to PPIs, develops in many patients, further diminishing the acid-suppressing ability of H2As.[17]

The first study demonstrating RAHS after discontinuation of PPI therapy was by Waldum et al in 1996. The authors found that 14 days after discontinuation of a three-month course of omeprazole in patients with reflux esophagitis, the median stimulated gastric acid secretory capacity was increased by 50% over the pretreatment baseline.[18] Other reseachers later found that this increased acid-secreting capacity persists for two months after cessation of PPIs.[19]

However, the early studies assessing RAHS in subjects on acid-suppressing therapy were inconsistent, lacking uniformity in their design and their results. One common trend in these studies, however, was that the therapies with a shorter duration often failed to show the RAHS phenomenon,[20,21,22,23] and conversely, some of the trials with longer therapies were able to show RAHS.[24,25,26] Thus, these early studies demonstrated that duration of therapy has a clear association with the development of RAHS — a key finding suggesting causality.

Potential for PPI dependence in healthy volunteers: RAHS not just a recurrence of previous symptoms

The resumption of symptoms after discontinuation of PPI therapy might simply indicate that the pretreatment symptoms had returned. However, two recent randomized, controlled trials have shown that even healthy volunteers have the potential for long-term dependence on these drugs. In 2009, Reimer et al demonstrated that symptomatic RAHS could occur even in previously healthy people.[27] In a randomized, double-blind, placebo-controlled trial of 120 healthy volunteers, subjects were randomized to either 12 weeks of placebo or eight weeks of once-daily esomeprazole (40 milligrams [mg]), followed by four weeks of a placebo. In the weeks after stopping treatment, almost three times as many subjects who had received esomeprazole for eight weeks experienced relevant acid-related symptoms compared to those who had received a placebo. In addition, almost five times as many subjects who had received esomeprazole needed "escape medications" to treat these symptoms as those in the placebo group. Gastrin levels for the esomeprazole group significantly increased after treatment started and were found to have a strong correlation with acid-related symptoms in weeks eight and 10 for this group. Chromogranin A (CgA) levels, reflective of ECL cell hyperplasia, rose for the esomeprazole group shortly after therapy began and remained elevated compared with baseline through the end of the study at week 12.

The results of this study suggest that RAHS is not a recurrence of previous symptoms but an effect of the PPI itself creating the symptoms it was originally intended to treat. The authors concluded, "These results justify the speculation that PPI dependency could be one of the explanations for the rapidly and continuously increasing use of PPIs."[28]

The trial is in agreement with earlier studies, mentioned above, that attempted to assess the effects of long-term PPI use. It must be noted that the eight-week period it took to develop

RAHS is within the FDA-approved time period for GERD treatment with most PPIs. This eight-week time frame is also consistent with the likelihood that ECL cell hyperplasia is triggering RAHS. Waldum et al, the original authors documenting RAHS with PPI therapy cessation, elaborated on the ECL cell hyperplasia mechanism, mentioning that the duration of RAHS (two to three months in some cases) correlates well with the relatively short life span of the ECL cell.[29] ECL cell hyperplasia and increased ECL cell volume have been confirmed in patients treated with omeprazole for periods of up to four or five years.[30] Other studies have shown elevated levels of mucosal histamine (a product of ECL cells) after PPI therapy.[31,32] These results all strengthen the likelihood that gastrin-induced ECL hyperplasia resulting from PPI therapy is the cause of RAHS.

The majority of earlier studies ignored whether their subjects were infected with *Helicobacter pylori*. This is important because other studies have demonstrated that there are differences in the acid-secreting abilities of *H. pylori*-positive and -negative individuals, as *H. pylori*-positive individuals may be less susceptible to the RAHS phenomenon than *H. pylori*-negative subjects.[33] Indeed, one limitation of the Reimer et al study was that a higher proportion of placebo subjects were positive for *H. pylori* (13% vs. 2% in the treatment group), possibly leading to a masking of symptoms in this group. However, as there was no difference in symptoms at baseline between the two groups, this difference likely did not affect the posttreatment outcome.

A more recent randomized, double-blind, placebo-controlled study by Niklasson et al addressed this potential confounder, while confirming the presence of RAHS in otherwise healthy subjects exposed to PPIs.[34] The trial differed from the Reimer et al study in that it used only *H. pylori*-negative individuals in a briefer, four-week, treatment period. The results, however, were similar to that study. The PPI group had significantly higher rates of dyspeptic symptoms in the first (44% vs. 9% in placebo group) and second (24% vs. 0% in placebo group) week after withdrawal. CgA and gastrin levels were significantly higher in the PPI-treated group than in the placebo group by the last week of treatment. This study demonstrated that significant rebound symptoms can develop with treatment periods as short as four weeks.

The theory of PPI dependence is further supported by empirical evidence from studies showing how difficult it is for patients initiated on PPIs to stop using their medication. In a randomized, double-blind trial in which subjects attempted to discontinue or taper long-term use, only 27% of patients were able to successfully remain off PPI therapy one year after the initial attempt to discontinue therapy.[35] All other patients had recurring symptoms or needed to resume PPI therapy. Patients with higher baseline serum gastrin levels and patients with GERD were more prone to resume PPI therapy than were others. As participants had been previously made aware that it would be a PPI withdrawal trial, it is unlikely that those with more severe symptoms would have offered to participate. Thus, this study may have underestimated the difficulty of discontinuing PPI treatment.

An editorial by McColl and Gillen accompanying the Reimer et al. study expressed concern over the risk posed by PPIs in causing the symptoms they purport to treat.[36] It is clear that many people are initiating PPI therapy and staying on it for months, or even years, beyond its indicated time frame.[37] A clear reason for this possible dependence stems from the development of RAHS. As McColl and Gillen stated in their editorial, "Now that rebound acid secretion has been

demonstrated to induce symptoms, we are probably obliged to inform them about rebound acid hypersecretion and its potential effects."[38] A black box warning and a patient Medication Guide are therefore necessary to warn about this well-documented danger of PPI dependence and the hazards therein.

C. Increased risk of fractures

On May 25, 2010, the FDA announced that it was requiring a change in prescription and over-the-counter labeling of PPIs to include safety information about the risk of hip, spine, and wrist fractures in response to a review of seven recent epidemiological studies (six of which associated PPI use with fracture risk).[39] Accordingly, a few months later, on September 3, 2010, the FDA approved a new label change for PPIs to include the risk of hip, wrist, and spine fracture from long-term and multiple daily-dose PPI therapy in patients with osteoporosis, but the agency has not required a black box warning.

The primary trial to influence this change came from an epidemiological study by Gray et al. that included women enrolled in the Women's Health Initiative and was published in May 2010.[40] The study involved 161,806 postmenopausal women, between the ages of 50 and 79, without a previous history of hip fracture. Outcomes measured were self-reported fracture (adjudicated) and bone mineral density (BMD) (baseline and three-year change). Results showed a significant increase in clinical spine (HR 1.47), forearm/wrist (HR 1.26) and total fracture (HR 1.25) risk, but not in hip fracture risk (HR 1.00), for PPI users. This translates to 47%, 26%, and 25% increased risks for clinical spine, forearm/wrist, and total fracture, respectively, for postmenopausal women on PPI therapy compared to nonusers. Although an increase in hip fractures was not noted, PPI use was associated with reduced BMD in the hip ($p=0.05$). In addition, although a dose-response analysis was unable to be conducted, and there was no association between duration of use and fracture risk, the results from this large study are fairly robust due to its large sample size and the amount of information available in patient records, which allowed for adjustment for numerous confounders.

Multiple studies have found increased fracture risks at higher PPI doses and with longer treatment durations, strengthening the proposed causal relationship. In a 2006 case-control study, Yang et al found an adjusted odds ratio of 1.44 for increased risk of hip fracture with PPI use for more than one year in adults over the age of 50.[41] Both longer duration and higher dose of PPI therapy were associated with a significant increase in the risk for hip fracture. In a recent review, PPI use of four years or more was associated with a significantly higher likelihood (OR 1.62-4.55) of hip fracture, with no effect seen with less than four years of use.[42] Finally, in a recent review of 14 studies comprising one million patients, an increased overall risk of fractures was found with one year of continuous PPI use, with both increased dose and duration linked with higher risk in a subgroup analysis.[43]

The precise mechanism for the increased fracture risk seen with PPI use is as yet unclear. Some speculate that decreased acidity in the stomach leads to calcium malabsorption and decreased bone mineral density, although study results have been mixed on this proposed mechanism.[44,45,46,47] Magnesium deficiency linked to long-term PPI use (see discussion below) could also contribute to fracture risk either independently[48] or through alteration of calcium

metabolism.[49] Others have proposed that PPIs may have a direct effect on bone resorption, with a hypothesis that PPI action on vacuolar ATPases might limit the ability to repair microfractures and increase overall fracture risk without lowering BMD.[50] Another possibility is that acid-suppressive interference in vitamin B12 absorption could lead to hyperhomocysteinemia, a predictive factor for hip fracture.[51]

One additional consideration is the potential for PPIs to attenuate the beneficial effect of medications, such as bisphosphonates, on preventing fractures. A recent Danish cohort study of 38,088 men and women on alendronate found that concomitant PPI therapy, in a dose-dependent manner, reduced the benefit of the medication on hip fracture risk.[52] Thus, in addition to increasing the risk of hip fracture, PPIs may also interfere with medications intended to decrease the risk of osteoporosis-related fractures.

Though the mechanism of PPI-associated fractures still needs to be further evaluated, and the role of confounding variables is still unclear, what is clear is that there is sufficient evidence associating PPI use with increased fracture risk. The FDA has acknowledged this association and acted accordingly by placing a warning of this risk in the label of all PPIs. However, this risk, particularly in the osteoporotic elderly population, carries with it the potential for significant morbidity and, in some cases, mortality resulting from such fracture events. Therefore, a black box warning — in addition to the current label change — is necessary to alert all prescription PPI users of this potentially fatal adverse event.

It should be emphasized that a prominent warning must also be restored on all OTC PPIs. The FDA recently reversed its original position and removed the existing warning on fracture risk from all OTC PPI labels, reasoning that these medications are approved only at lower doses and for short-term (14-day) courses.[53] However, in its updated Drug Safety Communication, the FDA acknowledges that "consumers … may take these products for periods of time that exceed the directions on the OTC label."[54] In addition, given that OTC PPIs are considerably less expensive than their prescription counterparts,[55] patients (or their doctors) may substitute OTC for prescription PPIs for long-term therapy. Therefore, the decision to remove this warning, while simultaneously conceding that patients may take these medications for long-term use, is a dangerous move by the FDA and ignores the need to inform those consumers of a potentially fatal adverse effect. Information on the risk for fractures needs to be reinstated on all OTC PPIs.

D. Development of GI infections and pneumonia

The presence of normal amounts of gastric acid is important for preventing gastrointestinal bacterial colonization. It is therefore biologically plausible that the use of PPIs and the subsequent reduction in gastric acidity would increase the likelihood for bacteria to thrive in the GI tract. Indeed, in several studies, including one randomized, controlled trial, patients on long-term PPI therapy have been shown to develop significantly higher rates of bacterial overgrowth in the stomach and small intestine, with longer duration of use and higher gastric pH both linked to higher rates of overgrowth.[56,57,58] Many patients in the hospital setting who are already susceptible to infections are frequently prescribed PPIs for unapproved indications, such as stress ulcer prophylaxis, which could make them even more vulnerable to illness.[59]

PPI use and Clostridium difficile *infection*

Clostridium difficile infection (CDI) has been clearly tied to PPI use. This bacterial infection is commonly seen in hospitals, and the toxin produced by the bacteria is associated with the development of severe diarrhea. It has been shown that more acidic gastric juice is better at killing this bacteria and neutralizing its toxin than less acidic gastric juice.[60] Therefore, lowering the acidity (increasing the pH) with PPI therapy could allow the bacteria to survive better and its toxin to remain active for a longer time.

Although there are numerous risk factors for CDI, results from recent trials suggest a clear association with PPI use. A five-year cohort study from Jayatilaka et al found a correlation between increased PPI use and the increase in annual incidence of CDI-associated diarrhea in an urban medical center, from 5.08 to 8.42 cases per 1,000 admissions (r_s=1.0; p=0.017).[61] In the last year of the study, a case-control analysis was performed comparing PPI and H2A use with the development of CDI. PPI therapy showed the highest risk if it was used before or upon admission (OR 2.75), and there was still a significantly high risk if initiated only upon admission (OR 1.88), compared to non-use. The weaker H2A therapy did not show increased risk. It is possible that, because the less potent H2As do not increase gastric pH as much as PPIs do, H2As do not allow *C. difficile* to flourish. All results were adjusted for antibiotic use, a potential confounder and known risk factor for CDI.

Other studies have come to similar conclusions about PPIs and CDI risk. Howell et al performed a comparable five-year cohort study that associated increased dosages of acid-suppressive therapy with an increased likelihood for developing nosocomial CDI.[62] Daily PPI therapy increased risk by 74%, and more frequent PPI use increased risk by 136% compared to no acid-suppressing therapy, thus demonstrating a dose-response relationship. PPI use has also been linked to greater severity of the illness. In a retrospective study of 627 patients with CDI and colitis (CDIC) in one hospital, there was a significant increase in adjusted risk (OR 1.65, 95% CI 1.05-2.61) of severe CDIC for patients who received a PPI within 30 days of admission compared to those who had not. Those on PPIs and concomitant antibiotics were at even greater risk of severe CDIC (OR 2.51, 95% CI 1.73-3.66) compared to those who received neither treatment.[63] Another study in predominantly older men at a Veterans Affairs hospital showed that patients placed on PPI therapy within 14 days after an initial episode of CDI were at a higher risk for recurrent CDI than patients not on therapy.[64]

PPI use and community-acquired pneumonia

PPI use has also been linked to higher risk of developing community-acquired pneumonia (CAP). Eom et al outlined several possible mechanisms by which PPI use may lead to CAP.[65] As described above, PPIs induce bacterial overgrowth in the upper (GI)tract. These infected secretions may be aspirated, particularly in older patients, leading to pneumonia. Alternatively, PPIs may inhibit the function of the hydrogen-potassium adenosine triphosphatase enzymes found in the respiratory tract, thereby altering the pH of the secretions, leading to bacterial growth in the respiratory tract itself and pneumonia development.

A 2004 cohort study of 364,683 patients in general practitioner offices by Laheij et al calculated an 89% increased risk of developing CAP in PPI users compared to those who had stopped using PPIs.[66] A dose-response effect was seen in PPI users, with those on the equivalent (adjusted odds ratio [aOR] 1.94; 95% CI 1.41, 2.68) or more than the defined daily dose (DDD) (aOR 2.28; 95% CI 1.26, 4.10) at increased risk for CAP relative to past users of acid suppressants, while those on low-dose PPIs (less than the DDD) were not at increased risk (aOR 1.23; 95% CI 0.78, 1.93). As is commonly the case, those with pneumonia (cases) had more comorbidities at baseline than those without pneumonia (controls). However, these were adjusted for in the risk calculations. In addition, current PPI users were compared to past PPI users, thus diminishing the likelihood that the increased risk of CAP was due to the fact that PPI users are often sicker than the general population. A subsequent, larger study reached a similar conclusion, with an increased risk of CAP seen only in current PPI users (aOR 1.5; 95% CI 1.3, 1.7) and not in recent past users (aOR 1.2; 95% CI 0.9, 1.6). Although in the latter study, a dose-response relationship was not found.[67]

Although a meta-analysis performed by Sultan et al did not find a statistically significant increase in overall risk of respiratory infections due to PPI use, there was an absolute increase in incidence.[68] Cumulative respiratory infections developed in 4.3% and 3.4% of the treatment and placebo groups, respectively (total OR 1.42, 95% CI 0.86, 2.35 for the treatment group). Only one of the seven included trials showed a significant association between PPI therapy and respiratory infection, with high-dose esomeprazole (40 mg) associated with respiratory infection in 4.3% of patients, compared to 0% in the placebo group.[69]

It would not be surprising to see this increased risk in certain kinds of patients more often than others. Older patients who have been admitted to the hospital for CAP are more likely to have recurrence if they are currently on PPI therapy. As calculated by Eurich et al, adjusted odds were increased by 83% for older patients (≥ 65 years of age) newly prescribed PPIs after their last hospital discharge for CAP.[70] Rodriguez et al showed that the risk was only increased with short-term use (between one month and 12 months after starting PPI treatment) and when a PPI was used for dyspepsia or peptic ulcer disease.[71] In a more recent meta-analysis of 31 studies by Eom et al, there was an association between PPI use and the occurrence of community-acquired pneumonia in a subgroup analysis (aOR 1.34, 95% CI 1.14, 1.57). A dose-response relationship was observed, with higher PPI dose associated with increased pneumonia risk. [72]

These findings point to a clear association between PPI use and potentially severe infections such as CDI and CAP. The significant morbidity and mortality that often results from these two conditions, particularly in elderly patients and other vulnerable populations, need to be considered in any analysis of harms and benefits of PPI therapy. Therefore, a black box warning and a patient Medication Guide are necessary to warn about the risk of developing these dangerous infections.

E. Magnesium deficiency

Another serious problem associated with long-term PPI use, and described more recently in multiple case series (and in a recent review), is severe hypomagnesemia.[73] Based on an extensive review of the literature and FDA Adverse Event Reporting System (AERS) database, the FDA

recently released a Drug Safety Communication confirming that magnesium deficiency has been linked to long-term (greater than one year) PPI use.[74] The agency recommended obtaining baseline magnesium levels in all patients prior to initiation of long-term PPI therapy, and in patients on digoxin, diuretics, or medications that also may cause hypomagnesemia.

Since the 2006 publication by Epstein et al[75] of two case reports detailing hypomagnesemia and hypoparathyroidism in PPI-treated patients, the number of hypomagnesemia cases has increased substantially. Although the exact mechanism is unknown, it is suspected that either a decrease in absorption or an increase in secretion of magnesium in the small intestine is responsible.[76] In severe cases of hypomagnesemia reported thus far in a recent review of all cases reported in the literature through July 2010 (28 patients; all over 50 years old), the factor most suggestive of a causal relationship has been evidence of resolution in all cases only after withdrawal of the PPI.[77] As the authors of this review point out, levels from 0.05 to 0.35 millimole per liter (mmol/L; less than half the lower limit of the normal range of 0.8-1.2 mmol/L) have been recorded in patients presenting symptoms of seizure, tetany, and other serious conditions. One additional consideration is the ability of long-term, profound hypomagnesemia to suppress parathyroid hormone secretion, thus leading to hypocalcemia in some cases.[78,79] Indeed, in the review above, those with severe hypomagnesemia commonly exhibited hypocalcemia.[80] This is particularly relevant to the association between fractures and PPI use, in which impaired calcium absorption is a possible contributor.

Although no large clinical trials have been conducted concerning the potential effect of PPIs on magnesium, the biological plausibility and available case series do exhibit some criteria (e.g., positive rechallenge and dechallenge) that suggest causality, as pointed out by the FDA's recent communication.[81]

The FDA has taken a good first step in its move to include this risk information under the *Highlights* section of all prescription PPIs. However, since magnesium levels as low as those seen in the published case series can cause fatal cardiac arrhythmias and other life-threatening complications, patients and providers need to be alerted of this possibility through a more prominent Black Box Warning. Furthermore, as stated above for fracture risk, a similiar warning should be placed on OTC PPIs as the FDA has acknowledged that patients may take these medications for longer than the indicated time period. In addition, patients taking OTC PPIs long-term may already be on magnesium-reducing medications, such as diuretics, and, in the absence of appropriate supervision by a medical professional, will incur an even greater risk. Thus, these and other patients on OTC PPI therapy need to be warned of this potentially life-threatening side effect.

F. Drug-drug interactions and other adverse reactions

PPIs have a wide array of potential interactions with normal metabolic systems and other drugs. Many of these interactions are caused by the significantly increased gastric pH induced by PPIs, as well as interference with cytochrome pathways responsible for the metabolism of certain drugs.

Inhibition of beneficial clopidogrel effect

One drug whose benefit may be significantly diminished by the concomitant use of PPIs is clopidogrel. Clopidogrel inhibits platelet aggregation and is indicated for the prevention of heart attacks and other cardiovascular events in patients with coronary artery disease (CAD). It is commonly combined in therapy with PPIs because clopidogrel also increases the risk of GI bleeding. It has been established that adding a PPI to a patient's drug regimen diminishes the risk of GI bleeding with anticoagulation.[82,83] A recent consensus statement from the American College of Gastroenterology (ACG), the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA) recommended the administration of a PPI to patients with CAD on antiplatelet therapy who have a history of, or multiple risk factors for, an upper-GI bleed.[84]

However, there have recently been a number of studies that have found that the anti-coagulant effect of clopidogrel may be diminished by concomitant administration of a PPI. Both PPIs and clopidogrel interact via the same metabolic (CYP2C19 cytochrome) pathway. It is currently thought that PPIs may competitively inhibit the anti-clotting action of clopidogrel by blocking the conversion of clopidogrel, a pro-drug, to its active metabolite. The FDA has also concluded that concomitant use of PPIs during clopidogrel therapy poses potential health risks. On November 17, 2009, the FDA proposed changes to the labeling for clopidogrel to note the dangers of interaction with omeprazole, recommending that other drugs that reduce stomach acid — namely, H2As — might be safer.[85]

Although some studies have shown a significant effect of PPIs on the antiplatelet effect of clopidogrel,[86] others have not.[87] Furthermore, it was initially unclear whether any such effect on the antiplatelet activity on clopidogrel has any clinical significance. In an attempt to answer this question, there have been several observational studies and one randomized, controlled trial designed to assess the potential interaction between clopidogrel and PPIs.

A 2010 cohort study by Stockl et al analyzed the risk of rehospitalization for myocardial infarction (MI) and coronary stent replacement in patients on the combined therapy. Using both clopidogrel and PPI increased the risk of rehospitalization for MI by 93% and the risk of rehospitalization for MI or coronary stent placement by 64%, compared with patients using clopidogrel alone. However, a potential confounding factor was that those on both clopidogrel and PPI had a higher rate of baseline comorbidities than those only on clopidogrel, a common limitation to many of the observational studies examining the interaction between the two drugs.[88] The interaction between clopidogrel and PPIs has been controversial due to this question of confounding, namely that those on PPIs tend to be sicker and at higher risk for adverse outcomes. Although some studies have suggested this confounding effect,[89,90] large studies have consistently shown a significant interaction between PPIs and clopidogrel even after controlling for all known confounders.[91,92]

To help clarify the role of confounding variables, a large, randomized, controlled trial (the COGENT trial) was recently undertaken to investigate whether PPI co-administration caused higher rates of adverse events in patients on clopidogrel, in addition to aspirin.[93] Patients on a combination of clopidogrel and omeprazole did not show higher rates of a composite end point of death from several cardiovascular adverse events than patients getting clopidogrel alone.

However, the study was terminated early due to loss of funding, thus limiting its detection power. In addition, the patient population and clinical end points were not consistent with the earlier studies that formed the basis for the FDA's determination that there was a significant interaction between omeprazole and clopidogrel.[94]

Genetic factors also may play a role in the effectiveness of clopidogrel therapy. Individuals with two "loss-of-function" alleles in the gene for the CYP2C19 enzyme responsible for activation of clopidogrel are considered poor metabolizers of the drug. Certain subpopulations, such as East Asians, with a higher prevalence of poor metabolizers[95] are particularly vulnerable to the inhibitory effects of PPIs. Huang et al showed significantly higher rehospitalization for CAD and overall mortality (but not revascularization) in East Asians using both drugs, as opposed to those solely on clopidogrel after percutaneous coronary intervention.[96] Poor metabolizers already experience reduced efficacy of clopidogrel due to their diminished ability to convert the inactive (swallowed) form of the drug to the active form. Therefore, any further reduction in clopidogrel's action by PPIs could be particularly dangerous in this population.

Interaction with clopidogrel is possibly classwide

Different drugs within the PPI class have been studied to assess whether the interaction with clopidogrel is confined only to certain PPIs. The FDA has acknowledged the presence of an interaction with the omeprazole 80 mg/day dose and placed a warning on the drug's label to reflect this concern.[97] It has been suggested that other PPIs (e.g., pantoprazole) may not share the same interaction potential with clopidogrel, as they do not have the same inhibitory effect on the metabolic (CYP2C19) pathways in question. Indeed, a recent randomized, crossover trial involving patients on dual antiplatelet therapy following an MI suggested that the interaction was limited to omeprazole.[98]

However, several studies have suggested a significant interaction between clopidogrel and other PPIs, including pantoprazole.[99,100,101] A randomized open-label trial involving 87 patients found that both omeprazole and rabeprazole lead to clopidogrel nonresponsiveness as measured by maximal platelet aggregation (MPA), and that the rate of nonresponsiveness was not significantly different between the two PPIs.[102] Kreutz et al, in a retrospective cohort study of 16,990 patients on clopidogrel who had undergone coronary artery stent placement, found that concomitant administration of omeprazole, esomeprazole, lansoprazole, or pantoprazole all raised the adjusted risk of cardiovascular events compared to clopidogrel alone over a one-year period.[103]

Thus, although the existing evidence is limited at this time, there is a suggestion of a classwide interaction between PPIs and clopidogrel. Therefore, patients need to be alerted to this possibility. Although the evidence on an interaction with high-dose omeprazole is more definitive at this point, patients and providers alike need to be informed that it is still unclear whether switching to another PPI while on clopidogrel is truly a safer option.

Other drug-drug interactions

Through increasing gastric pH so profoundly, PPIs have been shown in studies to alter the absorption of multiple medications. Indeed, as stated in the Nexium label, this alteration of gastric pH has been implicated in interactions with several drugs (e.g., ketoconazole, iron salts, and digoxin).[104] However, other medications whose plasma levels may be altered by PPI-induced hypochlorhydria (decreased acid secretion) — or other mechanisms — are not included in the label. Two such drugs whose levels in the blood may be affected by PPIs are listed below.

- Mycophenolate Mofetil (Cellcept): Decreased Absorption, Decreased Blood Levels

  One potential interaction not listed in the labels of PPIs involves mycophenolate mofetil (MMF or Cellcept), an immunosuppressant given to organ transplant recipients to stave off immunologic rejection of the transplanted organ. MMF is a pro-drug that is converted to the active metabolite mycophenolic acid. Two pharmacokinetic studies have shown a significant effect of various PPIs in reducing the plasma concentrations of the mycophenolic acid.[105,106] Although a new, enteric-coated version of MMF did not show the same interaction in a recent trial, this is a preliminary finding, and other results of a larger, currently planned study are pending.[107] Any decrease in the function of MMF could be serious, potentially resulting in transplant rejection.

- Methotrexate (Folex, Trexall): Decreased Clearance, Increased Blood Levels

  Methotrexate is a drug whose clearance, rather than absorption, may be affected by concomitant PPI use. In a recent retrospective study in France on patients undergoing treatment for certain malignancies, concomitant PPI use was found to be likely responsible for delayed renal elimination of methotrexate, thereby increasing plasma concentrations of the drug and its associated side effects.[108] Of 39 treatment cycles where delayed elimination was found, 17 were attributed to PPI co-administration. Serious adverse events, including acute renal failure, aplastic anemia, and tumor lysis syndrome, resulted from this delayed clearance. This study's results confirmed those of a prior study of 76 cancer patients, where PPIs decreased methotrexate plasma clearance by 27%, resulting in significantly increased plasma concentrations.[109] In the French study, the authors concluded that, based on their evidence and those of prior studies, "… proton pump inhibitor administration should be discontinued during methotrexate treatment."[110] Although the evidence on an interaction between PPIs and methotrexate may still be limited, the potential consequences resulting from methotrexate toxicity warrant the listing of appropriate risk information in all PPI labels.

Thus, there are two medications whose plasma levels have been shown to be significantly altered by concomitant PPI use, but these adverse interactions are not presently listed in the labels of PPIs. These medications, mycophenolate mofetil and methotrexate, are both used to treat or prevent serious conditions, such as cancer and organ transplant rejection. Therefore, any interactions related to these medications are concerning. Alerting health care providers to all possible interactions with PPIs through a comprehensive listing — not a partial list (e.g., for drugs affected by alterations in gastric pH), as is the case currently — of suspected medications is essential.

Vitamin B12 deficiency

PPIs can potentially affect the absorption and metabolism of many other substances. Anything that is dependent on gastric acid for absorption and metabolism would plausibly be affected. While vitamin and mineral deficiencies related to PPI use have not been shown consistently across all studies, overall, these may be important considerations in the elderly and other populations vulnerable to malnutrition.

Vitamin B12 (B12) is an essential nutrient that could be affected by PPI therapy. Pepsin, produced in the stomach, is needed to release B12 from foods but must first be converted from pepsinogen, a process that is dependent on high gastric acidity. Studies have not given consistent results on the effects of PPI use on B12 status,[111,112,113] although longer duration of PPI use has been linked to lower B12 levels.[114] A case-control study in 2004 found that subjects with B12 deficiency were more likely to have taken acid suppressants than those with normal B12 levels.[115] A key finding was that this association did not hold for past users of acid suppressants, diminishing the likelihood that an association was due to confounding. In addition, as B12 deficiency is a process that can take years to develop, no association was found with short-term acid-suppressant use. This was confirmed in a cross-sectional study of 542 older adults in long-term care facilities and outpatient clinics.[116] Longer duration of PPI use was significantly associated with lower serum B12 levels. However, another cross-sectional study of 125 couples in the Netherlands did not confirm this association, with no difference in serum B12 levels observed between long-term PPI users and their partners, or between long-term PPI users (≥ six years) and those on PPIs for shorter periods (three to five years).[117]

A major limitation of this and other studies is their cross-sectional nature. Therefore, more robust observational or randomized studies are needed to clarify the association between long-term PPI use and B12 deficiency. Until that time, the existing evidence needs to be made available to patients and providers alike.

Acute interstitial nephritis

A systematic review published in 2007 examined all published case reports of acute interstitial nephritis (AIN) associated with PPI therapy.[118] Of 60 case reports included in the review, 44% did not involve exposure to any other medications that were known to cause AIN or involved no other medication exposure at all. Four patients had a decrease in renal function after restarting the PPI, suggesting positive rechallenge. The authors concluded that 21 of the 60 cases had a "certain" or "probable" relation to PPI use, with another 37 classified as "possibl[y]" related. In addition, as AIN occurred with five different PPIs (omeprazole, pantoprazole, esomeprazole, lansoprazole, and rabeprazole), the effect may be classwide.

The majority of patients were elderly (mean age, 78 years), indicating that this age group may be particularly vulnerable to AIN from chronic PPI use. Although there were no deaths due to acute renal failure, one-third of the subjects required corticosteroid therapy, and three patients required dialysis, with one remaining on dialysis permanently. Thus, 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.

G. PPIs and the development of gastric cancer

Numerous animal studies have shown that PPIs may be associated with the development of gastric carcinoids and carcinomas, two types of stomach cancer. This is of particular concern in patients with the bacterial infection *H. pylori*, and the potential connection is biologically plausible.

Gastric cancers: carcinoma and carcinoid

Gastric cancer is a varied disease entity, with several risk factors and pathophysiologic pathways. Two common subtypes are adenocarcinoma, derived from glandular cells in the gastric mucosa, and carcinoid tumors, neuroendocrine neoplasms derived from ECL cells. Gastric adenocarcinoma is by far the more common, and the more lethal,[119,120] of the two and is known to be caused (in certain anatomic sites) by *H. pylori* infection[121] and other conditions that lead to atrophic gastritis, a chronic inflammatory state in the stomach that predisposes to carcinoma development. Gastric carcinoid is a neuroendocrine tumor originating from ECL cells within the gastric mucosa and is divided into three types, one of which (Type I) is thought to be caused by chronically low levels of gastric acid and high levels of gastrin (hypergastrinemia), which ultimately induces morphologic changes in ECL cells.[122] As seen below, high gastrin levels, in certain circumstances, have also been implicated in the development of gastric adenocarcinoma.

PPIs and gastric carcinoid tumors

A hypergastrinemic state induces ECL cell changes, which are thought to progress through hyperplastic and dysplastic states before finally becoming carcinoids. A dose-response relationship has been observed between the level of hypergastrinemia and the severity of change in ECL cells.[123,124,125] A recent study by Peghini et al observed that chronic hypergastrinemia alone in sporadic cases of Zollinger-Ellison Syndrome (ZES) (without gastric atrophy or other risk factors) was associated with significant ECL changes, with a highly significant direct correlation between fasting serum gastrin levels and ECL changes (r=0.62, $p<0.00001$).[126] These and other findings increasingly suggest that hypergastrinemia plays a central role in inducing ECL changes, which, in some cases, progress to gastric carcinoid tumors. Although gastrin levels seen in ZES[127] are generally higher than those seen with chronic PPI therapy,[128] the presence of a dose-response relationship in addition to the fact that, as seen below, *H. pylori* infection increases gastrin levels considerably in PPI-treated patients, are causes for concern.

One major cause of hypergastrinemia is long-term acid suppression.,. Chronic PPI therapy works by inducing profound acid suppression, resulting in chronically high levels of gastrin. Therefore, it is biologically plausible that long-term PPI therapy could lead to the development of gastric carcinoid tumors.

This has been borne out in animal studies. The FDA approval documents for several PPIs demonstrate a possible association between PPI use and gastric carcinoid development. In the

Clinical Pharmacology review of Nexium in 2000 (referring to data for omeprazole), a dose-response relationship was noted between omeprazole treatment and ECL cell hyperplasia and carcinoid development in two two-year rat studies. The reviewer went on to state that "due to genotoxic and tumorigenic potentials associated with esomeprazole and/or omeprazole …, approval of esomeprazole for long term use is not recommended. …"[129] The Prevacid label also includes a description of two two-year carcinogenicity studies in rats in which there was an increase in both ECL cell hyperplasia and carcinoid incidence in a dose-response fashion.[130]

Of particular concern is the fact that infection with *H. pylori* may further amplify the effects of PPI-induced hypergastrinemia. *H. pylori*-induced gastritis leads to atrophy of the parietal glands in the oxyntic (acid-releasing) mucosa of the stomach, a condition known as atrophic gastritis.[131] This gastritis results in diminished gastric acid release (hypoacidity) and subsequent hypergastrinemia. Through its own effects on gastrin, PPI therapy could amplify the effects of this *H. pylori*-induced hypergastrinemia, triggering the growth of ECL cells and possibly leading to carcinoid development. Indeed, as can be seen in Table 1 (taken from the approval documents for Protonix), in premarketing trials, there was a marked synergistic effect of *H. pylori* and PPI therapy on gastrin levels, with the *H. pylori*-positive patients exhibiting a much higher dose-response increase in gastrin levels compared with the *H. pylori*-negative patients.[132]

Table 1. Synergistic Effect of PPIs and *H. pylori* Infection on Serum Gastrin Levels [Taken from the Protonix FDA approval documents].

Study GMR-32022 (3001A1-300-US)

Median Serum Gastrin Levels (pg/ml)

	H. pylori Status [+]			H. pylori Status [-]		
Tx Group	Median [n] Basekube	Median [n] 4-week	Median [n] 8-week	Median [n] Baseline	Median [n] 4-week	Median [n] 8-week
PL	54 [17]	51 [12]	52 [13]	47 [63]	46 [40]	45.5 [42]
PANTO 10 mg	56 [30]	59 [19]	64.5 [16]	48.5 [140]	53 [94]	52 [61]
PANTO 20 mg	54 [30]	86.5 [24]	75 [7]	45.5 [138]	52 [100]	52.5 [54]
PANTO 40 mg	61.5 [42]	126.5 [30]	284 [5]	49 [126]	66 [93]	64.5 [30]

PPIs and gastric adenocarcinoma

In animals studies, high gastrin levels have also been associated with the development of gastric adenocarcinoma, a more common and lethal[133] variant of stomach cancer. Gastrin has a known trophic effect on the epithelial lining (mucosa) in the stomach, stimulating cell growth.[134] In animal studies, gastrin has been shown to be a significant factor in the development of carcinomas.[135] Although a mechanism has yet to be elucidated, it is concerning that there was an increased incidence of gastric intestinal metaplasia, a precursor of gastric adenocarcinoma, in rats treated with lansoprazole, as acknowledged in the label.[136] This association has also been suggested in animal studies with transgenic mice designed to have chronically increased gastrin levels. These mice developed intestinal metaplasia, dysplasia, and gastric adenocarcinoma at very high rates (75% with adenocarcinoma by 20 months of age). In addition, the presence of *Helicobacter* infection in this murine model of gastric cancer was shown to result in accelerated

development of adenocarcinoma.[137] A potentially synergistic effect of PPI therapy and *Helicobacter* infection on the risk for gastric carcinoma has been suggested in another animal trial. Hagiwara et al found much higher rates of gastric adenocarcinoma in a group of Mongolian gerbils both infected with *H. pylori* and on omeprazole (nine of 15 with adenocarcinoma) than in either the *H. pylori*-positive group (one of 15) or the group on omeprazole alone (none of 15).[138]

PPIs and gastric cancer: a plausible association?

Thus, PPI therapy, by inducing chronically high levels of gastrin — especially in the presence of *H. pylori* infection — can potentially lead to carcinoid tumors and, possibly, gastric adenocarcinoma. Widespread PPI use is a relatively recent phenomenon and adequately powered, long-term follow-up studies do not yet exist to examine a potential association. In other words, if there is a causal relationship between PPI use and gastric adenocarcinoma, there is likely a lengthy latency period between PPI exposure and cancer development, possibly limiting the current availability of human data. However, a biologically plausible mechanism, in addition to numerous animal studies, suggests a potential association between long-term PPI use and cancer development in humans, and careful follow-up studies are needed.

H. Overuse: inappropriate prescribing, unnecessarily high doses, empiric therapy, and inpatient initiation of PPI therapy

Use of PPIs has grown almost exponentially over the past couple of decades due to their considerable effectiveness for certain conditions, widespread inappropriate use for indications for which there is no evidence of benefit, and incorrectly perceived lack of side effects. All of this is worsened by massive promotion of these products. A 2009 analysis using the National Ambulatory Medical Care Survey found an increase in the frequency of prescription PPI treatment from less than five prescriptions per 1,000 GERD-related physician visits in 1995 to 43.9 prescriptions per 1,000 visits in 2006 in the U.S., a more than eight-fold increase.[139] In 2009, Nexium grossed the second highest amount ($5 billion) in U.S. retail sales — and had the second highest number of prescriptions (26.5 million) filled of all brand-name drugs.[140] There were a total of 119 million U.S. prescriptions filled in 2009 for all PPIs,[141] totaling $13.6 billion in U.S. sales.[142]

However, unnecessary and inappropriate use is widespread. Studies have estimated that potentially one-half to two-thirds of all patients on PPIs do not have an appropriate indication.[143,144] In addition, many patients are using PPIs chronically, beyond the indicated time frame, for conditions such as GERD.[145] Here we outline four key reasons for PPI overuse, followed by recommendations to mitigate this extensive and dangerous problem.

(1) Inappropriate prescribing

With time, it has become clear that some serious side effects for PPIs do, in fact, exist and that there is considerable misprescribing for indications for which PPIs have not been shown to be effective. However, many physicians have not changed their prescribing habits in response to this new information. The lack of awareness about the increasing evidence of serious adverse effects has allowed physician misprescribing and (for OTC versions of PPIs)

patient misuse, to continue. A recent study in Denmark involving 22 general practitioners and 42,634 patients found that 2.1% of all patients were on long-term PPI treatment, but only 27% of these patients had verified indications for the therapy.[146] The risk for dependence with long-term use due to RAHS is a serious concern, especially in the 73% of patients for whom this therapy is considered inappropriate. In 194 of the patients in the above study who lacked a verified indication, 119 (61%) had previously attempted withdrawal unsuccessfully.[147] A German study analyzing hospital discharge letters found that less than one-third of all patients with a hospital discharge letter recommending a PPI had an evidence-based indication.[148] In addition, in patients lacking a clear indication for the PPI, there was no reason given for the recommendation in 37.8% of these patients.

(2) Unnecessarily high doses

Another problem, even in patients for whom PPIs are indicated, is using doses that are unnecessarily high. Many argue that high-dose PPIs are neither necessary nor more effective than PPIs at low doses. In many cases, patients with common conditions such as GERD may be justifiably stepped-down to lower doses without affecting the treatment course. In one study, 79% of patients had no recurrence of heartburn or acid regurgitation six months after having been switched from multiple to single daily-dose PPI therapy.[149] As seen in Table 2, a high proportion of patients with GERD achieve both short- and long-term symptom relief with lower PPI doses. A recent systematic review concluded that "… a substantial proportion (26-71%) of GERD patients can be adequately managed with PPI treatment that is less intensive than that of continuous daily administration."[150]

In addition to decreased daily doses, a number of randomized trials have shown that on-demand PPI therapy is sufficient to treat symptoms of acid reflux, when compared to continuous therapy.[151,152] For example, a Swiss study randomized patients with GERD who had achieved remission of symptoms at four weeks on daily PPI to either on-demand or continued daily PPI treatment for maintenance.[153] They found that patients using PPIs on demand used 33% less medication and had only slightly lower rates of being heartburn free (80% vs. 86%, $p<0.001$) but similar rates of satisfaction with treatment, epigastric pain, and regurgitation.

Thus, taking lower or on-demand PPI doses may be just as effective for common conditions such as GERD, and could be key in helping to prevent dose-dependent risks such as ECL cell hyperplasia or hip fracture, not to mention lowering costs.

(3) Empiric PPI therapy for GERD

The American Gastroenterological Association (AGA) released a review on the management of GERD based on an extensive review of the literature in 2008 and noted that "… the current consensus is that empirical PPI therapy is appropriate for uncomplicated heartburn."[154] This is consistent with the labeling for multiple PPIs that have listed as an indication the short-term (four weeks) treatment of GERD. However, as the AGA noted in its review,[155] reflux symptom resolution with empiric PPI therapy does not necessarily represent a diagnosis of GERD.

A systematic review of trials of empiric PPI therapy showed that a successful trial of a PPI is not a reliable predictor of objective GERD.[156] Specifically, successful treatment with a PPI had a pooled sensitivity of only 78% and specificity of 54% when compared to abnormal 24-hour ambulatory esophageal pH monitoring. A recent open-label study in Korean patients showed similar results, with only modest sensitivity (77%) and specificity (56%) of empiric PPI therapy when compared with objective measures, including endoscopic findings of erosive esophagitis or abnormal 48-hour esophageal pH monitoring for diagnosing GERD.[157] This poor specificity confirms that a large percentage of patients "responding" to the PPI test do not in fact have GERD. In a recent retrospective study, 200 patients with suspected GERD symptoms, half of whom were on a PPI, were placed under pH monitoring while lying down.[158] The key finding was that in both patients on PPI therapy and those not on PPI therapy, the majority of the suspected GERD symptoms were atypical (89% and 67%, respectively) and not related to actual acid reflux into the esophagus (90% and 86%, respectively).

Given the propensity for a patient prescribed a PPI to remain on the drug in the long-term, the empiric treatment of many patients who do not in fact have physiologic GERD is likely a major contributor to the overuse of, and damage from, PPIs.

(4) Inpatient initiation of PPI therapy, often for stress ulcer prophylaxis

PPI overuse by patients is compounded by physician overprescribing during inpatient hospital admissions and discharges. It has been estimated that up to one-fourth of hospitalized patients outside of the intensive care unit (ICU) receive stress ulcer prophylaxis despite a lack of evidence for its use in this setting.[159] A retrospective chart review at the University of Florida Health Science Center found that 70% of patients admitted to the general medicine service over a three-month period were started on acid-suppressive therapy (AST) in the hospital. The most frequently prescribed ASTs were PPIs. Seventy-three percent of the AST prescriptions written at admission lacked accepted indications, and in 49% of cases, no indication was found for initiating AST.[160] When reported, the most common indication was for stress ulcer prophylaxis.

This inappropriate inpatient use is often extended into the outpatient setting. For example, in the University of Florida study, 69% of the patients with inappropriate prescriptions continued that same treatment upon discharge.[161] In another cost-analysis study, a 2.5 million member managed-care organization (MCO) examined the records of patients who were initiated (no use 90 days prior to hospitalization) on PPI therapy during an inpatient admission at a hospital and filled a prescription to resume that therapy within 30 days of discharge. Over 68% of the individuals who filled PPI prescriptions after discharge lacked an appropriate indication, costing the MCO and the patients an estimated $3,013,069 over the four-year course of the study.[162] Yet another study showed that at three months after hospital discharge on inappropriate AST therapy, 80% of patients available for follow-up were still taking the drugs, and at six months, 50% of patients were still taking these medications (all still without appropriate indications).[163]

I. Preventing overuse and PPI alternatives

Reasonable steps to mitigate PPI overuse in the inpatient setting

Significant mitigation of PPI overuse can be accomplished in the inpatient (hospital) setting, beginning at admission. The unjustified presence of a checkbox for GI prophylaxis on admission order sets has been shown to be an independent predictor of inappropriate prescribing of PPIs in the inpatient setting.[164] Therefore, a straightforward intervention to prevent this often automatic prescribing is to remove PPIs from routine admission order sets, instead placing them only on those order sets where a PPI may be appropriate (e.g., in an ICU setting).

Once patients are admitted to the hospital, the implementation of clearer prescribing guidelines for PPIs could be instituted to ensure more appropriate use. A study performed at Massachusetts General Hospital found significantly reduced rates of prescribing of PPIs the month after guideline implementation compared to the retrospective analysis of the month before.[165] Inpatient use dropped from 27% to 16% and prescriptions at discharge dropped from 16% to 10%. In the study, doctors were not bound to follow the rules but were encouraged to use them as they felt appropriate. Clinical guidelines would probably most benefit less experienced, younger doctors who, in other studies, have been noted to write a high percentage of inappropriate PPI prescriptions.[166]

In another recent survey of internal medicine physicians and residents, predictors of "low" PPI prescribing behavior for general medicine patients (in most of whom a PPI would be unnecessary) were knowledge about stress-ulcer-prophylaxis indications and concern about the side effects of PPI use.[167] Thus, educational interventions could also be instituted to help mitigate this knowledge gap. One hospital found that the implementation of didactic lectures for internal medicine residents on appropriate use of PPIs, in addition to removing stress ulcer prophylaxis from the internal medicine admission checklist, reduced inappropriate prescribing of PPIs both during hospitalization and after discharge.[168]

Finally, an important intervention that has been shown to improve the accuracy of prescribing is the implementation of more rigorous medication reconciliation procedures at discharge.[169] If an individual has no indication for a prescription, it should not be issued. Providers need to be alerted, either through a checkbox on the discharge form or through an electronic alert, to discontinue PPIs when appropriate.

Measures such as these would certainly help save costs and likely improve outcomes by reducing the widespread and unnecessary use of PPIs in the hospital setting — use that all too often translates to long-term inappropriate therapy and preventable adverse reactions after discharge.

Step-up therapy with safer alternatives instead of starting with PPIs: a reasonable approach

Physicians should encourage their patients to take a step-up approach in managing their reflux symptoms.[170,171] Given the known adverse effects with long-term PPI use, and the fact that empiric PPI therapy is inappropriately given as the first drug to be tried in so many patients with

no objective findings of acid reflux, step-up therapy, beginning with safer options, seems to be the most reasonable approach. As Table 2 shows, a substantial number of patients suffering from GERD would benefit from these safer pharmacologic approaches when used alone.

Moreover, in related conditions such as dyspepsia, when these treatments are combined into a step-up approach (beginning with antacids, progressing to H2As, and finally administering PPIs), an even larger number of patients have been shown to achieve long-term relief of their symptoms. A large randomized, controlled trial conducted on 645 patients complaining of new-onset dyspepsia in an outpatient setting found that a majority of patients (72%) achieved symptom relief at six months with step-up therapy, similar to the rate seen with step-down therapy with PPIs first (70%) (OR 0.92; 95% CI 0.7–1.3).[172] Not surprisingly, step-up therapy also resulted in lower treatment costs over the six-month period.

Thus, step-up therapy has been shown to achieve similar rates of symptom relief as step-down therapy, with the potential for lower costs and fewer serious adverse drug effects. Alternative pharmacologic therapies and lifestyle changes that could comprise a comprehensive step-up approach for conditions like GERD and dyspepsia are outlined in the following section.

Table 2. Efficacy of Alternative (Other Than Standard-Dose PPI) Pharmacologic Therapies for the Treatment of GERD.

Treatment	Patients with Short-term Relief of GERD Symptoms	Patients with Long-term Relief of GERD Symptoms
Antacids/Alginates[1]	20-79%[2]	N/A[3]
Histamine-2 Antagonists	24-57%[4]	43-72%[5]
Low-dose Proton-Pump Inhibitors[6]	79%[4]	56-69%[5]

1. Antacid/Alginate category includes acid neutralizers (antacids), physical/mucosal barrier compounds (alginates, sucralfate, etc.), or combination compounds.
2. Obtained from independent review of randomized, controlled trials evaluating efficacy of alginate and antacid compounds compiled in a review article (Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000 Jun;14[6]:669-90.) "Short-term relief" for this category included "improved" or "symptom-free" relief at four to eight weeks of treatment. All numbers are absolute rates of symptom relief with each therapy, derived from randomized, controlled trials.
3. Insufficient number or quality of trials evaluating long-term antacid/alginate efficacy.
4. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003244. "Short-term relief" for this category includes "relief of symptoms" of "reflux esophagitis" at four to 12 weeks of treatment. All numbers are absolute rates of symptom relief with each therapy, derived from randomized, controlled trials.
5. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev. 2005 Apr

18;(2):CD003245. "Long-term relief" defined as absence of significant symptoms (e.g., "acid regurgitation," "heartburn," or measurement of significant symptoms by GSRS scores) at 24-52 weeks of therapy. All numbers are absolute rates of symptom relief with each therapy, derived from randomized, controlled trials.

6. "Low-dose" PPI refers to a dose lower than (mostly half) the recommended dose listed in the label.

Components of step-up therapy

Lifestyle modification

The initial intervention in a step-up approach for reducing acid-related symptoms should be lifestyle modification. Although PPIs can limit gastric acid secretion by reducing acidity, they cannot change the strength of the lower esophageal sphincter. Reflux will still occur, but it might not feel as severe. By reducing food and liquid intake, altering body position (especially during sleep), and taking other nonpharmacologic measures, one can limit the symptoms caused by acid reflux. In addition, weight loss has been linked with a reduction in reflux symptoms.[173] In one small study, 88% of obese patients on daily PPI therapy for GERD symptoms were able to discontinue their PPI or take it less often after just one month of modifying their diets and achieving substantial (average 17.5 lbs) weight loss.[174] Before resorting to the extremes of PPI therapy, patients should try changing little things in their everyday lives to achieve symptom relief.

Antacids and alginates

Should lifestyle modifications fail to result in adequate relief, the use of antacids or an antacid/alginate combination is the next step in this approach. In a 2007 study that included a meta-analysis of three randomized trials, alginate/antacid combinations resulted in a clear improvement of reflux-related symptoms after two weeks compared to a placebo (26% absolute benefit over placebo; 95% CI 12-41%).[175] Although, in the same study, another analysis of four randomized trials involving only antacids did not show a significant benefit over a placebo in reducing symptoms after two to four weeks (absolute benefit over placebo 8%, p=0.06), two of the trials found that those on antacids were less likely to have heartburn episodes requiring rescue antacids. Antacids, alginates, and physical/mucosal barrier compounds are generally safe and without any major adverse effects, with the exception of aluminum-containing compounds in those with renal insufficiency.[176] As seen in Table 2, a substantial number of patients with GERD would benefit from the use of these compounds alone. Therefore, this therapy is a sufficient, and relatively safe, intervention for many people who would otherwise be placed unnecessarily on long-term acid suppression.

H2As

If antacids fail to yield sufficient relief, the next treatment option should be H2As, such as Tagamet. As noted in Table 2, a Cochrane review of randomized, controlled trials of H2As for maintenance treatment of GERD showed that approximately half (43-72%) of patients put on H2As achieved long-term symptom relief. In addition, H2As had significantly fewer side effects than maintenance-dose (but not healing-dose) PPIs in head-to-head trials.[177] Furthermore, when H2As are given as part of a comprehensive step-up approach, similar rates of symptom

resolution are seen compared with PPI therapy. In the randomized, controlled trial of 645 patients with new-onset dyspepsia mentioned earlier, those randomized to a step-up approach (antacids-H2As-PPIs) achieved similar rates of symptom resolution at six months (72%) as those given a step-down approach (PPIs initially).[178] An important reason to start with H2As as opposed to PPIs is the former's superior safety profile, as noted with several of the adverse effects (e.g., CDI and clopidogrel interaction) mentioned in this petition. Thus, H2As, as part of a comprehensive step-up therapeutic approach, achieve similar rates of symptom relief with less potential for some of the severe adverse effects associated with PPI use, and would seem a reasonable alternative to empiric PPI therapy.

Low-dose PPIs

As seen in Table 2, should PPI use become necessary, providers can begin with a lower dose than commonly prescribed. Given the large proportion of patients who achieve short (79%) and long-term (56-69%) symptomatic relief with these lower doses, and the multiple adverse effects noted in this petition that occur in a dose-dependent fashion, this would seem to be the most rational approach when initiating PPI therapy if the other step-up measures have not been effective.

Thus, given the safer options that are available to patients with uncomplicated GERD or dyspepsia, it is concerning that step-down therapy with PPIs is implied as an initial treatment option for these conditions on the PPI labels. As step-up therapy could have a dramatic impact on the problem of unnecessary, and often dangerous, overuse of PPIs, it seems reasonable to educate patients and providers alike on this alternative option for most of the circumstances in which PPIs are otherwise automatically prescribed as first-choice treatments.

J. Current labeling for PPIs is dangerously deficient

There are seven different prescription PPI medications and three OTC PPI medications available on the U.S. market. The prescription medications include Nexium, Dexilant, Prilosec, Zegerid, Prevacid, Protonix, and Aciphex. Another prescription drug, Vimovo, is an arthritis medication that also contains omeprazole in order to function as an acid-suppressor. The OTC medications are Prilosec OTC, Zegerid OTC, and Prevacid 24-Hr. The prescription medications have a variety of indications. The most prevalent indications are treatment of GERD/erosive esophagitis, maintaining healed erosive esophagitis, *H. pylori* eradication therapy, reducing NSAID-associated gastric ulcer, and treating pathological hypersecretory conditions (such as ZES). Treatment periods vary depending on indication but will typically last from four to eight weeks with single daily doses.

No prescription PPI has black box warnings on their labels for any side effect. Table 3 highlights the current labeling for the risk information being sought in this petition for both OTC and prescription PPIs. At present, the OTC labels contain scant, if any, information regarding many of the risks listed in Table 3. In a 2000 joint meeting of the Nonprescription Drugs and Gastrointestinal Drugs advisory committees of the FDA, a panel voted 9-3 that it was not certain consumers could take OTC omeprazole as directed without physician supervision.[179] Despite the

panel's findings, omeprazole and lansoprazole have both been approved by the FDA for OTC use.

As previously mentioned, the FDA has recently set a dangerous precedent in its move to eliminate a warning on fracture risk with long-term PPI use from the labels of all OTC PPIs, based on the reasoning that since these drugs are only indicated for short-term use, there is no need to disclose risks that are predominantly seen with longer-term use. This move was taken in spite of the fact that the agency itself acknowledged that "consumers … may take these products for periods of time that exceed the directions on the OTC label."[180] In addition, given that OTC PPIs are often considerably less expensive than their prescription counterparts[181], some health plans and/or providers may actually encourage (and patients may themselves often opt for) the substitution of OTC for prescription PPI formulations for long-term therapy of conditions such as GERD. Therefore, the decision to remove the warning on fracture risk from OTC PPIs must be reversed, and the labels must be expanded to include all other dangerous side effects outlined in this petition (e.g., magnesium deficiency). The precautionary principle requires that the FDA assume that many patients do indeed take OTC medications long-term, therefore necessitating complete disclosure of risks with both indicated (short-term) and off-label (long-term) use.

K. Conclusion

PPIs are now one of the most widely used classes of prescription drugs, with an estimated one out of every 20 people in the developed world currently taking the medications.[182] Given that the majority of this use is probably inappropriate and with minimal or no benefit to the patient, and that new, life-threatening risks with long-term therapy are continually emerging, it is time for the medical community to re-evaluate the role of PPIs in everyday practice. As a critical first step, the FDA must act immediately to require disclosure of the risk information outlined in the following recommendations to ensure that the benefits of PPIs are appropriately balanced with their harms when doctors and patients make the decision on whether or not to initiate therapy.

Table 3. Current Risk Information on PPI Labels for Adverse Reactions Being Sought in This Petition.

	Risk	Current Information in Label	Primary Location within Label	PPIs with this Information in Label
Proposed Black Box Warnings	**Rebound Acid Hypersecretion (RAHS)**	**No Black Box Warning** Nothing in label	N/A	**None**
	Fracture Risk	**No Black Box Warning** "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."	*Highlights: Warnings and Precautions*	**All prescription PPIs[1]**
	***Clostridium difficile* infection (CDI) and community-acquired pneumonia (CAP)**	**No Black Box Warning** CDI: "Treatment with proton-pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* in hospitalized patients." CAP: Nothing in label.	CDI: Nexium, Prilosec (*Microbiology* – 12.4); Vimovo (*Pharmacodynamics* – 12.2) CAP: N/A	CDI: **Nexium, Prilosec, Vimovo[2]** CAP: **None**
	Magnesium Deficiency	**No Black Box Warning** "Hypomagnesemia has been reported rarely with prolonged treatment with PPIs"	*Highlights: Warnings and Precautions*	**All prescription PPIs[3]**
Other Proposed Labeling Changes	**Adverse Interaction with clopidogrel**	"Drug Facts: Ask a doctor or pharmacist before use if you are taking • warfarin, **clopidogrel**,or cilostazol (blood-thinning medicine)" "Diminished anti-platelet activity of clopidogrel due to impaired CYP2C19 function by **80 mg omeprazole"**	*Drug Facts* (on OTC labels) *Highlights: Warnings and Precautions* (with further warnings in *Drug Interactions* and in the Full Prescribing Information)	**Prilosec OTC, Zegerid OTC[4]** ***Prilosec***
	Adverse Interaction with methotrexate and mycophenylate mofetil	"May interfere with the absorption of drugs where gastric pH is important for bioavailability."	*Highlights: Drug Interactions* (only a partial list of drugs potentially affected[5]). No mention of either methotrexate or mycophenolate mofetil here, or anywhere else, in the label[6]	**All prescription PPIs**
	Vitamin B12 Deficiency	"Generally, daily treatment with **any acid-suppressing medications** over a long period of time (e.g., longer than 3 years) may lead to malabsorption of…Vitamin B-12]…"	*Warnings and Precautions* (5.3)	**Protonix**
	Acute Interstitial Nephritis	"Hypersensitivity reactions may include…interstitial nephritis…"	*Contraindications* (4)	**Prilosec; Zegerid**

All information taken from most current label on either FDA or "DailyMed" websites: Prilosec (05/2011), Nexium (05/2011), Aciphex (05/2011), Dexilant (05/2011), Prevacid (06/2011), Protonix (05/2011), Zegerid (05/2011).

Prilosec OTC (03/2007, and "Dear Doctor" letters through 02/2011), Zegerid OTC (12/2009, and Letters through 12/2010), Prevacid 24-Hr (08/2009, and Letters through 04/2011).

Risks merely included within a list of potential adverse effects (such as in *Postmarketing Experience* or observations from clinical trials) and where there was no specific warning devoted to that risk were not considered as a labeled adverse effect.

1. On March 23, 2011, the FDA released an update of their March 25, 2010, Drug Safety Communication concerning fracture risk with long-term PPI use. It stated that the warning present on all prescription PPIs (above) is not necessary on OTC PPIs due to the fact that OTC PPIs come in lower doses and are only indicated for short-term use. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm).
2. All risk information attributed to the Vimovo label is included in this table only if the risk is attributed to the omeprazole (and not the NSAID) component in the label.
3. Updated label not available on the FDA website for Nexium, and no Letter on the site concerning hypomagnesemia. A label "revised" in May 2011 was found on the "DailyMed" site but did not include hypomagnesemia. It is unclear whether the label is out of date or whether Nexium was excluded from this classwide risk information for some reason. For all other PPIs, more detailed risk information is found in the "Warnings and Precautions," "Adverse Reactions," and "Patient Information" sections.
4. Provisionally. There are, so far, only letters from the FDA to manufacturers on the website recommending this change — the updated labels are not up yet. (Letter dated December 20, 2010, for Zegerid OTC only includes warfarin and clopidogrel, not cilostazol.)
5. All PPIs (except Protonix and Prevacid) include a list of three examples in "Highlights" of drugs affected by gastric pH (ketoconazole, iron salts, digoxin). Zegerid, Dexilant, and Prilosec labels also include ampicillin esters in "Highlights." Protonix and Prevacid do not include any drugs as examples in the "Highlights" section.
6. The following information is in the Prevacid label (12.5 — "Drug-drug Interactions"): "In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg twice daily and PREVACID 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted."

II. SUMMARY OF REQUESTED ACTIONS

1. There should be a black box warning on all prescription PPIs and equivalent, prominent warnings on OTC PPIs, including information about the following serious risks (there is currently no black box warning on PPIs for any side effect). We are suggesting the following wording:

- **Dependence on PPIs:**
  "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."

In addition, given the serious nature of the following adverse events, particularly in the elderly and other vulnerable populations, three other black box (and OTC) warnings are necessary:

- **Bone Fracture**: "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." This is already in the "Highlights" section but should be made a black box (and equivalent OTC) warning due to the potential morbidity and mortality resulting from this adverse effect.

- **Infection**: "An increased likelihood of certain serious infections, such as *C. difficile* diarrhea and community-acquired pneumonia, has been associated with long-term PPI use." Pneumonia risk is currently entirely missing from all PPI labels, while information on *C. difficile* infections — although attributed to *all* PPIs in the label — is, for some reason, only present on three (Nexium, Prilosec, and Vimovo). Given the potentially fatal nature of these two conditions, particularly in elderly and other vulnerable populations, both conditions need to be placed in a black box (and equivalent OTC) warning.

- **Magnesium deficiency**: "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."[183]

  At the FDA's behest, manufacturers recently placed warnings regarding the potential for hypomagnesemia in the "Highlights" section of all prescription (but not OTC) PPI labels. However, due to the potentially fatal consequences of hypomagnesemia, a more prominent black box warning is needed on all prescription PPIs. In addition, patients on OTC PPIs need to be made aware of this adverse effect through an equivalent, prominent warning.

2. **A patient Medication Guide**, approved by the FDA, should be required for all prescription PPIs, to inform patients of the variety of serious risks now known to accompany the use of these drugs. This should include the black box warnings previously mentioned and label changes mentioned below. In addition, the Medication Guide should include detailed information on step-up therapy, including lifestyle changes, antacids, and H2As. There are currently no Medication Guides for PPIs.

3. The FDA should request that the **sponsors of all prescription PPI medications send a "Dear Doctor" letter to physicians and other providers** that includes the black box warnings mentioned earlier and the other label changes mentioned below. The letter

should also include detailed information on the efficacy and safety of step-up therapy, including lifestyle changes, antacids, and H2A therapy. Health care providers should encourage their patients to take a step-up approach toward managing their acid-related symptoms. Lifestyle modifications and dietary changes should be tried before resorting to medication. When appropriate, use of antacids and H2As should precede PPI therapy. Only if these interventions prove ineffective should the patient then attempt treatment with PPIs. Finally, the letter should 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.

4. <u>Other label changes</u>

- **Drug-drug interaction**: Taking PPIs may reduce the effectiveness of clopidogrel, leading to an increased rate of serious adverse cardiovascular events, such as MI. Some PPIs (e.g., omeprazole) have been shown to have a higher likelihood of interaction than others (e.g., pantoprazole), but multiple PPIs have been implicated. Although a version of this warning is already on the omeprazole label, mention should be made in the "Highlights" section of all PPI labels that the potential for a classwide interaction cannot be ruled out at this time.

  Appropriate risk information on a potential interaction with at least two other medications used to treat serious conditions — methotrexate and mycophenolate mofetil — also needs to be listed in the label.

- **Vitamin B12 deficiency**: The available evidence on the potential for B12 deficiency with long-term PPI use needs to be placed in the appropriate section of the label. The FDA has deemed the evidence sufficient to place a warning of the potential for B12 deficiency on the Protonix label (under "Warnings and Precautions"). However, given the evidence presented in this petition, and the fact that the warning attributes the potential risk to all "acid-suppressing therapy" (not specifically to Protonix), this warning should be placed under "Warnings and Precautions" in the labels of all PPIs.

- **Acute interstitial nephritis**: The available evidence regarding the potential for acute interstitial nephritis with long-term PPI use, seen in at least 60 case reports, should be included in the appropriate section.

- **GERD-treatment length inconsistency for different PPIs**: All PPIs approved for the treatment of GERD should have specific recommendations for length of treatment beside all mentions of the indication in the label. Two PPIs do not currently have specified lengths for GERD treatment on the "Indications and Usage" sections of their labels. Aciphex includes a "4 week (with option for additional 4 weeks)" time frame only in the "Dosage and Administration" section (2.3) but not in the "Indications" section (1.3). The "4 week" time frame should be included in the "Indications and Usage" section in the full prescribing information and in both "Indications and Usage" and "Dosage and Administration" sections under "Highlights," on the Aciphex label. In addition, Protonix does not include an indication subheading for (non-erosive)

GERD in the "Indications and Usage" section but does seem to include an indefinite indication for "reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD" under another subheading in this section (1.2). If Protonix is indeed indicated for non-erosive GERD, then we ask that this be displayed prominently in the "Indications" section under a separate subheading with a specific recommended time course (four to eight weeks if appropriate).

III. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

IV. CERTIFICATION

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

Sincerely,

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