August 23, 2011

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

Dear Dr. Hamburg,

As a physician and life-long researcher on the adverse effects of proton pump inhibitors (PPIs), I strongly support the attached petition for Black Box Warnings and other labeling changes to the labels of all PPIs currently on the market and have joined Public Citizen as a co-petitioner.

My research began in 1974 on the regulation of gastric acid secretion, and particularly the central role of gastrin in this process. Through *in vitro* studies in isolated organs, in addition to *in vivo* animal and, most importantly human studies, our group was the first to show that gastrin, a critical hormone in regulating digestion, functionally stimulates acid secretion primarily through effects on histamine release. A key finding was that, once the PPIs were discontinued, ECL cell hyperplasia persisted for weeks and even a few months causing levels of acid secretion higher than those seen before starting PPI therapy.

From these initial animal data on the effect of PPIs on gastrin with secondary ECL cell hyperplasia, it was difficult to accept that these drugs should not induce a rebound acid hypersecretion (RAHS) in humans, and in a 1996 study on patients with reflux esophagitis, we were the first to show such an effect. We reasoned that this RAHS effect was the cause of the "dependence" on PPIs that many clinicians in the field have described. As outlined in the petition, our findings have been confirmed by a wave of subsequent studies showing, in randomized-controlled trials, that patients with gastroesophageal reflux disease (GERD) can become "dependent" on PPIs through the RAHS effect after as little as 2 weeks of therapy. In 2009 in another randomized trial, even previously healthy subjects – with no history of GERD – showed the RAHS effect after two weeks of PPI therapy, thus confirming that the effect is not merely a recurrence of symptoms after stopping therapy.

This area of research has become increasingly important since the proliferation of PPI use over the past 10-15 years to become one of the most widely used classes of medications in the world. However, throughout my career I have been struck by the difficulties in getting manuscripts published describing this and other adverse effects of PPIs. Furthermore, it has been disappointing to experience that clinicians and scientists dismiss

the alteration by PPIs of central biological functions and believe that some of these basic functions can be removed without adverse consequences.

For instance, one of the most important functions of the acidic gastric juice is to kill swallowed micro-organisms. Thus, by suppressing gastric acid secretion and removing this critical protective mechanism against infection, PPIs have been shown to increase the risk of several infections, such as pneumonia and *C. difficile* diarrhea. This represents just one of many life-threatening side effects that have been associated with long-term PPI use. In addition, several animal studies have shown a possible link between PPI use and gastric cancer, particularly in patients with a common stomach infection, *H. pylori*, the same bacteria implicated in peptic ulcer disease.

Given that most people on PPIs long-term do not even have a documented need for the medication, and that for those that are on these drugs for legitimate reasons, several safer alternatives exist, the risks greatly outweigh any benefit in most patients on PPIs. I therefore urge the FDA to act promptly on the recommendations outlined in Public Citizen's petition to require urgent labeling changes to all PPIs, including Black Box Warnings describing these serious adverse effects.

Sincerely,

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