FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors

Update: 3/23/2011
FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication "Drug Facts" label is not indicated at this time. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely.

The available data show that patients at highest risk for fractures received high doses of prescription PPIs (higher than OTC PPI doses) and/or used a PPI for one year or more.

In contrast to prescription PPIs, OTC PPIs are marketed at low doses and are only intended for a 14 day course of treatment up to 3 times per year. FDA acknowledges that consumers, either on their own, or based on a healthcare professional's recommendation, may take these products for periods of time that exceed the directions on the OTC label. Healthcare professionals should be aware of the risk for fracture if they are recommending use of OTC PPIs at higher doses or for longer periods of time than in the OTC PPI label.

Safety Announcement

[05-25-2010] The U.S. Food and Drug Administration (FDA) is revising the prescription and over-the-counter (OTC) labels for a class of drugs called proton pump inhibitors to include new safety information about a possible increased risk of fractures of the hip, wrist, and spine with the use of these medications.

Proton pump inhibitors work by reducing the amount of acid in the stomach. Nexium, Dexilant, Prilosec, Zegerid, Prevacid, Protonix, Aciphex, and Vimovo are available by prescription to treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus. Prilosec OTC, Zegerid OTC, and Prevacid 24HR are sold over-the-counter (OTC) for the treatment of frequent heartburn.

The new safety information is based on FDA's review of several epidemiological studies that reported an increased risk of fractures of the hip, wrist, and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more (see Data Summary section).The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group.

While the greatest increased risk for fractures in these studies involved people who had been taking prescription proton pump inhibitors for at least one year or who had been taking high doses of the prescription medications (not available over-the-counter), as a precaution, the "Drug Facts" label on the OTC proton pump inhibitors (indicated for 14 days of continuous use) also is being revised to include information about this risk.

Healthcare professionals and users of proton pump inhibitors should be aware of the possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors, and weigh the known benefits against the potential risks when deciding to use them.

Additional Information for Patients and Consumers

- Proton pump inhibitors are effective in treating a variety of gastrointestinal disorders. Do not stop taking your proton pump inhibitor unless told to do so by your healthcare professional.
- Be aware that an increased risk of fractures of the hip, wrist, and spine has been reported in some studies of patients using proton pump inhibitors. The greatest increased risk for these fractures was seen in patients who receive high doses of these medications or use them longer (a year or more).
- Read and follow the directions on the OTC *Drug Facts* label, when considering use of OTC proton pump inhibitors.
- Be aware that the OTC proton pump inhibitors should only be used as directed for 14 days for the treatment of frequent heartburn. If your heartburn continues, talk to your healthcare professional. No more than three 14-day treatment courses should be used in one year.
- Talk to your healthcare professional about any concerns you may have about using proton pump inhibitors.
- Report any side effects with proton pump inhibitors to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

- Proton pump inhibitors provide important benefits for many patients in treating or preventing conditions such as erosive esophagitis, nonsteroidal anti-inflammatory drug-induced ulcers and gastroesophageal reflux disease.

- Be aware of the increased risk of fractures of the hip, wrist, and spine seen in some observational studies in patients using proton pump inhibitors.
- When prescribing proton pump inhibitors, consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.
- Follow the recommendations in the product labeling when prescribing proton pump inhibitors.
- Individuals at risk for osteoporosis should have their bone status managed according to current clinical practice, and should take adequate vitamin D and calcium supplementation.
- Report any adverse events with proton pump inhibitors to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Data Summary

To date, randomized clinical trials of proton pump inhibitors have not found an increased risk of fractures of the hip, wrist, or spine. These studies are generally six months in duration and there is limited information on effects of higher than recommended doses.

The decision to revise the *Warnings and Precautions* section of the prescription labeling as well as the OTC *Drug Facts* label for proton pump inhibitors is based on FDA's review of the findings from seven published epidemiological studies.[1-7] These studies used claims data from computerized administrative databases to evaluate the risk of fractures of the hip, wrist, and spine in patients treated with proton pump inhibitors compared to individuals who were not using proton pump inhibitors (The findings from these studies are found in the Table below).

In these studies:

- Six reported an increased risk of fractures with the use of proton pump inhibitors [1,2,3,5,6,7].
- Exposure to proton pump inhibitors ranged from a period of 1 to 12 years, depending on the study.
- The emergence of fractures varied among studies; with one study reporting an increase in fractures with use of proton pump inhibitors in the previous year [2] and another study finding an increase after 5 to 7 years of proton pump inhibitor use[3].
- The increased risk of fractures was primarily observed in older individuals.
- Two studies reported an increase in fractures with higher doses of proton pump inhibitors [2,5].
- Two studies reported an increase in fractures with longer duration of use [2,3].
- One study did not find a relationship between proton pump inhibitor use and fractures [4]. This study limited the study population to those without major risk factors for fracture.

FDA does not have access to the data or the protocols for these studies, so our ability to verify that the studies were conducted as described in the original publications is limited. Based on our review of the published articles, the key strengths of these studies are that they appear well-designed, considered the effects of both dose and duration of use of proton pump inhibitors on fracture risk, and used appropriate statistical methods to reduce bias by adjusting for potential factors that are known to be associated with the occurrence of fractures such as age, gender, presence of co-existing conditions and use of co-prescribed medications.

Several study limitations, however, make understanding the clinical relevance of the reported findings difficult to determine. Administrative claims databases do not typically contain information on all potential factors that could influence the relationship between proton pump inhibitors use and fracture risk. These studies were not able to account for missing or incomplete information on family history of osteoporosis, smoking history, weight and height measurements, alcohol use, history of dietary and supplement use (calcium and vitamin D), OTC medication use, presence of digestive diseases, such as ulcers, reasons for proton pump inhibitor use, and recent history of immobility, dizziness, or falls. In addition, in most studies where a possible link with osteoporotic fracture was reported, no information was collected about the timing of proton pump inhibitor use in relation to onset or worsening of osteoporosis.

However, the exact mechanisms for an increased risk of fractures with proton pump inhibitor use are not known. Three epidemiologic studies found no consistent association between chronic proton pump inhibitor use and bone mineral density [6,7,8].

Based on the available data, at this time it is not clear if the use of proton pump inhibitors is the cause of the increased risk of fractures seen in some epidemiologic studies.

To further investigate this issue, the FDA plans to analyze data from several large, long-term, placebo-controlled clinical trials of bisphosphonates (drugs used to prevent fractures) to assess the risk of fractures in women at risk for osteoporosis-related fractures who used or did not use proton pump inhibitors.

FDA is also working with the manufacturers of these products to further study this possible risk. For example, as part of the Dexilant (dexlansoprazole) approval, (January 2009), the manufacturer was required to perform a postmarketing clinical trial to evaluate the effects of dexlansoprazole and esomeprazole on bone homeostasis, including changes in biomarkers of bone formation and bone resorption.The results from this trial are expected at the end of 2011.

In summary, the available data, including findings from several epidemiological studies, suggest a possible increased risk of fractures of the hip, wrist, and spine in patients using proton pump inhibitors. The data suggest that the increased risk may be dependent upon dose, duration of use, or both. At the present time, there is uncertainty about the magnitude of this risk. In light of this uncertainty, when prescribing proton pump inhibitors, healthcare professionals should consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.

Table of epidemiological studies evaluating fracture risk with proton pump inhibitors

Study	Study Time Period	Study Population	Findings related to Proton Pump Inhibitors (PPIs)
Vestergaard 2006	1/1/2000 – 12/31/2000	• 124,655 cases with fractures • 373,962 matched controls • All ages Data source: Denmark health database[1]	PPI use within the last year • Overall fracture risk, Odds Ratio (OR) = 1.18 (95% CI, 1.12–1.43) • Risk of hip fracture, OR = 1.45 (95% CI, 1.28–1.65) • Risk of spine fracture, OR = 1.60 (95% CI, 1.25–2.04) • Risk of forearm fracture, OR = 0.95 (0.82-1.11) • No dose-response relationship seen with PPIs and fracture risk: *(DDD [defined daily doses] were the number of doses in a year)*
Yang 2006	1987 - 2003	• 13,556 cases with fractures • 135,386 matched controls • Ages ≥ 50 years • Data source: U.K./GPRD[2]	• Risk of hip fracture, PPI use > 1 year adjusted Odds Ratio (aOR)± = 1.44 (95% CI, 1.30–1.59) • Risk of hip fracture increased with high-dose PPI use > 1 year: *(dose defined as dose/day, >1.75 doses/day)* aOR = 2.65 (95% CI, 1.80-3.90) • Risk of hip fracture increased with longer duration of PPI use ◦ 1 yr, aOR = 1.22 (95% CI, 1.15-1.30) ◦ 4 yr, aOR = 1.59 (95% CI, 1.39-1.80)
Targownik 2008	1996 - 2004	• 15,792 cases with fractures • 47,289 matched controls • Ages ≥ 50 years • Data source: PHRDR/[3] Manitoba, Canada	• Risk of hip, wrist, spine fractures with PPI use ≥ 7 years adjusted Odds Ratio (aOR) ¥ = 1.92 (95% CI, 1.16–3.18) • Risk of hip fracture increased with longer duration of use ◦ PPI use ≥ 5 years, aOR = 1.62 (95% CI, 1.02–2.58) ◦ PPI use ≥ 6 years, aOR = 2.49 (95% CI, 1.33-4.67) ◦ PPI use ≥ 7 years, aOR = 4.55 (95% CI, 1.68–12.29)

Kaye 2008	1995 - 2005	• 1,098 cases with fractures • 10,923 matched controls • Ages 50 – 70 years • Data source: U.K/GPRD[2]	• Estimated Relative Risk (RR) of hip fracture = 0.9 (95% CI, 0.7–1.11) *(Patients at risk for fracture were excluded from the analysis)* • Risk of hip fracture not detected with increased number of PPI prescriptions
Corley 2010	1995-2007	• 33,752 cases with fractures • 130,471 matched controls • Ages ≥ 18 years • Data source: KPNC/[4] California, USA	• Risk of fracture with ≥ 2 years of PPI use and 1 other risk factor Odds Ratio (OR) = 1.30 (95% CI, 1.21–1.39) ◦ Risk factors: alcohol abuse, arthritis, diabetes, kidney disease, glucocorticoids, cerebrovascular disease, dementia, epilepsy, gait disorder, hemiplegia, psychoses, smoking, visual impairment, anxiolytic use • Risk of fracture increased with higher PPI dose: *(dose = number of pills per day >1.5)* OR = 1.41 (95% CI, 1.21-1.64) • Risk of fracture did not consistently increase with longer duration of use
Yu 2008	Women: 7.6 years mean follow-up Men: 5.6 years mean follow-up	• Women (4,574 non-PPI users and 234 PPI users) • Men (4,920 non-PPI users and 487 PPI users) Ages ≥ 65 years • Data source: MrOS/SOF[5]	• Risk of hip fracture ◦ Women: adjusted Relative Hazard (aRH)£ = 1.16 (95% CI, 0.80-1.67) ◦ Men: aRH = 0.62 (95% CI, 0.26-1.44) • Risk of nonspine fracture ◦ Women: aRH = 1.34 (95% CI, 1.10-1.64) ◦ Men: aRH = 1.21 (95% CI, 0.91-1.62)

Gray 2010	7.8 years, mean follow-up	• 2,831 PPIs users • 127,756 non-PPIs users • Post-menopausal women ages 50 – 79 years • Data source: WHI OS/WHI CT[6]	• Risk of total fractures adjusted Hazard Ratio (aHR) ≠ = 1.25 (95% CI, 1.15-1.36) • Risk of hip fracture, aHR = 1.00 (95% CI, 0.71-1.40) • Risk of spine fracture, aHR = 1.47 (95% CI, 1.18-1.82) • Risk of wrist fracture, aHR = 1.26 (95% CI, 1.05-1.51) • No consistent trend for fracture risk with duration of use

Data Source: 1. Denmark Health Database; 2. United Kingdom, General Practice Research Database; 3. Population Health Research Data Repository (Manitoba, Canada); 4. Kaiser Permanente Northern California; 5. Osteoporosis fractures in Men Study/Study of Osteoporotic Fractures; 6. Women's Health Initiative Observation Study/Women's Health Initiative Clinical Trials

± Adjusted for sex, age, body mass index, medication use (anxiolytics, antidepressants, NSAID/aspirin, thiazide diuretic, antipsychotic, antiparkinsonian, antiseizure, hormone therapy, corticosteroid, thyroxine), health condition (alcoholism, arthritis, stroke, asthma or COPD, dementia, diabetes mellitus, congestive heart failure, impaired mobility, myocardial infarction, peptic ulcer disease, seizure disorder, peripheral vascular disease, visual impairment, current smoker, prior fractures).

¥ Adjusted for income, region of residence, diagnoses (short or long-term diabetes, epilepsy, ischemic heart disease, myocardial infarction, hypertension, arthritis, solid organ transplant, chronic obstructive pulmonary disease, substance use, depression, schizophrenia, dementia), home care use and multiple medications.

£ Adjusted for age, clinic, race, body mass index, alcohol use, exercise, oral or inhaled corticosteroid use, NSAID use, calcium supplement use, osteoporosis medication use, and self-reported health, concurrent weight change, and initial total hip bone mineral density. SOF group is also adjusted for caffeine intake and estrogen use. MrOS group is also adjusted for smoking and history of stomach surgery.

≠Adjusted for age, race/ethnicity, body mass index, enrollment in clinical trial status, indicator for cohort, smoking, physical activity (metabolic equivalent tasks), self-reported health, having a parent who broke a hip after age 40 years, treated diabetes mellitus, history of fracture at 55 years or older, and corticosteroid use, physical function score, history of myocardial infarction or angina, asthma or emphysema, arthritis, stomach or duodenal ulcer, moderate or severe heartburn, osteoporosis, number of psychoactive medications, and use of hormone therapy and bisphosphonates.

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Contact FDA

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