Dear Doctor,

As you are aware, chronic use of Proton Pump Inhibitors (PPIs) has been associated with several side effects, what has received increasing attention from different authorities including FDA. Those side effects are, among others, risk of osteoporotic fractures, hypomagnesemia, decreased absorption of cyanocobalamin and increased risk of *Clostridium difficile* associated diarrhea. Side effects of PPIs are produced, in part, due to alteration in the absorption of calcium, magnesium, iron, vitamin B12 and modification of gastrointestinal microflora.

1.- Food and Drug Administration (FDA) released this safety announcement: ***"Possible Increased Risk of Bone Fractures with Certain Antacid Drugs"*** [1]. In this publication, FDA warns: ***"There is a possible increased risk of fractures of the hip, wrist, and spine if you take certain drugs for heartburn, acid reflux, or ulcers. The drugs belong to a class of medications called proton pump inhibitors (PPIs), which work by reducing the amount of acid in the stomach"***.

FDA announcement was based on a systematic review of seven published studies, six of which reported an increased risk of fractures of the hip, wrist, and spine with the use of PPIs [2-7]. Also, a recent meta-analysis of 11 studies identified an overall odds ratio of 1.30 for all fracture types combined in subjects taking PPIs [8].

An acidic environment in the stomach facilitates the release of ionized calcium from insoluble salts. PPIs increase gastric pH, which may decrease calcium absorption [9]. Studies with calcium carbonate have shown a significant reduction of calcium absorption in patients taking PPIs, due in part to the lower solubility of this salt at high pH [10]. In contrast, **calcium citrate malate** is 9 times more soluble than either citrate or malate alone and 200 to 780 times more soluble than calcium carbonate [11]. In addition, its solubility is not affected by gastric pH.

2.- FDA approved label for all PPIs declare: ***"Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI"***. In a recent review of 10 cases, patients taking PPIs during a mean of 8.3 years developed severe hypomagnesemia (≤0.54 mmol/L) with symptoms including fatigue, unsteadiness, paresthesia, tetany, seizures and cardiac arrhythmias [9].

3.- Approved labels for PPIs also declare: ***"Daily treatment with any acid-suppressing medications over a long period of time may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo-or achlorhydria"***. Vitamin B12 is present in foods bound to proteins, and gastric acid is required for the peptic enzymes, mainly pepsin, to cleave the vitamin B12 from the proteins, enabling its absorption [9]. In short-term studies, various acid suppressants (H2RAs and PPIs) have been reported to decrease the absorption of vitamin B12 from foods, but not from

crystalline vitamin B12 which is not protein bound [9]. **Crystalline methylcobalamin** is an appropriate source of vitamin B12 for patients taking PPIs.

4.- Approved labels for PPIs also declare: ***"Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients."*** The Gastrointestinal tract has three different defense mechanisms: integrity of the membranes and mucous layer, GI microflora, and gastric acidity. Acid suppressive therapy may cause bacterial overgrowth in the upper GI tract and gastric colonization by several pathogen microorganisms including *Clostridium difficile*. **Probiotics** may help maintain a balance between good and harmful bacteria such as *Clostridium difficile*. According to the Cochrane review, [12] probiotics have been shown to be beneficial in the prevention of *Clostridium difficile* associated diarrhea.

5.- Iron: The absorption of iron seems to be markedly increased by gastric acidity. In rats taking a low iron diet, PPI treatment decreased iron absorption. [9] The dissolution and subsequent absorption of non-HEME iron is affected by the suppression of hydrochloric acid. **Iron bisglycinate chelate** is not affected by pH changes between 2 to 6, being bioavailable even under achlorhydria condition. [13]

6.- Vitamin K2 + Vitamin D3: Recently, vitamin K2 has been shown to work synergistically with calcium and vitamin D. When vitamin D is ingested, the body creates more vitamin K2-dependent proteins, the proteins that will move the calcium around. Vitamin K2 has been revealed to be effective in the prevention and treatment of osteoporosis. [14]

Proton Support is a patent pending product that helps you and your patients to reduce the risk of suffering these side effects.

Composition: Calcium (as citrate-malate): 250 mg; Vitamin D3 (as cholecalciferol) 800 IU; Vitamin K (as menaquinone-7): 100 µg; Magnesium (as magnesium oxide): 100 mg; Iron (as Ferrochel® ferrous bisglycinate): 18 mg; Vitamin B12 (as methylcobalamin): 100 µg; *Lactobacillus acidophilus*: 5 Billion CFU; *Lactobacillus casei*: 5 Billion CFU; FOS (fructooligosaccharides): 50 mg; Inulin: 50 mg.

Proton Support contains novel forms of highly soluble calcium and iron, whose absorption does not depend on the gastric pH, which guarantees its bioavailability, even under conditions of gastric acid lack. The proprietary blend or probiotics contained in Proton Support helps maintain a digestive balance, which may be disturbed by the regular use of proton pump inhibitors.

Proton Support contains also vitamin D3 and vitamin K2, which work in tandem to increase bone mineral density, and help to reduce the risk of osteoporosis development due to calcium deficiency.

References:

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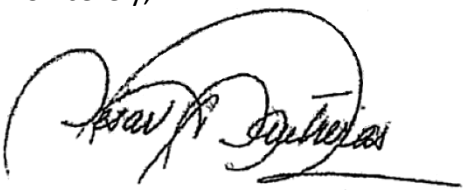
Sincerely,



Cesar Contreras, MD, FACP.
Medical Director
Companion Therapeutics LLC.