Proton pump inhibitors (PPIs) are effective gastric acid inhibitory agents indicated for numbers of gastrointestinal conditions. Nowadays, PPI use is rapid growing due to its availability and lower price that may cause inappropriate prescribing or “off-label” use, especially for long-term treatment. PPIs are generally considered safe and well tolerated for short-term treatment. Nonetheless, recent data have revealed an association between long-term PPI use and wide range of adverse events. Appropriate use or “rational drug use” (RDU) will maximize benefits and minimize risks for patients. Important considerations of proper PPI use include indications, drug interactions, dose, method of administration, duration of treatment, cost, monitoring, and safety. Accepted indications for long-term PPI use consist of maintenance of symptom control in GERD, healing of erosive esophagitis, Barrett’s esophagus, NSAID users at increased risk, antiplatelet agent users with increased risk, and pathological hypersecretory conditions (e.g. Zollinger-Ellison syndrome). Most PPIs are metabolized via hepatic cytochrome P450 enzymes; CYP2C19 and CYP3A4. Thus, potential of drug interactions should be considered before prescribing certain PPIs. Several safety concerns have been associated with long-term PPI use, but few of these concerns demonstrate a causal relationship. The association with acute interstitial nephritis, hypomagnesemia, vitamin B12 deficiency, and small intestinal bacterial overgrowth (SIBO) are likely causative suspected. Bone fractures, Clostridium difficile infection, chronic kidney disease, dementia, and pneumonia related to PPI use are inconsistent with unclear causation. Screening or monitoring of these adverse events is not routinely recommended. Reviewing treatment indications, on-demand therapy, prescribing the lowest effective dose, and transition to histamine2-receptor antagonists (H2RAs) may be strategies to mitigate risks of long-term PPI use.

**Keywords:** Proton pump inhibitor, Side effect, Rational drug use