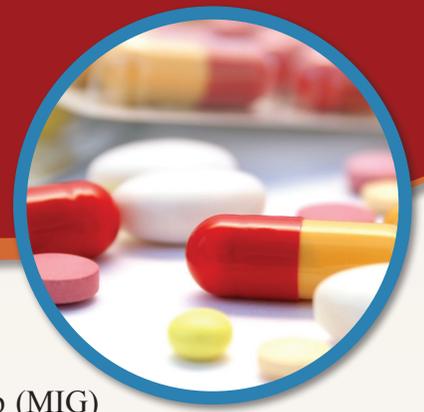


Proton Pump Inhibitors: Use in Adults



The Centers for Medicare & Medicaid Services (CMS), Medicaid Integrity Group (MIG) has identified issues with the utilization of medications in the proton pump inhibitor (PPI) drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed PPIs outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS's goal is to improve quality of care and enhance patient safety by educating providers on the proper use of PPIs in adults.

This fact sheet summarizes for providers the current FDA-approved product labeling for the use of PPI medications in adult patients. After reading this fact sheet, providers should be able to accurately:

- Recall the FDA-approved indications for PPI use in adults and the specific indications for each PPI;
- Recall the FDA-approved dosing options for adults; and
- Describe the adverse reactions of and risks related to long-term use of PPIs.

Overview of Proton Pump Inhibitors

PPIs block the acid-producing enzyme system in the stomach wall and prevent acid production in the stomach. Lack of acid in the stomach prevents ulcer formation; promotes healing of existing ulcers in the esophagus, stomach, and duodenum; and provides symptom relief. PPIs differ in how they are metabolized by the body, how they interact with other medications, and the length of time they are active in the body. However, there is no evidence that one PPI is more effective than another.

FDA-Approved Indications for Proton Pump Inhibitors in Adults

PPIs are used for the prevention and treatment of gastric acid related conditions. The FDA-approved indications for use include:

- Healing of erosive esophagitis (EE);
- Maintenance of healed EE;
- Treatment of gastroesophageal reflux disease (GERD);
- Risk reduction for gastric ulcer (GU) associated with nonsteroidal anti-inflammatory drugs (NSAIDs);
- *Helicobacter pylori* (*H. pylori*) eradication to reduce the risk of duodenal ulcer (DU) recurrence, in combination with antibiotics;
- Pathological hypersecretory conditions, including Zollinger-Ellison (ZE) syndrome; and
- Short-term treatment and maintenance of DUs.



August 2013

The dose and length of therapy are dependent upon the medication and the indication. Not all PPIs are approved for every indication. Please review the document “Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults” for more information.

Lansoprazole and omeprazole are two PPIs that are available without a prescription. Over-the-counter (OTC) PPIs are FDA approved for the treatment of frequent heartburn in patients 18 years old and older. Frequent heartburn is considered when symptoms are experienced at least two times per week.

Treatment Guidelines for Gastroesophageal Reflux Disease

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. Please search “proton pump inhibitors,” or any of the gastric acid related conditions for which a PPI is an indicated treatment, in the AHRQ’s National Guideline Clearinghouse at <http://www.guideline.gov> for information on the available treatment guidelines.

Adverse Reactions and Risks of the Use of Proton Pump Inhibitors in Adults

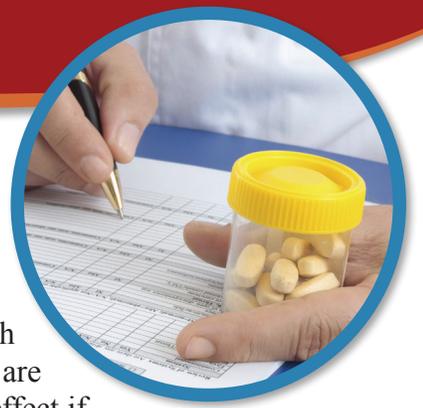
PPIs are generally well tolerated. The most common adverse reactions seen in adults are flatulence, headache, diarrhea, nausea, abdominal pain, and vomiting.[1, 2, 3, 4, 5, 6] The use of PPIs has also been associated with drug interactions, fractures, hypomagnesemia, and *Clostridium difficile*-associated diarrhea (CDAD).

Risk of Drug Interactions

Clinically significant drug interactions with PPIs are rare. Chronic acid suppression can minimize the effectiveness of any medication requiring an acidic environment for absorption. Commonly prescribed medications affected by acid suppression are ampicillin esters, digoxin, atazanavir, ketoconazole, and iron salts.[7]

There is also risk of drug interactions between PPIs and other medications that are metabolized via the cytochrome P450 system. While specific interactions are not well documented, there is substantial evidence regarding an interaction between clopidogrel and omeprazole.[8] Other drug interactions that may be clinically significant are dependent on the specific cytochrome P450 enzyme substrates and the specific PPI. The prescribing information for each PPI provides more detailed information on drug interactions. Search the medication name at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda> on the FDA website to retrieve prescribing information and detailed drug interactions for each PPI medication.





Concomitant Use of Omeprazole with Clopidogrel

Omeprazole reduces the efficacy and ability of clopidogrel's antiplatelet effect, which may increase the risk of a heart attack. Patients at risk for heart attacks or strokes who are given clopidogrel to prevent blood clots may not get the full protective anticlotting effect if they also take omeprazole. In a crossover clinical study, the mean inhibition of platelet aggregation decreased by 39 percent on day 1 and 21 percent on day 5 when omeprazole and clopidogrel were administered together. In another study, results showed that administering the medications 12 hours apart did not prevent this drug interaction.[9] As a result, the FDA recommends avoiding the simultaneous use of omeprazole and clopidogrel.[10] Other medications inhibiting CYP2C19, the drug-metabolizing enzyme, should be avoided in combination with clopidogrel. The FDA notified health professionals of possible interactions between omeprazole and clopidogrel and included the following considerations:

- Separating the time of clopidogrel and omeprazole administration will not reduce this drug interaction;
- Esomeprazole may have a drug interaction with clopidogrel similar to omeprazole; and
- Histamine blockers and antacids have not been shown to interfere with the anticlotting activity of clopidogrel.[11]

In October 2010, the FDA posted a reminder to avoid concomitant use of clopidogrel and omeprazole, emphasizing that the recommendation applied only to omeprazole and not all PPIs.[12]

Risk of Fractures

The FDA requires that labeling for PPIs include safety information about a possible increased risk of fractures of the hip, wrist, and spine. This requirement is based on an FDA review of several epidemiological studies with findings indicating that patients who may bear the highest risk for these fractures received a high dose of a PPI or had a duration of PPI therapy lasting longer than one year. The majority of these studies included individuals 50 years old or older.[13] The FDA requires that a Medication Guide be dispensed with every new or refilled PPI prescription. The Medication Guide informs patients and providers about the risk of bone fractures that may occur when taking a PPI. Links to the Medication Guides can be found at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> on the FDA website.

ACRONYMS

AHRQ	Agency for Healthcare Research and Quality
CDAD	Clostridium difficile-associated diarrhea
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
DU	duodenal ulcer
EE	erosive esophagitis
FDA	U.S. Food and Drug Administration
GERD	gastroesophageal reflux disease
GU	gastric ulcer
MIG	Medicaid Integrity Group
NSAID	nonsteroidal anti-inflammatory drugs
OTC	over the counter
PPI	proton pump inhibitor
ZE	Zollinger-Ellison

Risk of Hypomagnesemia

In March 2011, the FDA published a Drug Safety Communication to inform consumers and health professionals that long-term use of PPIs can cause hypomagnesemia. In 25 percent of patients, magnesium supplementation was not sufficient to correct PPI-induced hypomagnesemia; rather, PPI therapy had to be discontinued. The deficiency did not appear to be dose-related and reappeared after rechallenge with a PPI. The FDA recommends obtaining a serum magnesium level prior to initiation of therapy if a patient is to be on prolonged treatment.[14]

Risk of Clostridium difficile-Associated Diarrhea

On February 8, 2012, the FDA published a Drug Safety Communication to inform patients and providers that PPIs may be associated with an increased risk of CDAD. Symptoms of CDAD include abdominal pain, fever, and watery stools. Patients who take a PPI and develop diarrhea that does not improve should be evaluated for CDAD. Patients with advanced age, certain chronic medical conditions, and patients taking broad spectrum antibiotics are at greatest risk for developing CDAD. The FDA recommends using the lowest dose and shortest duration of PPI therapy possible and recommends advising patients to seek medical attention if they develop symptoms of CDAD.[15] The previously mentioned Medication Guide also informs patients and providers about the risk of CDAD when taking a PPI.

Resources

Please visit <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html> for links to State Medicaid program websites.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on OTC and prescription drugs. Visit <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals> to access drug-related databases, information on drug recalls and alerts, current information on new and generic drug approvals, and information on drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit http://www.ssa.gov/OP_Home/ssact/title19/1927.htm for information on the compendia.



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