



# CIGNA PHARMACY COVERAGE POLICY

*This Coverage Policy should NOT be used for Great-West benefit plans.*

Effective Date ..... 12/15/2008  
Next Review Date.....7/15/2009  
Coverage Policy Number ..... 4005

**Subject Proton Pump Inhibitor Therapy**

## Table of Contents

Coverage Policy .....	1
General Background .....	2
Coding/Billing Information .....	4
References.....	4

## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Policy

**Proton Pump Inhibitor Therapy includes the following drugs:**

- Omeprazole (Prilosec®) – generic
- Lansoprazole (Prevacid®) – formulary / preferred brand
- Pantoprazole (Protonix®) – generic and formulary / preferred brand
- Esomeprazole (Nexium®) – non-formulary / non preferred brand
- Rabeprazole (Aciphex®) – non-formulary / non preferred brand
- Omperazole/ Sodium Bicarbonate (Zegerid®) – non-formulary / non preferred brand

**CIGNA HealthCare covers brand Proton Pump inhibitor Therapy as medically necessary when the following criteria are met:**

- failure, contraindication, or intolerance to **ONE** of the following: omeprazole, pantoprazole, lansoprazole (Prevacid®), or pantoprazole (Protonix®)

**Note: depending upon individual client benefit plan selection, criteria requirements may consist of one of the following criteria options of a Generic First, Generic or Preferred Brand First, or a Dual Requirement of a Generic First and then a Preferred Brand:**

- failure, contraindication, or intolerance to omeprazole **OR** pantoprazole

- failure, contraindication, or intolerance to **ONE** of the following: omeprazole, pantoprazole, lansoprazole (Prevacid<sup>®</sup>), or pantoprazole (Protonix<sup>®</sup>)
  - failure, contraindication, or intolerance to omeprazole **OR** pantoprazole, **AND** failure, contraindication, or intolerance to Lansoprazole (Prevacid<sup>®</sup>), **OR** Pantoprazole (Protonix<sup>®</sup>)
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## General Background

Proton pump inhibitors are highly effective in the management of acid-related diseases, including duodenal ulcer (DU), gastric ulcer (GU), gastroesophageal reflux disease (GERD), erosive esophagitis, hypersecretory syndromes like Zollinger-Ellison, and Helicobacter pylori (H. pylori) infection. There are currently five different proton pump inhibitors (PPIs) available, including esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

These agents are all substituted benzimidazoles that inhibit the final common pathway of gastric acid secretion. The gastric H<sup>+</sup>K<sup>+</sup>ATPase, or gastric acid pump, is the molecular target for the proton-pump inhibitors. This H<sup>+</sup>K<sup>+</sup>ATPase pump is the final common pathway for acid secretion in the stomach. Inhibitors of this pump are the most effective antisecretory agents currently available. The parietal cell is responsible for gastric acid secretion. Hydrochloric acid secretion from the parietal cell is regulated by gastrin, acetylcholine, histamine, and the H<sup>+</sup>K<sup>+</sup>ATPase proton pump. Inhibiting the proton pump is the most efficient means to reduce gastric acid, as it stops both basal and meal-stimulated gastric acid secretion. Proton pump inhibitors irreversibly inhibit the proton pump, and acid production can only be restored through endogenous synthesis of new proton pumps. In order for proton pumps to be inhibited, they must be activated. Proton pumps are maximally activated in the presence of food. In the fasting state, only 10% of the pumps are active. Proton pumps in the resting state escape initial inhibition. Additionally, any proton pumps synthesized after the plasma levels of the PPI fall will not be blocked.

There are differences in both the pharmacokinetics and pharmacodynamics of the PPIs. In general, potency (acid suppression) correlates with the area under the plasma concentration-time curve (AUC). PPIs are acid labile and thus are formulated to avoid contact with acid in the stomach. Esomeprazole, omeprazole and lansoprazole are formulated as enteric-coated granules in a gelatin capsule, while pantoprazole and rabeprazole are enteric-coated delayed-release tablets. Protonation (acidification) of the PPIs appears to be the rate-limiting step in H<sup>+</sup>K<sup>+</sup>ATPase inhibition. The PPIs pKa largely determines the rate at which they are activated. Rabeprazole has the highest pKa and is therefore converted to its active form the fastest. Pantoprazole has the slowest activation. The clinical significance of acid activation is that these drugs should be given 30 to 60 minutes prior to a meal such that the parietal cell is secreting acid when the PPI reaches it.

The PPIs are extensively used in the management of gastroesophageal reflux disease, peptic ulcer disease, hypersecretory syndromes, and Helicobacter pylori infection. The PPIs are superior to the H<sub>2</sub> Receptor Antagonists, (H<sub>2</sub>RAs), in the healing, symptom relief and maintenance therapy of erosive and nonerosive GERD.

The American College of Gastroenterology (ACG) published updated guidelines for the diagnosis and treatment of GERD in 2005. One significant change in these disease management guidelines is the promotion of empiric therapy of GERD without performing endoscopy for patients with uncomplicated disease and no alarm symptoms. These guidelines indicate that the PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. H<sub>2</sub>-antagonists are less effective than the PPIs, but when given in divided doses may be effective in some patients with less severe GERD. Healing rates for esophagitis correlate with the degree and duration of acid suppression. However, there is a poor correlation between the severity and frequency of GERD symptoms and the degree of esophageal injury.

According to a position paper from the American College of Gastroenterology, the PPIs provide symptomatic relief in 83% of patients compared to only 60% with the H<sub>2</sub>RAs. A meta-analysis of 48 randomized, short-term trials showed that the healing rate of omeprazole 40 mg/day was 95% compared

to 81% to ranitidine 600 mg per day, and 60% with ranitidine 300 mg per day. Omeprazole is more effective than ranitidine for treating refractory GERD and in preventing stricture recurrence.

There are 44 studies comparing the PPIs and H<sub>2</sub>-antagonists for GERD. There are 11 studies comparing a PPI to an H<sub>2</sub>-antagonist for empiric treatment of heartburn symptoms and 33 studies comparing a PPI to an H<sub>2</sub>-antagonist for GERD diagnosed via endoscopy. In general, PPI therapy is superior to the H<sub>2</sub>-antagonists. Continuous therapy with the PPIs or H<sub>2</sub>-antagonists has been traditionally used to treat GERD, and the studies comparing the two agents have been focused on endoscopic healing. Recently, more studies have focused on symptom control and patient satisfaction as the primary outcomes instead of endoscopic healing.

Endoscopic healing of GERD for short-term treatment (four to 20 weeks): Fifteen studies reported results on complete heartburn relief at week four. The percentage of patients who were symptom-free at week four in the PPI treated groups ranged from 45% to 95% (mean 68.6%), and the percentage of patients in the H<sub>2</sub>-antagonist treated groups ranged from 12% to 61% (mean 38.5%). Fifteen studies reported endoscopic healing rates after four weeks of treatment. PPI treated patients had healing rates that ranged from 50% to 85% (mean 70%) compared to H<sub>2</sub>-antagonist patients whose healing rates ranged from 21% to 57% (mean 36%). Fourteen studies reported endoscopic healing at eight weeks. Results for the PPI treated groups ranged from 71% to 95% (mean 85%) compared to the H<sub>2</sub>-antagonist groups that ranged from 23% to 78% (mean 50%).

Endoscopic healing of GERD for longer durations of treatment (> six months): Ten studies compare the PPIs and H<sub>2</sub>-antagonists for six months or longer and report results on symptomatic or endoscopic healing. The PPIs were superior to the H<sub>2</sub>-antagonists for preventing relapse and maintaining remission at 12 months in nine studies. Symptomatic remission rates at 12 months for the PPIs ranged from 62% to 72% compared with the H<sub>2</sub>-antagonists, which ranged from 39% to 45%. Endoscopic remission rates at 12 months for the PPIs ranged from 50% to 89% compared to the H<sub>2</sub>-antagonists, which ranged from 9% to 49%. Two studies reported the combined symptomatic and endoscopic remission rates at 12 months; for the PPIs, the rate was 66% to 67% and for the H<sub>2</sub>-antagonists, the rate ranged from 10% to 34%.

Empiric treatment and symptom control: Eleven studies compare a PPI to an H<sub>2</sub>-antagonist for empiric treatment of heartburn symptoms. Six studies evaluate the short-term use of PPI and H<sub>2</sub>-antagonist therapy in patients with uninvestigated heartburn. Five studies evaluate the long-term administration ( $\geq$  six months) of PPIs and H<sub>2</sub>-antagonists in patients with uninvestigated heartburn symptoms. In the short-term trials, two studies compared a PPI (pantoprazole or lansoprazole) to an H<sub>2</sub>-antagonist (ranitidine). The percentage of patients who were symptom-free at week four in the PPI group was 68%, and in the ranitidine group it was 43%.

Two studies compared step-up or step-down regimens. Continuous PPI therapy is superior to either step-up or step-down therapy using both PPIs and H<sub>2</sub>-antagonists. The PPIs or H<sub>2</sub>-antagonists are similar for time to relapse after stopping therapy. In one study, the relapse rate after stopping PPI therapy was 78%, and in the H<sub>2</sub>-antagonist group it was 75%. There is only one study that evaluated patients who took the same drug and dose continuously for one year. Pantoprazole was superior to ranitidine for complete symptom control at four weeks, six months, and one year. There was a significantly higher study withdrawal rate in the ranitidine group (46%) compared to the pantoprazole group (34%),  $p=0.04$ , due to lack of efficacy.

Intermittent or on-demand therapy: Alternative dosing schedules for acid suppressive medications have been evaluated in an effort to maximize patient quality of life and minimize costs. Four studies compare a PPI to an H<sub>2</sub>-antagonist for intermittent or on-demand therapy. Two studies showed no difference between on-demand treatment groups at six or 12 months of therapy. The third study compared continuous and on-demand esomeprazole to continuous ranitidine in patients with uninvestigated GERD. Continuous therapy was better than on-demand esomeprazole, and both groups were superior to ranitidine. The fourth study compared daily omeprazole, daily ranitidine, and three times per week omeprazole in patients with esophagitis. Daily omeprazole was superior to intermittent omeprazole and ranitidine. There was no difference between intermittent omeprazole and ranitidine.

There are no significant differences in the healing rates between the various PPIs. The Food and Drug Administration approved doses for treating GERD are: esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg. There are two published studies comparing esomeprazole to omeprazole. In both of these studies, endoscopic healing rates were higher with esomeprazole. There are at least nine reported studies comparing omeprazole and lansoprazole. Of those comparing omeprazole 20 mg with lansoprazole 30 mg, there was no significant difference in endoscopic healing rates at four and eight weeks. In three of the studies, there was a trend for earlier symptom relief with lansoprazole. Both omeprazole 20 mg and lansoprazole 30 mg are superior to lansoprazole 15 mg for the healing of esophagitis. Three studies comparing omeprazole 20 mg and pantoprazole 40 mg have shown no difference in healing rates or symptom relief of esophagitis. Also, no studies have shown a difference in healing rates of esophagitis between omeprazole 20 mg and rabeprazole 20 mg.

A review of the clinical efficacy and safety for all of the PPIs indicate they are similar. There are minor pharmacokinetic differences between the agents; however, these differences are not clinically meaningful. Each of the PPIs has different FDA-labeled indications, but they can all be used for acid suppression and *H. pylori* eradication. The PPIs also differ with regard to their drug interaction profiles; however, the only clinically significant interaction with all of the PPIs is with omeprazole and warfarin. This interaction is manageable with increased INR (International Normalized Ratio) monitoring. Because pantoprazole and rabeprazole tablets cannot be crushed or made into a suspension formulation, these two PPIs are not well suited for pediatric patients or patients with swallowing difficulties.

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## Coding/Billing Information

**Note:** This section is not in use.

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