

## Therapeutic Class Overview Proton Pump Inhibitors

### Therapeutic Class

- Overview/Summary:** The proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available.<sup>1</sup> Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K<sup>+</sup>) for hydrogen ions (H<sup>+</sup>) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid.<sup>1</sup> Approximately 70 to 80% of the proton pumps will be active following a meal.<sup>2</sup> As a result, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in three to four days.<sup>1-3</sup>

There are currently a number of PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant<sup>®</sup>, Dexilant SoluTab<sup>®</sup>), esomeprazole (Nexium<sup>®</sup>, Nexium<sup>®</sup> 24HR), lansoprazole (Prevacid<sup>®</sup>, Prevacid SoluTab<sup>®</sup>, Prevacid<sup>®</sup> 24HR), omeprazole (Prilosec<sup>®</sup>, Prilosec OTC<sup>®</sup>, Zegerid<sup>®</sup>, Zegerid OTC<sup>®</sup>), pantoprazole (Protonix<sup>®</sup>) and rabeprazole (Aciphex<sup>®</sup>, Aciphex Sprinkle<sup>®</sup>), of which esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, pantoprazole and rabeprazole are available generically in at least one dosage strength or formulation. Esomeprazole strontium was Food and Drug Administration (FDA)-approved in August 2013 without a proprietary name; it was approved based on bioequivalence of esomeprazole strontium 24.65 mg and 49.3 mg delayed-release capsules to esomeprazole magnesium 20 and 40 mg delayed-release capsules. No other reference to esomeprazole strontium will be made in this review as all data is similar between esomeprazole magnesium and esomeprazole strontium.<sup>4-17</sup> In addition, lansoprazole, esomeprazole and omeprazole are available over-the-counter in a variety of formulations. All of the PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small and the clinical significance has not been established.<sup>3</sup> When administered in equivalent dosages the PPIs have generally demonstrated a comparable efficacy to one another. Dexlansoprazole, the enantiomer of lansoprazole, is the first PPI with a dual delayed-release formulation designed to provide two separate releases of medication. It contains two types of enteric-coated granules resulting in a concentration-time profile with two distinct peaks: the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. In addition, it can be taken regardless of meals.<sup>16</sup> All approved indications listed in Table 1 are for the prescription products unless otherwise specified.

**Table 1. Current Medications Available in the Therapeutic Class<sup>4-17</sup>**

| Generic (Trade Name)                          | Food and Drug Administration Approved Indications   | Dosage Form/Strength                       | Generic Availability |
|---|---|--|----------------------|
| Dexlansoprazole (Dexilant <sup>®</sup> )      | Treatment of erosive esophagitis.<br>Maintaining healing of erosive esophagitis.<br>Treatment of symptomatic gastroesophageal reflux disease. | Delayed-release capsule:<br>30 mg<br>60 mg | -                    |
| Esomeprazole magnesium (Nexium <sup>®</sup> ) | Treatment of erosive esophagitis.<br>Maintaining healing of erosive esophagitis. <sup>†</sup>   | Delayed-release capsule:<br>20 mg          | -                    |

| Generic (Trade Name)  | Food and Drug Administration Approved Indications   | Dosage Form/Strength  | Generic Availability |
|---|---|---|----------------------|
|   | <p>Treatment of symptomatic gastroesophageal reflux disease.<sup>†</sup></p> <p><i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence.<sup>†§</sup></p> <p>Risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer.<sup>†</sup></p> <p>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.<sup>†</sup></p>  | <p>40 mg</p> <p>Delayed-release suspension:</p> <p>2.5 mg</p> <p>5 mg</p> <p>10 mg</p> <p>20 mg</p> <p>40 mg</p>                  |                      |
| Esomeprazole sodium (Nexium IV <sup>®</sup> )                           | Treatment of erosive esophagitis.   | Powder for injection:<br>20 mg<br>40 mg   | ✓                    |
| Lansoprazole (Prevacid <sup>®</sup> *, Prevacid SoluTab <sup>®</sup> *) | <p>Treatment of erosive esophagitis.</p> <p>Maintaining healing of erosive esophagitis.</p> <p>Treatment of symptomatic gastroesophageal reflux disease</p> <p><i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence.<sup>§</sup></p> <p>Treatment of active duodenal ulcers.</p> <p>Maintenance of healing duodenal ulcers.</p> <p>Treatment of active, benign gastric ulcer.</p> <p>Healing of nonsteroidal anti-inflammatory drug-associated gastric ulcer.</p> <p>Risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer.</p> <p>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.</p> <p>Treatment of frequent heartburn for up to 14 days.<sup>¶</sup></p> | <p>Delayed-release capsule:</p> <p>15 mg</p> <p>30 mg</p> <p>Delayed-release disintegrating tablet:</p> <p>15 mg</p> <p>30 mg</p> | ✓                    |
| Omeprazole (Prilosec <sup>®</sup> *)                                    | <p>Treatment of erosive esophagitis.</p> <p>Maintaining healing of erosive esophagitis.</p> <p>Treatment of symptomatic gastroesophageal reflux disease.</p> <p><i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence.<sup>§</sup></p>   | Delayed-release capsule:<br>10 mg<br>20 mg<br>40 mg   | ✓                    |

| Generic (Trade Name)                           | Food and Drug Administration Approved Indications  | Dosage Form/Strength  | Generic Availability |
|--|--|---|----------------------|
|  | Treatment of active duodenal ulcers.<br>Treatment of active, benign gastric ulcer.<br>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.   |   |                      |
| Omeprazole magnesium (Prilosec®*)              | Treatment of erosive esophagitis.<br>Maintaining healing of erosive esophagitis.<br>Treatment of symptomatic gastroesophageal reflux disease.<br><i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence. <sup>§</sup><br>Treatment of active duodenal ulcers.<br>Treatment of active, benign gastric ulcer.<br>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.<br>Treatment of frequent heartburn for up to 14 days. <sup>¶</sup> | Delayed-release suspension:<br>2.5 mg<br>10 mg  | ✓                    |
| Omeprazole with sodium bicarbonate (Zegerid®*) | Treatment of symptomatic gastroesophageal reflux disease.<br>Treatment of active, benign gastric ulcer.<br>Treatment of active duodenal ulcers.<br>Maintaining healing of erosive esophagitis.<br>Risk reduction of upper gastrointestinal bleeding in critically ill patients. <sup>  </sup><br>Treatment of frequent heartburn for up to 14 days. <sup>¶</sup>   | Capsule:<br>20 mg/1100<br>40 mg/1100<br><br>Powder for oral suspension:<br>20 mg/1680<br>40 mg/1680                         | ✓                    |
| Pantoprazole (Protonix®*, Protonix IV®)        | Treatment of erosive esophagitis.<br>Maintaining healing of erosive esophagitis.<br>Treatment of symptomatic gastroesophageal reflux disease. <sup>‡</sup><br>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.   | Delayed-release suspension:<br>40 mg<br><br>Delayed-release tablet:<br>20 mg<br>40 mg<br><br>Powder for injection:<br>40 mg | ✓                    |
| Rabeprazole (Aciphex®*)                        | Treatment of erosive esophagitis   | Delayed-release tablet:   | ✓                    |

| Generic (Trade Name) | Food and Drug Administration Approved Indications   | Dosage Form/Strength                                    | Generic Availability |
|----------------------|---|---|----------------------|
|                      | Maintaining healing of erosive esophagitis.<br>Treatment of symptomatic gastroesophageal reflux disease.<br><i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence. <sup>§</sup><br>Treatment of active duodenal ulcers<br>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. | 20 mg<br><br>Delayed-release capsules:<br>5 mg<br>10 mg |                      |

OTC=over the counter

\*Generic available in at least one dosage form or strength.

†Oral formulations only.

‡Intravenous formulation indicated for treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis.

§As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).

|| Zegerid<sup>®</sup> powder for oral suspension only.

¶Over-the-counter formulation only.

### Evidence-based Medicine

- Clinical trials have consistently demonstrated that PPIs are highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.<sup>18-43</sup>
- Meta-analyses and head-to-head trials have demonstrated comparable healing rates, maintenance of healing or symptomatic relief of GERD between lansoprazole, omeprazole, pantoprazole and rabeprazole.<sup>18-23</sup>
- The results of several meta-analyses and clinical trials show that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole at four and eight weeks; however, the differences between treatments were generally small and the clinical significance of such differences has not been established.<sup>18,20,24-29</sup>
- Dextansoprazole has been shown to significantly improve control of heartburn symptoms, nighttime heartburn symptoms, and healing of erosive esophagitis compared to placebo.<sup>30-32</sup> Head to head studies comparing dextansoprazole to other PPIs are limited.
- Meta-analyses and head-to-head trials comparing PPIs for the treatment of peptic ulcer disease with *Helicobacter pylori* have shown comparable rates of eradication when paired with comparable antibiotic regimens.<sup>33-41</sup> One small trial reported higher eradication rates for patients treated with esomeprazole compared to pantoprazole.<sup>42</sup> In a recent meta-analysis by McNicholl et al, both esomeprazole- and rabeprazole-based *Helicobacter pylori* regimens were considered to be more effective with regard to eradication rate compared to traditional PPIs (lansoprazole, omeprazole and pantoprazole).<sup>43</sup>

### Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Acid suppression is the mainstay of GERD therapy and PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. Histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) given in divided doses may be effective in some patients with less severe GERD; however, they are less effective compared to the PPIs.<sup>44,45</sup>
  - Twice-daily PPI therapy is recommended in patients with an inadequate symptom response to once-daily PPI therapy. There is no evidence of improved efficacy by adding a nocturnal dose of an H<sub>2</sub>RA to twice-daily PPI therapy.<sup>44,45</sup>

- In the management of dyspepsia, treatment with a PPI for four to eight weeks as an initial therapy option is recommended in dyspeptic patients  $\leq 55$  years of age without alarm features (e.g., bleeding, dysphagia, family history of gastrointestinal cancer, weight loss) and where *Helicobacter pylori* prevalence is low ( $<10\%$ ).<sup>46</sup>
- The recommended primary therapies for *Helicobacter pylori* infection include a PPI, clarithromycin and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70 to 85%. Alternatively, a regimen of a PPI or H<sub>2</sub>RA, bismuth, metronidazole and tetracycline (bismuth-based quadruple therapy) for 10 to 14 days produces eradication rates of 75 to 90%.<sup>47</sup>
- The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once-daily dosing.<sup>47</sup>
- Attempts to eliminate esophageal acid exposure (PPIs in doses greater than once-daily, esophageal pH monitoring to titrate PPI dosing, or antireflux surgery) for the prevention of esophageal adenocarcinoma is not recommended.<sup>48</sup>
- Other Key Facts:
  - Currently, esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, pantoprazole and rabeprazole are available generically in at least one dosage strength or formulation.<sup>4</sup>
  - Furthermore, lansoprazole, esomeprazole, omeprazole, omeprazole magnesium and omeprazole with sodium bicarbonate are available over-the-counter in a variety of formulations.<sup>4</sup>
  - Dexlansoprazole was formerly known by the brand name Kapidex<sup>®</sup> but has since been changed to Dexilant<sup>®</sup>.<sup>49</sup>

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