Proton Pump Inhibitor Drug List Selection

Selection of proton pump inhibitors (PPIs) for our Drug List was influenced by similar efficacy rates and safety profiles among the agents.
Proton pump inhibitors (PPIs) are most commonly used for prevention and treatment of gastroesophageal reflux disease (GERD). Other FDA-approved indications include treatment of erosive esophagitis, Helicobacter pylori (H. pylori) infection, active duodenal or gastric ulcers, and non-steroidal anti-inflammatory drug (NSAID)-associated ulcers.  

The PPIs are considered comparable to each other in efficacy due to similar clinical outcome improvements reported in clinical trials.

As you know, the goals of GERD therapy include:
- Controlling symptoms
- Healing esophagitis
- Managing or preventing complications
- Maintaining GERD remission

We critically evaluated studies with outcomes reflecting these goals. These outcomes, along with safety profile information and meta-analyses of PPI use in pregnancy, were the primary measures used in our Pharmacy & Therapeutics Process to select PPIs for our Drug List.

Clinical review
Our clinical review focused on the efficacy and safety of PPIs for eradication rates of H. pylori, healing rates for reflux esophagitis and symptom control of GERD. 

### Summary of selected evidence for PPIs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Products compared</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori eradication rates*</td>
<td>omeprazole triple therapy* vs. lansoprazole triple therapy</td>
<td>75% vs. 76%</td>
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<tr>
<td></td>
<td>omeprazole triple therapy vs. Aciphex triple therapy</td>
<td>78% vs. 81%</td>
</tr>
<tr>
<td></td>
<td>omeprazole triple therapy vs. Nexium triple therapy</td>
<td>88% vs. 89%</td>
</tr>
<tr>
<td></td>
<td>lansoprazole triple therapy vs. Aciphex triple therapy</td>
<td>81% vs. 86%</td>
</tr>
</tbody>
</table>

Conclusion: No statistically significant differences in H. pylori eradication rates were reported for omeprazole compared with lansoprazole, Aciphex or Nexium use over seven to 10 days (P-value = not significant for all comparisons). Rates were also similar for lansoprazole compared with Aciphex.

| Reflux esophagitis healing rates*    | Nexium 40 mg vs. lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg | Four weeks: 76% vs. 70% P-value = .0001 |
|                                      | Study 1: Nexium 40 mg: 85% vs. lansoprazole 30 mg: 79% vs. pantoprazole 40 mg | Eight weeks: 89% vs. 85% P-value = .0001 |

Conclusion: Based on one meta-analysis, Nexium provides a modest benefit over lansoprazole, omeprazole or pantoprazole use in healing reflux esophagitis after four and eight weeks of therapy. The absolute risk reduction for reflux esophagitis healing rates is 4% to 6% with Nexium versus other PPIs. To heal one patient, 17 to 25 patients need to be treated with Nexium, instead of an alternative PPI, for four to eight weeks.

| Reflux esophagitis healing rates*    | Dexilant 60 mg vs. lansoprazole 30 mg | Study 1: Dexilant 60 mg: 65% vs. lansoprazole 30 mg: 79% P-value < .05 |
|                                      | Study 2: Dexilant 60 mg: 87% vs. lansoprazole 30 mg: 85% P-value = not significant |

Conclusion: Use of Dexilant 60 mg shows similar or modestly-improved benefit in healing erosive esophagitis compared with lansoprazole 30 mg over eight weeks, as measured by crude rate analysis. The absolute risk reduction for reflux esophagitis healing rates is 6% with Dexilant 60 mg versus lansoprazole. Seventeen patients need to be treated with Dexilant, instead of a lansoprazole, for eight weeks to heal one additional patient.

| GERD symptom control*               | lansoprazole 30 mg vs. Nexium 40 mg | Days or nights with heartburn: 36% vs. 38% to 38% vs. 39% P-value = not significant |

Conclusion: No statistically significant difference in GERD symptom control was reported for lansoprazole compared with Nexium use over two weeks (P-value = not significant).

*Triple therapy combines a PPI with clarithromycin and amoxicillin or metronidazole.
PPIs have a good overall safety profile and are well tolerated by the majority of patients. However, overuse of these medications is a concern. Judicious use of PPIs is advised to decrease the risk of serious events potentially associated with PPI use. There are conflicting reports about several possible PPI-related safety concerns, highlighted below.

### Possible PPI-related safety issues

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium difficile-associated disease (CDAD)</td>
<td>Results of case-control studies suggest an increased risk with PPI use, while other articles state there is no difference in risk.</td>
</tr>
<tr>
<td>Fracture risk</td>
<td>Three large database reviews and an analysis of a prospective study found an increase in osteoporosis-related fractures following one or more years of PPI therapy. A fourth database review found no increase in the risk of hip fractures in subjects without major risk factors for osteoporosis who received any PPI prescription, compared with those with no PPI prescription.</td>
</tr>
<tr>
<td>Drug interaction with Plavix (clopidogrel)</td>
<td>The FDA recently issued a public health advisory regarding the drug interaction between Plavix (clopidogrel), omeprazole, and Nexium. There is potential for increased risk of cardiovascular events due to CYP2C19 inhibition by omeprazole and Nexium. CYP2C19 converts Plavix to an active metabolite which inhibits platelet aggregation. Avoid concomitant use of these medications. The FDA does not have enough information about drug interactions between Plavix and other PPIs to advise on their concomitant use.</td>
</tr>
</tbody>
</table>

All PPIs are rated as pregnancy category B, with the exception of omeprazole-containing products (omeprazole, Prilosec, Zegerid) and Prevpac, which are pregnancy category C. The most documented data and clinical experience during pregnancy are with use of omeprazole.

Based on critical appraisal of the clinical data, the Clinical Review Committee determined that all PPIs are safe, effective and comparable to each other at equivalent doses. The PPIs are considered comparable in their efficacy due to similar clinical outcome improvements reported in clinical trials. These agents are also well tolerated by the majority of patients.

### Value assessment

Internal analyses revealed the most prescribed PPIs are:
- Nexium
- Generic omeprazole
- Prevacid

The least costly PPIs for <health plan name> include:
- Generic lansoprazole
- Nexium
- Generic omeprazole
- Generic pantoprazole

### Tier placement

Final placement of the PPI products on our Drug List was determined based on the clinical review conclusions, followed by considerations from the value assessment, to make evidence-based, informed tier placement decisions. The lower, moderate and higher tiers of our PPI coverage are outlined below.

### PPI coverage on the Drug List

<table>
<thead>
<tr>
<th>Lower Member Cost</th>
<th>Moderate Member Cost</th>
<th>Higher Member Cost</th>
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</thead>
<tbody>
<tr>
<td>lansoprazole 30 mg capsules*</td>
<td>Nexium</td>
<td>Dexilant (formerly Kapidex)</td>
</tr>
<tr>
<td>omeprazole capsules*</td>
<td>Aciphex</td>
<td>Apocynin suspension</td>
</tr>
<tr>
<td>pantoprazole tablets</td>
<td>Prevacid solutab</td>
<td>Protonix injection &amp; suspension</td>
</tr>
<tr>
<td>Generic lansoprazole</td>
<td>Generic omeprazole</td>
<td>Prevpac*</td>
</tr>
<tr>
<td>Nexium</td>
<td>Generic pantoprazole</td>
<td>Zegerid†</td>
</tr>
</tbody>
</table>

* Lansoprazole 15 mg capsules, omeprazole 20 mg tablets and Zegerid 20 mg/1100 mg capsules are available over the counter.
† Prevpac contains lansoprazole, amoxicillin and clarithromycin and is only indicated for _H. pylori_ eradication.
‡ Zegerid contains omeprazole and sodium bicarbonate.

For more information about our Pharmacy & Therapeutics Process, visit empireblue.com, select “Providers & Facilities” on the left and click “Enter.” From the “Provider Home” page, choose “Plans & Benefits” at the top of the page and click “Pharmacy Management.” Select the “Pharmacy & Therapeutics” link and then “Learn more about our Drug List selection process.”
References


