For the **GenRx Closed & Medicaid** formularies, step therapy will target Nexium suspension packets. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **GenRx Open & Health Insurance Marketplace** formularies, step therapy will target ALL brand PPIs and generic omeprazole/sodium bicarbonate. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **FlexRx Closed** formulary, step therapy will target Nexium suspension packets. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **FlexRx Open** formulary, step therapy will target ALL brand PPIs and generic omeprazole/sodium bicarbonate. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

This program is a GenRx Standard and FlexRx Standard Step Therapy Program.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
<th>Aciphex (^a) (\text{rabeprazole b) tablet})</th>
<th>Dexilant (^c) (\text{dexlansoprazole capsule})</th>
<th>Dexilant Solutab (^c) (\text{dexlansoprazole oral disintegrating tablet})</th>
<th>Nexium (^d) (\text{esomeprazole , \text{strontium capsule, suspension}})</th>
<th>Prevacid (^e) (\text{lansoprazole, capsule, suspension, disintegrating tablet})</th>
<th>Prilosec (^g) (\text{omeprazole , \text{capsule, suspension}})</th>
<th>Prilosec (^g) (\text{omeprazole , \text{sodium bicarbonate capsule, suspension}})</th>
<th>Protonix (^h) (\text{pantoprazole , \text{tablet, suspension}})</th>
<th>Zegerid (^i) (\text{omeprazole, sodium bicarbonate capsule, suspension}})</th>
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<tbody>
<tr>
<td>Healing of Erosive Esophagitis</td>
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<td>✓</td>
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<td>✓</td>
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<tr>
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<td>✓</td>
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<tr>
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<tr>
<td>FDA Approved Indications</td>
<td>Aciphex (^b) (r)abeprazole (^n) tablet</td>
<td>Dexilant (d)exlansoprazole capsule</td>
<td>Dexilant (d)exlansoprazole oral disintegrating tablet</td>
<td>Nexium (^b) esomeprazole (^n) capsule, (^c)eprazole (^n) suspension</td>
<td>Prevacid (^b) (^n) Lansoprazole (^c) capsule, (^c)eprazole (^n) suspension, (^c)eprazole (^n) disintegrating tablet</td>
<td>Prilosec (^b) (^n) Omeprazole (^c) capsule, (^c)eprazole (^n) suspension</td>
<td>Protonix (^b) (^n) Pantoprazole (^c) tablet, (^c)eprazole (^n) suspension</td>
<td>Zegerid (^b) (^n) Omeprazole (^c) sodium (^n) bicarbonate capsule, (^c)eprazole (^n) suspension</td>
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<td>Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome</td>
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<tr>
<td>Symptomatic Gastroesophageal Reflux Disease/ Erosive Esophagitis in Pediatrics</td>
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<td>✓ (Nexium suspension)</td>
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<tr>
<td>Reduction of Risk of Upper GI Bleeding, Critically Ill Patients.</td>
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</table>

\(^a\) – Lansoprazole 15 mg, omeprazole 20 mg, and omeprazole 20 mg/sodium bicarbonate 1100 mg are available as nonprescription (over the counter or OTC) products; \(^b\) – available as generics.

**Dosing:** All available proton pump inhibitors (PPIs) are available as delayed release products except for omeprazole/sodium bicarbonate (Zegerid). Dosing of PPIs is once daily for most conditions per the prescribing information. More frequent daily dosing may be used in pathologic hypersecretory conditions (Zollinger-Ellison), *Helicobacter pylori* (*H. pylori*) eradication, and patients failing treatment with once daily PPI.

**Maximum Daily Dosage:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciphex</td>
<td>20 mg once daily (adult, adolescent); 5 mg, 10 mg once daily (based on weight, children 1 to 11 years) 20 mg twice daily for <em>H. pylori</em> 100 mg once daily or 60 mg twice daily for Zollinger-Ellison Syndrome</td>
</tr>
<tr>
<td>Dexilant</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>Esomeprazole strontium</td>
<td>24.65 – 49.3 mg once daily 49.3 mg twice daily for Zollinger-Ellison Syndrome</td>
</tr>
<tr>
<td>Nexium</td>
<td>40 mg once daily (adult, adolescent); 20 mg once daily (children ≤11) 2.5 mg, 5 mg, 10 mg (based on weight, children 1 month to 1 year) 40 mg twice daily for Zollinger-Ellison Syndrome</td>
</tr>
<tr>
<td>Prevacid/lansoprazole</td>
<td>30 mg once daily; 30 mg twice or three times daily for <em>H. pylori</em> 60 mg once daily for Zollinger-Ellison Syndrome</td>
</tr>
<tr>
<td>Prilosec/omeprazole</td>
<td>40 mg once daily (adult), 20 mg once daily (children) 40 mg once daily or 20 mg twice daily for <em>H. pylori</em> 120 mg three times daily for Zollinger-Ellison Syndrome</td>
</tr>
<tr>
<td>Protonix/pantoprazole</td>
<td>40 mg once daily</td>
</tr>
</tbody>
</table>
**CLINICAL RATIONALE**

Medical Letter Treatment Guidelines (2014) on Peptic Ulcer Disease (PUD) and GERD suggest PPIs inhibit a higher percentage of 24-hour acid secretion and heal peptic ulcers more rapidly than H2RAs. PPIs are more effective than H2RAs in relieving symptoms of GERD and in healing erosive esophagitis. PPIs have a longer duration of action vs. H2RAs, allowing for once-daily dosing in most patients. Unlike H2RAs, tolerance does not occur with PPIs. All PPIs appear similar in efficacy.

- **PUD:** Eradication of H. pylori can promote healing and prevent recurrences of both duodenal and gastric ulcers. Quadruple therapy (including a PPI or H2RA) is more effective vs. triple therapy for eradication of H. pylori and is now recommended as initial treatment. If the underlying cause is identified and addressed (e.g., eradicating H. pylori or stopping the NSAID), long-term anti-secretory therapy may not be needed. For patients with idiopathic peptic ulcers, however, long-term use of a PPI is recommended.

- **GERD:** Medications that suppress gastric acid are the mainstay of therapy. Choice of drug depends on the severity and frequency of symptoms and the presence or absence of esophagitis. For mild, intermittent symptoms, as needed therapy with an H2RA or antacid may be sufficient. For more severe symptoms or erosive esophagitis on endoscopy, a PPI is recommended.

- **Non erosive reflux disease (NERD):** Antacids and H2RAs may be adequate for symptom relief in patients with mild NERD. While these agents have similar peak potency, antacids have a faster onset of action and H2RAs have a longer duration of action (up to 10 hours). PPIs are used less frequently for symptom relief due to delayed onset of action. Patients with more severe NERD may require more frequent dosing or continuous therapy with an H2RA or a PPI. PPIs have been shown to maintain remission of symptoms and are generally preferred. For patients with severe nocturnal symptoms, the addition of an H2RA at bedtime to a twice-daily PPI may be effective.

The American College of Gastroenterology (ACG) Guidelines for the Diagnosis and Management of GERD (2013) includes the following recommendations:

- A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a proton pump inhibitor (PPI) is recommended in this setting.

- An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis.

- Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett’s esophagus.

- For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy.

- There are no major differences in efficacy between the different PPIs.

- PPIs are safe in pregnant patients if clinically indicated.

- In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief.

The American Academy of Pediatrics guidelines for treatment of gastroesophageal reflux (2013) suggest PPIs are uniquely able to inhibit meal-induced acid secretion and have a capacity to maintain gastric pH >4 for a longer period of time than H2RAs. These properties contribute to higher and faster healing rates for erosive esophagitis with PPI therapy vs. H2RA therapy. Unlike H2RAs, acid suppression ability of PPIs has not been observed to diminish with chronic use. A guideline algorithm recommends education and lifestyle changes, along with 2 week PPI therapy.
for children/adolescents with chronic heartburn. If patients improve after 2 weeks of PPI, they may continue another 8-12 weeks. 

PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients with GERD of any of the available medical treatments. The PPIs may be considered therapeutically interchangeable because of their comparable pharmacologic properties, clinical efficacy and safety profiles. Consistent results of clinical trials in patients with duodenal ulcers, gastric ulcers, GERD, hypersecretory conditions, and other acid-related disorders strongly suggest that there is a class effect of PPIs for these disorders, although differences in dosage formulations and drug interactions may occasionally influence choice of PPI in individual cases.

The ACG Guideline for prevention of NSAID related ulcer complications recommends patients requiring NSAID therapy who are at high risk (e.g., prior ulcer bleeding) should receive alternative therapy, or if anti-inflammatory treatment is necessary, a cyclooxygenase (COX)-2 inhibitor, and co-therapy with misoprostol or high-dose PPI.

A review (2014) suggests surgery plays a key role in the treatment of Zollinger-Ellison syndrome, an endocrinopathy characterized by gastrin-secreting tumors responsible for causing multiple recurrent and often refractory ulcers in the GI tract. Although medical therapy with PPIs has virtually eliminated the need for acid-reducing surgical procedures in patients with this condition, resection of the primary lesion is still indicated in most cases. Today, as PPIs are highly effective and well tolerated and have few long-term negative side effects even with chronic use at high doses, these medications have become the first-line therapy for patients with hypergastrinemia.

A prospective pharmacoepidemiologic cohort study evaluated the incidence of hospital-acquired pneumonia in patients exposed and unexposed to acid-suppressive medication (n=63,878); hospital-acquired pneumonia occurred in 2219 admissions (3.5%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid suppressive medication than in the unexposed group (4.9% vs 2.0%; odds ratio [OR], 2.6 95% CI, 2.3-2.8). The adjusted OR of hospital-acquired pneumonia in the group exposed to acid suppressive medication was 1.3 (95% CI, 1.1-1.4). A population-based cohort study examined the association between the use of acid suppressive drugs and the occurrence of community acquired pneumonia (CAP; n=364,683). The incidence rates of pneumonia in non-acid suppressive drug users and acid suppressive drug users were 0.6 and 2.45 per 100 person-years, respectively. The adjusted relative risk for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% CI, 1.36-2.62).

The interaction of PPIs and clopidogrel is believed to be due to decreased CYP2C19 conversion of clopidogrel to the active metabolite. Omeprazole has been implicated in the interaction due to the moderate inhibition of CYP2C19. Avoid using omeprazole concomitantly or 12 hours apart with clopidogrel. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established.

In February 2012 the FDA issued a safety warning to healthcare professionals as well as patients that PPIs may be associated with increased risk of C diff associated diarrhea (CDAD). "FDA has reviewed reports from the FDA's Adverse Event Reporting System (AERS) and the medical literature for cases of CDAD in patients undergoing treatment with PPIs. Many of the adverse event reports involved patients who were elderly, had chronic and/or concomitant underlying medical conditions, or were taking broad spectrum antibiotics that could have predisposed them to developing CDAD. Although these factors could have increased their risk of CDAD, the role of PPI use cannot be definitively ruled out in these reviewed reports."
The FDA also reviewed 28 observational studies and stated that most studies found the risk of *C. diff* infection or disease, including CDAD, ranged from 1.4 to 2.75 times higher among patients with PPI exposure compared to those without PPI exposure.

Acute interstitial nephritis has been observed in patients taking PPIs. This may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction.  

Daily long-term use of PPIs (>3 years) may lead to malabsorption or a deficiency of cyanocobalamin. Hypomagnesemia has also been reported rarely with prolonged treatment with PPIs.  

Most adverse outcomes associated with PPIs occurred among patients who received long-term therapy. Minimizing the duration of therapy by reviewing periodically a patient’s need for acid-suppressive therapy could reduce the risk of adverse outcomes.  

For additional clinical information see Prime Therapeutics Formulary Chapter 7.4C Proton Pump Inhibitors.

**REFERENCES**


Proton Pump Inhibitors (PPIs) Step Therapy

OBJECTIVE
The intent of the Proton Pump Inhibitors (PPIs) Step Therapy (ST) program is to encourage the use of the cost-effective preferred generic PPIs prior to the use of brand PPIs and nonpreferred generic PPIs, and to accommodate for use of nonpreferred brand or generic PPIs when preferred generic PPIs cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for nonpreferred PPIs will be reviewed when patient-specific documentation has been provided. Only oral dosage forms of the PPIs are included in this program.

TARGET DRUGS (all brands and nonpreferred generics, determined by client and benefit structure)
- Aciphex® (rabeprazole)a
- Dexilant™ (dexamethasone)
- Esomeprazole Strontium® (brand agent)
- Nexium® (esomeprazole)a
- Prevacid® (lansoprazole)a
- Prilosec® (omeprazole)a
- Protonix® (pantoprazole)a
- Zegerid® (omeprazole/sodium bicarbonate)a
  a - available as a generic; designated target or prerequisite as determined by client

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Brand and Nonpreferred PPIs will be approved when ANY ONE of the following is met:
1. The patient’s medication history includes use of a preferred prescription strength generic PPI in the past 90 days
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to one of the preferred generic PPI prerequisites

Length of approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.