



Proton Pump Inhibitors Step Therapy Criteria

Program may be implemented with the following options:

- Option One - 1 step, preferred generic PPI before brand or nonpreferred generic PPI
- Option Two - 1 step, preferred PPI (generic or brand) before nonpreferred PPI (generic or brand)
- Option Three - 2 step, preferred generic PPI before preferred brand PPI and both preferred generic PPI and preferred brand PPI before any nonpreferred PPI (brand or generic)

For BlueCross BlueShield of New Mexico and BlueCross BlueShield of Oklahoma, Option 2 (one-step, preferred PPI before nonpreferred PPI) will apply.

For BlueCross BlueShield of Illinois and BlueCross BlueShield of Texas plans implementing this program *prior to 2/1/2010*, Option 1 (one-step, preferred generic PPI [omeprazole or lansoprazole] before brand PPIs or nonpreferred generic PPIs) will apply.

For BlueCross BlueShield of Illinois and BlueCross BlueShield of Texas plans implementing this program *on or after 2/1/2010*, Option 2 (one-step, preferred PPI before nonpreferred PPI) will apply.

For Atmos Energy with BlueCross BlueShield of Texas, Option1 (one step, preferred generic PPI [omeprazole, lansoprazole, or pantoprazole] before brand PPIs) will apply as of 1-1-10.

Brand	generic	Dosage Form
Aciphex [®]	rabeprazole	delayed-release tablets
Kapidex [™]	dexlansoprazole	delayed-release capsules
Nexium [®]	esomeprazole	delayed-release capsules, delayed-release oral suspension
Prevacid [®]	lansoprazole ^b	delayed-release: capsules ^a , orally disintegrating tablets, oral suspension
Prilosec [®]	omeprazole ^b	delayed-release capsules ^a delayed-release oral suspension
Protonix [®]	pantoprazole	delayed-release tablets ^c , delayed-release oral suspension
Zegerid [®]	omeprazole/sodium bicarbonate	immediate-release capsules, powder for oral suspension

a - Indicates generic availability

b - Indicates over-the-counter availability

c - Indicates possible generic availability; marketed generics will be included in quantity limit program and as targets in the step therapy program

FDA APPROVED INDICATIONS^{1-6,28,30}

The following table summarizes the FDA-approved indications of the available proton pump inhibitors.

Table 1. Proton Pump Inhibitors Treatment Indications^{1-6,28,30}

FDA Indications	Nexium	Prevacid	Omeprazole ER (Prilosec)	Omeprazole IR (Zegerid)	Protonix	Aciphex	Kapindex
Healing of Erosive Esophagitis	✓	✓	✓	✓	✓	✓	✓
Maintenance of Healing of Erosive Esophagitis	✓	✓	✓	✓	✓	✓	✓
Symptomatic Gastroesophageal Reflux Disease	✓	✓	✓	✓	✓	✓	✓
<i>H. pylori</i> eradication in combination with antibiotics	✓	✓	✓			✓	
Short-Term Treatment of Active Gastric Ulcer		✓	✓	✓			
Short-Term Treatment of Active Duodenal Ulcer		✓	✓	✓		✓	
Maintenance of Healed Duodenal Ulcer		✓					
Healing of NSAID-Associated Gastric Ulcer		✓					
Risk Reduction of NSAID-Associated Gastric Ulcer	✓	✓					
Risk Reduction of Upper Gastrointestinal Bleeding in Critically Ill Patients				✓			
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	✓	✓	✓		✓	✓	
Symptomatic Gastroesophageal Reflux Disease/Erosive Esophagitis in children	✓ ^a	✓ ^a	✓ ^b			✓ ^c	

a - Indicated for children ages 1-17 b - Indicated for children ages 1-16 c – Indicated for adolescents ages 12 and above

RATIONALE FOR SELECTING PROTON PUMP INHIBITORS FOR STEP THERAPY

The proton pump inhibitors (PPIs) step therapy program encourages the use of cost-effective preferred generic PPIs before brand and nonpreferred generic PPIs and also preferred brand PPIs prior to the use of nonpreferred brand PPIs for the indications listed in Table 1. The program has been developed with the opportunity to implement one of three options:

- 1) a one-step edit that requires therapy with a preferred generic PPI before any brand PPI or nonpreferred generic PPI;
- 2) a one-step edit that requires therapy with a preferred PPI (generic or brand) before a nonpreferred PPI (generic or brand); or
- 3) a two-step edit that requires use of a preferred generic PPI before use of a preferred brand PPI, and therapy with both a preferred generic PPI and a preferred brand PPI when a nonpreferred PPI (brand or generic) is requested.

PPIs are used to treat peptic ulcers (duodenal and gastric), gastroesophageal reflux disease (GERD), and drug-induced ulcers. For peptic ulcer disease, PPIs are given with antibiotics to eradicate *Helicobacter pylori* (*H. pylori*), the bacteria that cause ulcers.^{1-6,28} All of the available FDA-approved proton pump inhibitors (PPIs) are potent acid suppressing medications.^{1-6,28} Studies evaluating the endpoints of in vitro pH and acid suppression suggest minimal differences between agents.⁷ The PPIs may be considered therapeutically interchangeable because of their identical mechanisms of action and comparable clinical efficacy and safety profiles.⁸

A 2001 meta-analysis compares the effectiveness of all five PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) in the healing of reflux esophagitis.⁹ In this analysis esomeprazole at a dose of 40 mg daily demonstrated higher healing rates than omeprazole 20 mg daily at four and eight weeks.⁹ The other PPIs were equivalent in esophageal healing. This meta-analysis did not include two unpublished studies (studies 173 and 174) submitted to the FDA in Nexium's New Drug Application. These studies found no significant difference between esomeprazole and omeprazole. Based on the results from all four controlled trials comparing esomeprazole to omeprazole that were submitted to the FDA, the FDA review summary concludes that "a superiority claim of esomeprazole (Nexium) over omeprazole is not supported by either the comparison of esomeprazole 20 mg to omeprazole 20 mg or the comparison of esomeprazole 40 mg versus esomeprazole 20 mg."¹⁰

The efficacy of the PPIs in preventing esophagitis relapse has been compared in at least four randomized controlled trials.¹¹⁻¹⁴ In these trials no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole were found at six months to five years of treatment.¹¹⁻¹⁴ In one of the trials esomeprazole 20 mg daily compared to lansoprazole 15 mg daily demonstrated a higher percentage of patients administered esomeprazole remained in remission (83 percent versus 74 percent, respectively).¹⁴ The dose of lansoprazole used in this study for the maintenance of healed esophagitis was lower than is typically used and the dose comparison is not considered equipotent.

The Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease from the American College of Gastroenterology¹⁵ state that “All of these agents [omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole] have been demonstrated to control GERD symptoms and heal esophagitis when used at prescription doses.”¹⁵

In studies comparing PPIs for the treatment of duodenal ulcers only minimal differences have been found in outcomes assessed at two and four weeks.⁷ Trials of lansoprazole versus omeprazole indicated greater healing at two weeks with lansoprazole but at four weeks in all trials there was no difference in healing.¹⁶⁻¹⁸ No difference in healing rates were demonstrated in trials comparing omeprazole versus pantoprazole¹⁹ or omeprazole versus rabeprazole²⁰ although in this study symptoms resolved sooner for patients treated with rabeprazole.²⁰ In the few studies comparing PPIs for the treatment of gastric ulcers there were minimal differences between agents at assessments done at six and eight weeks.²¹⁻²³

A Cochrane Collaboration meta-analysis examined randomized controlled trials of PPIs for treatment of peptic ulcer bleeding.²⁹ This analysis showed that treatment with PPIs consistently reduced the rate of rebleeding after an episode of ulcer bleeding and also reduced the requirement for surgical treatment. The authors found that regular to high-dose (usually oral) PPI treatment likely promoted ulcer healing among patients without high-risk endoscopic stigmas. No distinction among PPIs was made.²⁹

Proton pump inhibitors have been used successfully in combination therapy regimens with antibiotics for the eradication of *H. pylori*.¹⁻⁴ In two meta-analyses, no differences in *H. pylori* eradication or cure rates among omeprazole, lansoprazole, and pantoprazole were demonstrated.^{24,25} The recent American Gastroenterological Association (AGA) Technical Review on Evaluation of Dyspepsia²⁶ recommends triple therapy (PPI plus amoxicillin plus clarithromycin) for 7, 10, and 14 day regimens as first-line therapy for *H. pylori* eradication. Further, the AGA recommends a PPI plus metronidazole plus bismuth plus tetracycline as second-line treatment. No differentiation among PPIs is made.²⁶

Head-to-head comparisons of PPIs for short term treatment show very low withdrawal due to adverse events, and there were no differences among them.²⁷ The adverse event profiles of the individual agents appear similar and the most frequently reported adverse events (occurring in greater than or equal to one percent of patients) are headache, diarrhea, abdominal pain, and nausea.^{1-6,27,28}

The only contraindication for the PPIs is a known hypersensitivity to the agent. They should be used with caution in patients with severe hepatic disease.^{1-6,28} Omeprazole is a pregnancy category C agent while the other PPIs are pregnancy category B medications. PPIs are not recommended for therapy in breast-feeding mothers.^{1-6,28}

All of the PPIs cause significant increases in gastric pH, which may alter the bioavailability of drugs whose absorption is pH-dependant such as ketoconazole, iron salts, and ampicillin.^{1-6,28} There have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving PPI and warfarin concomitantly.^{1-6,28}

PPIs are metabolized by the hepatic cytochrome P450 enzyme system and may alter drug metabolism by induction or inhibition of the cytochrome P450 enzymes.^{1-6,28} Omeprazole has differential affinity for selected P450 enzymes and the greatest potential to cause drug interactions. Overall, there are few clinically relevant drug interactions with the PPIs that involve the CYP450 isoenzymes, and none have been reported for pantoprazole and rabeprazole.^{1-6,28}

The Oregon Health Resources Subcommittee Report on Proton Pump Inhibitors (Final Report, Update #4, July 2006)²⁷ concludes that “the evidence does not demonstrate a clinical difference in efficacy to justify selection of any PPI as clinically superior to the other drugs in the class. This includes consideration of comparative effectiveness and incidence and nature of adverse events between omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. There are no clinically demonstrable differences amongst the PPIs whether treatment is for GERD, peptic ulcer, non-steroidal

ulcer, duodenal ulcer, or eradication of *Helicobacter Pylori*. No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.²⁷ In addition, this subcommittee agreed by consensus that "Based on uncontrolled studies in healthy adults, omeprazole may have more interactions with other drugs than newer PPIs, but monitoring for needed dose adjustments is the only action required."²⁷

Four of the available PPI agents have established safety and effectiveness in pediatric populations less than 18 years of age: Omeprazole delayed-release in the age group 1 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis;^{4,28} and Prevacid and Nexium in the age group 1 year to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis.^{2,3} AcipHex is currently labeled to treat symptomatic GERD and erosive esophagitis in children aged 12 to 17.¹ There are no adequate and well-controlled studies in pediatric patients with Zegerid (omeprazole/ sodium bicarbonate).⁶

ELECTRONIC EDIT

The overall process for step therapy requires that another drug or drugs be tried in a designated previous time period before the claim drug. The patient must have evidence of the applicable drug-specific edit(s) in the patient's prescription drug history. If the patient does not meet the step therapy criteria, then the system will reject with a message indicating that prior authorization is necessary. The PA criteria for approval would then be applied to requests submitted by the patient's practitioner for evaluation.

The intent of the initial PPI step therapy edit is to electronically identify patients and automatically pay for drug claims for a nonpreferred PPI if the patient has a prior medication history of one preferred PPI within a 90-day look back period or two preferred PPIs within a 180-day look back period, depending on the option implemented. The 90-day search period was chosen to capture the most recent or current therapy for one preferred agent; the 180-day search period is longer to review claims history for two preferred therapies. The claims system is designed to identify and count any prerequisite drug claim with a days supply that overlaps into the 90-day or 180-day look back period. If applied step therapy requirements are not met, a Point of Sale message stating that a Prior Authorization (PA) is required will accompany the claim rejection. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

Patients who are currently receiving therapy with a nonpreferred PPI will be allowed continuation of therapy without meeting the above edit requirements if a claim for the nonpreferred PPI is identified within 90 days prior to the new claim. The claims system is designed to identify any claim with a days supply that ends within the 90-day look-back parameter.

Specifics for each option are detailed below.

Option 1. One-Step Edit – Preferred Generic PPI before Brand or Nonpreferred Generic PPI

The implementation of this option encourages the use of a cost-effective preferred generic PPI prior to use of any brand or nonpreferred generic PPI. In order for a claim for a brand or nonpreferred generic PPI to pay automatically, the patient must have medication history of a previous claim for a preferred generic PPI (GPI 492700*****, multi-source code Y, set up at the drug or GPI 10 level; for example, generic omeprazole with GPI 4927006000**** or generic lansoprazole with GPI 4927004000****, both multi-source code Y) [NOTE: as of November 11, 2009, the preferred generic agents are generic omeprazole (GPI 4927006000****, multi-source code Y) and generic lansoprazole (GPI4927004000****, multi-source code Y)] within 90 days prior to the current brand or nonpreferred generic PPI claim [as of November 11, 2009, these agents include generic pantoprazole (GPI 4927007010****, multi-source code Y) and all brand PPIs (GPI 4927**** and 499960****, multi-source code M, N, O)]. If the patient has met this requirement, the requested brand or nonpreferred generic PPI agent will be paid automatically at the applicable copayment under the patient's current prescription drug benefit. If a preferred generic PPI is not found, the Point of Sale message will be returned to the pharmacy stating the step is not met and prior authorization is required. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

Option 2. One-Step Edit - Preferred PPI (Generic or Brand) before Nonpreferred PPI (Generic or Brand)

The implementation of this option encourages the use of a cost-effective preferred PPI (generic or brand) prior to use of any nonpreferred PPI (generic or brand). In order for a claim for a nonpreferred PPI (generic or brand) to pay

automatically, the patient must have medication history of a previous claim for a preferred PPI [as of November 11, 2009, the preferred agents include generic omeprazole (GPI 4927006000****, multi-source code Y), generic lansoprazole (GPI4927004000****, multi-source code Y), and brand Nexium (GPI 49270025****, multi-source code M, N, O)] within 90 days prior to the current nonpreferred PPI claim [as of November 11, 2009, the nonpreferred agents include generic pantoprazole (GPI 4927007010****, multi-source code Y) and all OTHER brand PPIs (GPI 4927**** and 499960****, multi-source code M, N, O)]. If the patient has met this requirement, the requested nonpreferred PPI agent will be paid automatically at the applicable copayment under the patient's current prescription drug benefit. If a preferred PPI is not found, the Point of Sale message will be returned to the pharmacy stating the step is not met and prior authorization is required. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

Option 3. Two-Step Edit – Preferred Generic PPI before Preferred Brand PPI, and BOTH Preferred Generic PPI and Preferred Brand PPI before Nonpreferred PPI (Brand or Generic)

The implementation of this option encourages the use of a cost-effective preferred generic PPI prior to use of *preferred* brand PPI agents, and the use of both a preferred generic PPI and a preferred brand PPI prior to use of a *nonpreferred* PPI (brand or generic). This step edit option has been designed as two edits; one for *preferred* brand PPIs and one for *nonpreferred* PPIs (brand or generic). In order for a claim for a *preferred* brand PPI to pay automatically, the patient must have medication history of a previous claim for a preferred generic PPI (GPI 492700****, multi-source code Y, set up at the drug or GPI 10 level; for example, generic omeprazole with GPI 4927006000**** or generic lansoprazole with GPI 4927004000****, both multi-source code Y) within 90 days prior to the current brand PPI claim. In order for a claim for *nonpreferred* PPI (brand or generic) to pay automatically, the patient must have medication history of both a previous claim for a preferred generic PPI (GPI 492700****, multi-source code Y, set up at the drug or GPI 10 level; for example, omeprazole with GPI 4927006000**** or generic lansoprazole with GPI 4927004000****) and a claim for a preferred brand PPI within 180 days prior to the new claim for a nonpreferred PPI (brand or generic). If the patient has met the requirements defined above, the requested preferred brand PPI or nonpreferred PPI (brand or generic) will be paid automatically at the applicable copayment under the patient's current prescription drug benefit. If the step therapy edit is not met, a Point of Sale message will be returned to the pharmacy stating the step is not met and prior authorization is required. The *Prior Authorization (PA) Criteria for Approval* would then be applied to requests submitted by the patient's practitioner for evaluation.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the PA Criteria for Approval is to ensure that patients who have been unable to tolerate the preferred PPI agent(s) or have not had adequate response to one of these agents have the option of treatment with another PPI. Approval will be given to patients who have a history of use and failure outside of the 90 and 180 day look-back periods or outside of the current benefit plan. A nonpreferred agent may also be approved if the patient has tried the required preferred PPI(s) and discontinued due to allergy, intolerance, or contraindication to the agent or if the physician has submitted documentation to support the use of the nonpreferred PPI in the patient. Patients who are currently receiving therapy with a nonpreferred PPI will be allowed continuation of therapy.

One-Step Edit (Option 1 or Option 2) – Preferred PPI (Generic and/or Brand) before Nonpreferred (Generic and/or Brand) PPI

Initial and Renewal Evaluation

1. Has the PPI criteria been implemented with a one-step option (Option 1 or Option 2)?
If yes, continue to 2. If no, go to appropriate criteria question set.
2. Has the patient been previously treated with the requested nonpreferred PPI?
If yes, approve for 12 months. If no, continue to 3.
3. Has the patient tried and failed at least one preferred PPI?
If yes, approve for 12 months. If no, continue to 4.
[As of November 11, 2009, the preferred Option 1 agents are generic omeprazole and generic lansoprazole. As of November 11, 2009, the preferred Option 2 agents include generic omeprazole, generic lansoprazole, and brand Nexium.]
4. Does the patient have an allergy, contraindication, or intolerance to one or more of the preferred PPIs?
If yes, approve for 12 months. If no, deny.

Two-Step Edit (Option 3) – Preferred Generic PPI before Preferred Brand PPI and BOTH Preferred Generic PPI and Preferred Brand PPI before Nonpreferred PPI (Brand or Generic)

Initial and Renewal Evaluation

1. Has the PPI criteria been implemented with a two-step option (Option 3)?
If yes, continue to 2. If no, go to appropriate criteria question set.
2. Has the patient been previously treated with the requested nonpreferred PPI?
If yes, approve for 12 months. If no, continue to 3.
3. What drug is requested?
 - a. Preferred generic PPI
 - b. Preferred brand PPI
 - c. Nonpreferred PPI (brand or generic)If a, review is not necessary; claim should pay. If b, continue to 4. If c, continue to 6
4. Has the patient tried and failed at least one preferred *generic* PPI?
If yes, approve for 12 months. If no, continue to 5.
5. Does the patient have an allergy, contraindication, or intolerance to at least one preferred generic PPI?
If yes, approve for 12 months. If no, deny.
6. Has the patient tried and failed at least one preferred *generic* PPI?
If yes, continue to 8. If no, continue to 7.
7. Does the patient have an allergy, contraindication, or intolerance to at least one preferred generic PPI?
If yes, continue to 8. If no, deny.
8. Has the patient tried and failed at least one preferred *brand* PPI?
If yes, approve for 12 months. If no, continue to 9.
9. Does the patient have an allergy, contraindication, or intolerance to at least one preferred brand PPI?
If yes, approve for 12 months. If no, deny.

SUMMARY

Step therapy electronic edits are designed to identify patients electronically by their medication history. Claims for drugs specified in the step edit that would otherwise require prior authorization will pay automatically for these identified patients. The Proton Pump Inhibitor (PPI) Step Therapy edit allows for automatic payment of claims for brands or nonpreferred generics after preferred generics, (one-step option); nonpreferred brand or generic PPIs after preferred brand or generic PPIs (one-step option); or nonpreferred brands or generics after BOTH preferred generics and preferred brands (two-step option) when the patient's medication history indicates prior use of the required agents, bypassing the manual PA process. Patients who are currently receiving therapy with a nonpreferred PPI will be allowed continuation of therapy. The PA process provides a member-specific review process where practitioner provided patient-specific parameters are taken into consideration and are reviewed by a physician. The step therapy protocol for PPIs optimizes the utilization of cost-effective agents for the individual benefit plan.

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Document History

Original Prime Standard approved by UMC 11/2003

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Administration revision to remove Zegerid 03/2006

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Mid-year Administrative Addition, Client Specific Criteria (addition of generic lansoprazole; revision textbox with clarification of option 1 and 2 for IL, TX) 01/2010

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