



PROTON PUMP INHIBITORS

Preauthorization Criteria for Approval

Medications and Dosage Forms Included in Criteria

Generic Name	Brand Name	Dosage Form(s)
Dexlansoprazole	Kapidex™	Delayed-release capsules
Esomeprazole	Nexium®	Delayed-release capsules, delayed-release oral suspension
Lansoprazole ^{†, ‡}	Prevacid® Prevacid® SoluTab™	Delayed-release capsules ^{†, ‡} , delayed-release oral suspension, delayed-release orally disintegrating tablets
Omeprazole ^{†, ‡}	Prilosec®	Delayed-release capsules
Omeprazole/sodium bicarbonate	Zegerid®	Capsules, powder for oral suspension
Pantoprazole [†]	Protonix®	Delayed-release tablets, delayed-release oral suspension*
Rabeprazole	Aciphex®	Delayed-release tablets

[†] Generics available

[‡] Over-the-counter (OTC) products available

* No generic products available

FDA Approved Indications

All proton pump inhibitor (PPI) medications listed above are approved for the following conditions:^{1-6,36}

- Symptomatic Gastroesophageal Reflux Disease (GERD)
- Healing of erosive esophagitis
- Maintenance of healing of erosive esophagitis

Other FDA approved indications are specified in the table below.¹⁻⁶

TABLE

Indications	Omeprazole	Aciphex	Pantoprazole	Lansoprazole	Nexium	Zegerid
<i>H. pylori</i> eradication in combination with antibiotics to reduce the risk of duodenal ulcer disease	X	X		X	X	
Short-term treatment of active benign gastric ulcer	X			X		X
Short-term treatment of active duodenal ulcer	X	X		X		X
Maintenance of healed duodenal ulcer				X		
Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome	X	X	X	X	X	
Reduce the risk of NSAID-associated gastric ulcer				X	X	
Healing of NSAID-associated gastric ulcer				X		
Reduce the risk of upper gastrointestinal bleeding in critically ill patients						X

	Omeprazole	Aciphex	Pantoprazole	Lansoprazole	Nexium	Zegerid
Indications						
Pediatrics						
Treatment of symptomatic gastroesophageal reflux disease and erosive esophagitis:						
1-17 years of age				X	X	
1-16 years of age	X					
Short-term treatment of GERD in adolescent patients 12 years and older		X				

NSAID = non-steroidal anti-inflammatory drug; *H. pylori* = *Helicobacter pylori*

Description

The proton pump inhibitor (PPI) preauthorization program is intended to optimize the utilization of cost-effective medications in the PPI class. Based on available medical literature there is little evidence that there is a difference in efficacy and safety among the different PPIs. Therefore, the PPI preauthorization program utilizes a protocol where patients must have tried and failed 3 of the 4 formulary agents prior to receiving a non-formulary agent. An electronic claim edit will review the history of the patient's prescription record for a 30 days supply of at least 3 of the 4 formulary PPIs. The edit protocol utilizes electronic prescription claims history to identify those patients that meet the criteria and automatically adjudicates the claim for the non-formulary agents specified in the program.

Criteria

1. Has the patient tried and failed 3 of the 4 formulary PPI agents (generic omeprazole, generic pantoprazole, generic lansoprazole, and Aciphex[®])?
If yes, approve for 3 years.
If no, continue to 2.
2. Does the patient have any contraindications to the formulary PPI agents (generic omeprazole, generic pantoprazole, generic lansoprazole, and Aciphex[®])?
If yes, approve for 3 years.
If no, continue to 3.
3. Are there other clinical considerations that would require a non-formulary PPI agent?
If yes, please explain.
If no, deny.

Rationale

The proton pump inhibitor (PPI) class is used to treat a variety of gastrointestinal conditions and diseases that includes, but not limited to: gastroesophageal reflux disease (GERD), healing and maintenance of healing of erosive esophagitis.^{1-6,36} Other approved indications vary by product and are summarized in the Table (on pages 1 and 2). The medications in the PPI class are effective suppressors of gastric acid secretion^{1-6,36} and according to a review on the class there are little differences in potency.⁷

The agents in the PPI class are all indicated for and have demonstrated effectiveness in treating symptomatic GERD and healing esophagitis.^{1-6,8,36} Numerous studies have been conducted comparing the available PPIs in their ability to treat symptomatic GERD, and heal and maintain erosive esophagitis.⁹⁻¹⁶ A review conducted examining the PPI class for treatment of reflux esophagitis showed that esomeprazole provided higher healing rates compared to omeprazole at 4 and 8 weeks, whereas pantoprazole, rabeprazole, and lansoprazole showed no difference when compared to omeprazole.¹⁷ The studies using esomeprazole as a treatment option versus omeprazole 20mg¹² and lansoprazole 30mg¹³ demonstrated significantly greater efficacy for esomeprazole in treating erosive esophagitis. This

is in contrast to studies 173 and 174 submitted to the FDA included in the Nexium[®] New Drug Application (NDA).¹⁸ These studies demonstrated no significant difference in erosive esophagitis healing between esomeprazole 40mg and omeprazole 20mg (study 173), and esomeprazole 20mg and omeprazole 20mg (study 174).¹⁸ Supported by these results the FDA concluded esomeprazole is not superior to omeprazole and a claim of such is unjustified.¹⁸ A Cochrane Collaboration review concluded that there was no statistically significant difference in healing of reflux esophagitis of the different PPI medications when given in equivalent dosage.¹⁹ The American College of Gastroenterology has formerly stated in their practice guidelines that all of the available medications (omeprazole, pantoprazole, rabeprazole, lansoprazole, and esomeprazole) “have been demonstrated to control GERD symptoms and to heal esophagitis when used at prescription dosages.”⁸

The studies comparing PPIs in the treatment of gastric ulcer have provided evidence of small differences between the PPIs.^{7,20-22} These studies included comparisons between lansoprazole and omeprazole²⁰, pantoprazole and omeprazole²¹, and rabeprazole and omeprazole.²² Similar studies have been conducted examining the efficacy of the different PPIs in the treatment of duodenal ulcers. These studies have shown little differences between the PPIs under study.²³⁻²⁸ In the studies examining lansoprazole versus omeprazole no differences in healing rates were shown at 4 weeks.²³⁻²⁵ In the studies comparing pantoprazole to omeprazole no differences in healing rates were seen at 2 weeks²⁷ and 4 weeks.²⁶⁻²⁷ One study has examined the comparison of rabeprazole to omeprazole and no differences in healing rates was noted at weeks 2 and 4.²⁸

Some of the available PPIs have been shown to eradicate *Helicobacter pylori* (*H. pylori*) when used in combination with antibiotics.¹⁻⁴ Meta-analyses conducted have shown no differences between the studied PPIs (omeprazole, pantoprazole, and lansoprazole) and have suggested combination regimen therapy cure rates of upwards to 85%.²⁹⁻³⁰ Current *H. pylori* management guidelines published by the American College of Gastroenterology have stated that primary treatment regimens should include “a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H₂RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10-14 days.”³¹ The PPI class was stated generally and no individual products were differentiated in the statement.³¹

A recent Cochrane Collaboration review examined the clinical effect of PPIs in the treatment of peptic ulcer bleeding.³² The review determined that mortality due to ulcer bleeding was not decreased in patients receiving PPI therapy, however, PPIs significantly reduced the rate of rebleeding and the need for surgery.³² The dosages of PPIs used were considered standard to high-dose, however, the intent of the analysis was not a comparison in different dosing among the PPI agents so no conclusion can be drawn. The authors were aware of head-to-head studies of different PPI agents, but no conclusion can be made on the difference in efficacy of the medications if there is any.

No available PPI is FDA approved to treat or prevent Barrett’s esophagus, however, their use is common in patients diagnosed with the disease. Research is currently underway to determine, prospectively, if acid suppression prevents cancer.³³ According to the American College of Gastroenterology Practice Guidelines on Barrett’s esophagus, the goal of acid suppression is to control reflux symptoms and most patients can be controlled with PPIs.³³

The available PPIs have demonstrated high tolerability in short- and long-term clinical trials.^{1-6,36} The most common adverse effects shown in these clinical trials have affected the central nervous and/or gastrointestinal systems. This includes headache, diarrhea, and abdominal pain.¹⁻⁶ No head-to-head trials have been conducted examining the differences in adverse effects and short-term head-to-head trials have shown no differences among the different PPIs in this regard.³³

All available PPIs are metabolized hepatically through cytochrome P450 enzymes.^{1-6,36} With the exception of omeprazole, the PPI class has limited clinically relevant drug-drug interactions.^{1-6,36} Omeprazole has been shown to prolong the elimination of diazepam, warfarin, phenytoin, and drugs metabolized through oxidation in the liver.^{4,6} For most PPIs, postmarketing reports have shown increases in the International Normalized Ratio (INR) and prothrombin time in patients on a PPI and warfarin concomitantly.^{1-6,36} Most recently, the FDA has commented on the interaction between omeprazole (and

possibly esomeprazole) and clopidogrel where the combination should be avoided if possible.³⁷ This interaction is based on the inhibitory nature omeprazole plays on CYP2C19 which is responsible for the conversion of clopidogrel to its active metabolite.³⁷ Due to profound and long-lasting inhibition of gastric acid secretion, theoretically, PPIs may interfere with absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).^{1-6,36} PPIs are not recommended to be used concomitantly with atazanavir.^{1-6,36} According to the Drug Class Review on PPIs by the Oregon Evidence-based Practice Center, “based on primarily uncontrolled studies in healthy subjects, omeprazole has more drug interactions than the newer drugs. However, the numbers of drugs with clinically significant interactions are few and monitoring for needed dose adjustments is the only action required.”³⁴

PPIs are contraindicated in patients with a known hypersensitivity to the particular medication.^{1-6,36} Zegerid is contraindicated in patients with metabolic alkalosis and hypocalcemia and should be used with caution in patients with Bartter’s syndrome, hypokalemia, respiratory alkalosis, and acid-base balance disorders due to Zegerid containing sodium bicarbonate.⁶ With the exception of omeprazole (pregnancy category C), all PPIs are listed with a pregnancy category B.^{1-6,36} For nursing mothers, a decision should be made to discontinue breast feeding or discontinue the medication, taking into account the importance of the drug to the mother.^{1-6,36}

Three PPI products have been approved for use in the pediatric population. The use of esomeprazole and lansoprazole for short-term treatment of GERD and lansoprazole for the short-term treatment of erosive esophagitis have been approved for use in children 1-17 years of age.²⁻³ The use of omeprazole has been approved for use in children 1-16 years of age 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 Zegerid contains omeprazole along with sodium bicarbonate, however, this combination has not been studied in patients younger than 18 years of age.⁶

A PPI drug class review conducted by the Veterans Health Administration Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel concluded “the PPIs may be considered for therapeutic interchange because of their comparable pharmacologic properties and clinical efficacy and safety profiles.”³⁵ In addition, the conclusion stated, “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.”³⁵ Furthermore, a Drug Effectiveness Review Project conducted by the Oregon Evidence-based Practice Center at Oregon Health & Science University summarized a review of the PPI class stating “In general, there is very little evidence that there are any important differences in the effectiveness or safety of the five PPIs in the general population, or in relevant subgroups.”³⁴

The formulary medications are those medications considered the most cost-effective by Blue Cross and Blue Shield of Nebraska (BCBSNE). The cost-effective evaluation takes prescription benefit design, utilization, member contribution, and drug cost into consideration. In most cases, formulary status will position those medications considered most cost-effective. For the PPI class of medications, BCBSNE has selected the following agents as formulary:

- omeprazole
- pantoprazole
- lansoprazole
- Aciphex[®]

All other PPI agents are considered non-formulary.

The process of preauthorization requires that 3 of the 4 formulary PPI medications be tried for a specific quantity prior to a claim adjudicating for a non-formulary PPI medication. Evidence of the formulary medications filled prior to the non-formulary medication must be documented in the electronic prescription drug history. A non-formulary PPI will automatically adjudicate at a non-formulary copay without preauthorization if the claims system edit notices documentation of at least one fill for a 30 days supply of therapy for 3 of the formulary PPIs. If the edit is met a Point of Sale message will indicate which agents

are on formulary. If there is no evidence of use of 3 of the formulary PPIs, the claim will reject with a Point of Sale message indicating that preauthorization is necessary. The Criteria documented previously may then be applied to requests submitted by the patient's practitioner.

Exception – The edit just described does not apply to patients six years of age and younger. Claims for the oral dissolving tablet (Prevacid SoluTab) and the Prevacid oral suspension will automatically pay when the age edit is met. In the event generic options are not available for these formulations, the brand name products will adjudicate without preauthorization when the age edit is met. Nexium will not automatically adjudicate in these patients.

References

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Billing/Coding

CODES	NUMBER	DESCRIPTION
GPI	492700*****	Proton pump inhibitors
	4999600260****	Omeprazole/sodium bicarbonate
Type of Service	Prescription Drug	
Place of Service	Outpatient	

Update Information

Date	Action	Reason
07/01/08	Replace PA criteria	New PA criteria
02/01/09	Update PA criteria	Formulary removal of brand name Protonix and requirement of trial of generic pantoprazole. Add information on the use of PPIs to treat Barrett's esophagus.
03/01/09	Update PA criteria	Include newly approved PPI, Kapidex, to non-formulary list of medications requiring preauthorization. Also, updated clinical information Kapidex and other PPIs.
10/22/09	Update PA Criteria	Incorporate addition of generic lansoprazole (Prevacid) for inclusion as a formulary agent and including requirement to be tried along with other formulary options.
12/10/09	Update PA Criteria	Criteria update to reflect use of 3 of 4 formulary products in the claims history and updated interaction section with guidance from the FDA on PPI use with clopidogrel.

Preauthorization Criteria History

05/22/08	Reviewed by QMC
07/01/08	Preauthorization criteria original effective date
01/22/09	Update reviewed by QMC
02/01/09	Updated preauthorization criteria effective date
02/26/09	Update provided to QMC as informational
03/01/09	Updated preauthorization criteria effective date
10/22/09	Updated preauthorization criteria
12/10/09	Updated preauthorization criteria
December '10	Next Review