

PHARMACY FORMULARY STATEMENT

Original Issue Date	Next Annual Review	Effective Date
12/01/2016	12/01/2017	12/01/2016
Statement Name		Statement Number
Proton Pump Inhibitors		N/A

A. BACKGROUND

Proton pump inhibitors (PPIs) are indicated for gastroesophageal reflux disease, peptic ulcer disease, Barrett's Esophagus, and Zollinger-Ellison Syndrome.¹⁻⁹ **These medications are indicated for long-term usage only for Barrett's Esophagus and Zollinger-Ellison Syndrome.**^{1,2} Length of therapy for other disease states, such as gastroesophageal reflux disease (GERD), dyspepsia, or peptic ulcer disease, ranges from 8 – 12 weeks.³⁻⁸

Proton pump inhibitors include the following agents: esomeprazole (Nexium), omeprazole (Prilosec), lansoprazole (Prevacid), pantoprazole (Protonix), rabeprazole (Aciphex), and dexlansoprazole (Dexilant). Although PPIs are only indicated for short-term therapy for most indications, many patients are receiving long-term treatment for GERD and peptic ulcer disease.

Current guidelines from the American College of Gastroenterology (ACG) for the management of GERD recommend weight loss, head of bed elevation and avoiding meals 2-3 hours before bedtime if symptoms occur overnight, and an 8 week course of PPIs for symptom relief and healing of erosive esophagitis once a day before the first meal of the day.¹ If patients do not completely respond to once daily dosing, the timing of administration can be adjusted or twice daily dosing may be considered.¹ For maintenance therapy, PPI should be continued for GERD patients who continue to have symptoms after the PPI is discontinued or in patients with complications including erosive esophagitis and Barrett's esophagus.¹ If long-term therapy with PPIs is to continue for GERD, it should be administered in the lowest effective dose including on demand or intermittent dosing strategies.¹ H2 antagonists are also an option for maintenance therapy for patients without erosive disease.¹

According to the ACG guidelines for the management of peptic ulcer disease (PUD), long-term therapy with PPIs is indicated in a few instances:

- 1) If the ulcer is an NSAID-associated bleeding ulcer and the NSAID is continued after the ulcer is healed, long-term PPI therapy should continue
- 2) If the ulcer is an *H Pylori*-associated bleeding ulcer, long-term PPI therapy is indicated if the patient also requires NSAIDs or antithrombotic therapy
- 3) If the ulcer is a low-dose aspirin associated bleeding ulcer, long-term PPI therapy should be continued if aspirin is continued for secondary prevention
- 4) If the ulcer is idiopathic (non-*H Pylori*, non-NSAID), long-term PPI therapy should be continued.⁹

Recent evidence from several studies shows that long-term use of PPIs may pose risks not seen in the short-term clinical studies these agents have undergone; and, these newly identified risks are in addition to previously associated risks. Recent data is important as PPIs have been considered relatively safe; however, the studies for approval were for short-term use for most indications.³⁻⁸ In addition, there are limited long-term studies that support long-term safety of PPIs. One long-term study looked at nearly 12,000 patients receiving therapy for just an average of 26 weeks.¹⁰⁻¹¹ Another smaller study of 230 patients (mean age 63) found that over a mean follow-up period of 6.5 years omeprazole to be safe when used to control GERD.¹² In this latter study, the researchers found 0.52 adverse events per year over approximately 1500 patients years; however, the types of adverse events were not reported in the published article.¹²



The previously identified potential risks of long-term therapy with PPIs include the following:

- An increased risk of osteoporosis and decreased bone mineral density and an increased risk of fractures.¹³
- Patients on high doses of PPIs and those on PPIs for an extended period of time (> 1 year) are at higher fracture risk.^{14,15}
- All PPIs are associated with decreased magnesium absorption and in March 2011 the FDA released a warning regarding low magnesium levels associated with long-term use of PPIs.¹⁶⁻¹⁸
- Patients on PPIs were at increased risk of *C. difficile* associated-diarrhea compared to those not on a PPI; and a later study found patients exposed to PPIs within 14 days of treatment for *C. difficile* infection were 42% more likely to have recurrent infection.¹⁹⁻²¹
- Increased risk of community acquired pneumonia appears in the short-term but long-term risk is not clear.¹ However, data on the risk for community acquired pneumonia is unclear due to conflicting data.²²⁻²⁵
- Prolonged PPI therapy can lead to hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy leading to rebound acid hypersecretion²⁶
- PPIs are the most common cause of acute interstitial nephritis (AIN) and all PPIs have been associated with AIN.²⁷⁻²⁹ PPI-related AIN is rare, idiosyncratic and difficult to predict.²⁷⁻²⁹

In addition to the risks listed above, more recently additional risks have been associated with long-term use of PPIs including chronic kidney disease (CKD), dementia, and first stroke.

- Three recent studies published in 2016 indicate that long-term use of PPIs may be associated with an increased risk of CKD.^{27,30,31}
 - A study by Lazarus et al evaluated the risk of renal dysfunction in patients without CKD at baseline from two registries (10,482 patients in the Atherosclerosis Risk in Communities (ARIC) study (prospective cohort) and 248,751 patients receiving care through Geisinger Health System (replication cohort)).³⁰
 - The cohort of patients from the ARIC study indicated increased risk of CKD in users of PPIs in unadjusted (HR 1.45, 95% CI 1.11-1.90, p = 0.006) and adjusted analyses (HR 1.50, 95% CI 1.14-1.96, p = 0.003) and similar findings were identified in the analysis of patients in the Geisinger Health System (adjusted HR 1.24, 95% CI 1.20-1.28, p < 0.001).³⁰
 - The adjusted analyses adjusted for the following factors age, sex, race, baseline eGFR, cigarette smoking, BMI, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use.
 - The study also found that patients on high-dose PPIs (defined as twice daily dosing) were associated with higher risk of developing CKD than low dose (once-daily).³⁰
 - The study also demonstrated an associated increased risk in developing CKD when compared to non-users as well as H2-receptor antagonist users.³⁰
 - A retrospective study by Xie et al demonstrated an increased association of PPI use in the development of renal insufficiency in 173,321 patients within the Department of Veterans Affairs who had recently initiated treatment with a PPI vs those initiating an H2 antagonist (n=20,270).³¹
 - The study looked at new users of PPIs and H2-receptor antagonists and followed the patients for 5 years finding that the PPI group had an increased risk of incident eGFR <60 mL/min per 1.73 m² and of incident CKD (HR 1.22, 95% CI 1.18 to 1.26 and HR 1.28, 95% CI 1.23 to 1.34 respectively).³¹
 - The study also detected an association between duration of PPI exposure and risk of renal outcomes among those exposed to a PPI for 31 days or more (up to 720 days) compared to those exposed for 30 days or less.³¹
 - A retrospective case-control study by Anora et al looked at 180,553 patients from administrative claims from the VA Health Care Upstate New York network and included 76,462 patients in the analysis (22,734 PPI users).²⁷



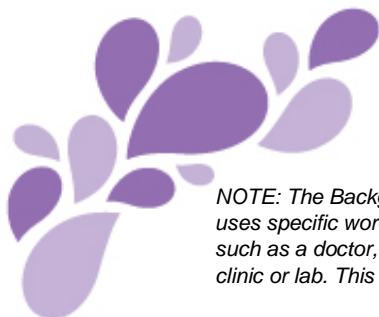
- The unadjusted analysis identified approximately a 10% increase in the risk of developing CKD in patients receiving PPIs (OR 1.10, 95% CI 1.05-1.16, $p < 0.0001$).²⁷

Two recently published studies indicated an increased risk of dementia was associated to the use of PPIs.³²⁻³⁴

- In a study by Haenisch et al, which included 3327 patients age 75 years or older, the unadjusted analysis showed PPI use associated with an increased risk of dementia (HR 1.38, 95% CI 1.04-1.83, $p=0.02$).³² The secondary analysis adjusted for confounders and identified risk of dementia in PPI users as well (HR 1.44, 95% CI 1.10-1.90, $p=0.008$).³²
 - The risk of any dementia as well as Alzheimer's disease alone was increased in patients taking PPIs, with 90% of patients treated for longer than 12 months.³²
 - Authors concluded the data showed statistical association between PPI use and risk of dementia but that the underlying mechanism would be investigated in further studies.³²
- An observational study by Gomm et al evaluated 73,679 patients age 75 and older without dementia at baseline analyzing for factors associated with incident diagnoses of dementia; however, again the authors stated further investigation into this association is needed.
 - In 2950 patients who used PPIs regularly vs. 70,729 patients who did not, there was a significantly increased risk of developing dementia (HR 1.44, 95% CI 1.36-1.52, $p < 0.001$) after adjusted for potential confounders (age, sex, comorbidities, polypharmacy).³³
- In a meta-analysis published in 2016, four observational studies were evaluated which compared PPI users with non-users (included 2 cohort studies, 1 case-control, 1 cross-sectional).³⁴ Across all four studies included, the pool relative risk was statistically insignificant (RR 1.08, 95% CI 0.82-1.43) but when only cohort studies were included there was a statistically significant association between PPI use and dementia (RR 1.44, 95% CI 1.36-1.52).³⁴ The authors concluded findings demonstrated an association but were unable to establish causality and association potentially could be result of confounding.³⁴ Although the risk of dementia has not been fully elucidated, it is important to consider along with all other identified potentially associated risks.

Most recently, data presented at the 2016 American Heart Association Scientific Sessions in November 2016 indicated the use of PPIs may be associated with an increased risk of first stroke.³⁵ The researchers stated that PPIs have been associated with unhealthy vascular function, including heart attacks, kidney disease, and dementia and they wanted to see if they also posed a risk for ischemic stroke; thus, they conducted a retrospective cohort study of Danish registries identifying patients older than 30 years who had an elective endoscopy between 1997 and 2012.³⁵ The study included 244,679 patients with a mean age of 57 years, 44% filled a prescription for a PPI, and patients with baseline cardiovascular disease were excluded.³⁵ It is important to note that PPI users were older and had more comorbidities including atrial fibrillation compared to non-users so this risk needs further clarification as well. However, during the follow up period, 9489 first-time stroke events occurred.³⁵ After adjusting for age, sex, atrial fibrillation, hypertension, diabetes, heart failure, peptic ulcer, cancer, CKD, and NSAID use, the study found a time-dependent association between PPI use and stroke (IRR 1.21, 95% CI 1.16-1.27, $p < 0.001$) as well as a dose-response relationship.³⁵ Specifically for pantoprazole, the increased risk was as much as 94%.³⁵ No observed risk was found for H2 antagonists (IRR 0.99 (95% CI 0.83-1.21, $p = 0.99$)).³⁵

Given available evidence and FDA approved uses and duration of therapy, CareSource limits the use of PPIs to 180 days in a 365 day period. For therapy with PPIs beyond 180 days in a 365 day period, a prior authorization supporting medical necessity will be required.



NOTE: The Background section is for your general knowledge and is not to be construed as coverage criteria. The statement uses specific words and concepts familiar to medical professionals and is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider can also be a place where medical care is given, like a hospital, clinic or lab. This policy informs providers about when a service may be covered.

B. COVERAGE CRITERIA

CareSource will approve the use of PPIs and consider its use medically necessary beyond 180 days in a 365 day period when the criteria below are met. Prior authorization should be submitted with chart notes and documentation supporting medical necessity.

Condition	Coverage criteria:
Erosive esophagitis or Barret's Esophagus	1) Documented diagnosis supported by chart notes.
Hypersecretory condition, such as Zollinger-Ellison Syndrome	1) Documented diagnosis supported by chart notes.
Continuous drug therapy requiring the concurrent use of a PPI	1) Documented diagnosis of peptic ulcer disease or gastrointestinal bleeding 2) Chart notes indicated the need for chronic therapy with an non-steroidal anti-inflammatory drug (NSAID) or antiplatelet agent 3) At least 90 days of consecutive use of NSAID or antiplatelet agent supported by pharmacy claims
Gastroesophageal reflux disease	1) Documented diagnosis supported by chart notes 2) Continued symptoms after PPI was discontinued while other treatment alternatives were used (lifestyle, antacids, H2-receptor antagonists) 3) No claims for PPI in the last 60 days

Notes:

- Documented diagnosis must be confirmed by portions of the individual's medical record which need to be supplied with prior authorization request. These medical records may include, but are not limited to test reports, chart notes from provider's office, or hospital admission notes.
- Patient is required to have completed the trial(s) listed in the above criteria unless the patient is unable to tolerate or has a contraindication to trial medications. Documentation such as chart notes or pharmacy claims may be requested to verify trial(s), intolerance, or contraindication(s).
- Refer to the product package insert for dosing, administration and safety guidelines.

C. AUTHORIZATION PERIOD

Condition	Approval Period
Erosive Esophagitis or Barret's esophagus	12 months
Hypersecretory condition (i.e. Zollinger-Ellison Syndrome)	12 months
Continuous drug therapy requiring concurrent use of a PPI	12 months
Gastroesophageal disease	6 months



D. REVIEW/REVISION HISTORY

DATE	ACTION/DESCRIPTION
12/01/2016	Formulary statement created.

E. REFERENCES

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