The Value of Branded Proton Pump Inhibitors
Formulary Considerations

David A. Peura, MD; Rosemary R. Berardi, PharmD; Javier Gonzalez, PharmD; and Louis Brunetti, MD, JD

ABSTRACT
The prevalence of gastroesophageal reflux disease (GERD) continues to rise, placing an increasing burden on our health care system. Proton pump inhibitors (PPIs) are the most effective and widely used therapy for GERD. Many PPIs are now available in generic and over-the-counter forms, and managed care formularies often choose these as their preferred drug for GERD treatment. However, newer-generation branded PPIs, as a result of differences in their pharmacokinetic and pharmacodynamic profiles, may offer clinical advantages over generic PPIs. This article discusses these differences and the advantages they offer and suggests possible ways to incorporate the newer PPIs into formularies.

INTRODUCTION
Over the previous two decades, the prevalence of gastroesophageal reflux disease (GERD) has increased by 5% annually.1 GERD now affects up to 20% of adults in the U.S.,2 making the disease an important concern in managed care. The disease has a negative effect on quality of life and is associated with substantial costs, both in terms of health care utilization and loss of productivity.4 The $12.2 billion in direct medical costs attributed to GERD* is far exceeded by indirect costs.5 Estimated at $81.7 billion, indirect costs include absence from work (absenteeism) and reduced effectiveness while working (presenteeism).6* Symptom severity and nocturnal heartburn are significantly associated with reduced work productivity, particularly when nocturnal heartburn interferes with sleep.7 Up to 89% of GERD patients report nighttime symptoms,8 which are generally more difficult to adequately resolve than daytime symptoms.9

Proton pump inhibitors (PPIs) are the most effective acid-suppressing agents used in the treatment of GERD10 and are among the most widely prescribed drugs on the market today.11,12 Four brand-name PPIs are currently available that do not have available generic equivalents: Aciphex (rabeprazole, Janssen/Eisai), Nexium (esomeprazole, AstraZeneca), Zegerid (omeprazole/sodium bicarbonate, Santarus), and Dexilant (dexlansoprazole, Takeda), although Zegerid is available in nonprescription form. The most recent entrants to the PPI class—esomeprazole, omeprazole/sodium bicarbonate, and dexlansoprazole—have been formulated to either improve the acute dosing interval or extend the duration of effect, compared with older, generic PPIs.

Esomeprazole, an isomer of omeprazole (Prilosec, AstraZeneca), was developed to increase the efficacy and duration of effect over omeprazole. Omeprazole/sodium bicarbonate offers a complementary acid-reducing mechanism to help raise gastric pH in an attempt to increase the short-term efficacy of the product without altering the long-term effect of omeprazole. Dexlansoprazole, an isomer of lansoprazole (Prevacid, Takeda), is delivered as a modified-release (MR) formulation, which employs an innovative dual-delayed-release technology designed to improve the drug’s efficacy and duration of effect when compared with lansoprazole. Rabeprazole extended release (ER), also formulated to extend duration of effect, is currently under consideration by the FDA for approval.13 Although the original PPIs, including pantoprazole (Protonix, Wyeth/Pfizer), are now all available as generic brands and have been remarkably successful in providing relief from GERD, the enhanced pharmacokinetic properties of the new generation of branded PPIs may help to fill the remaining unmet needs in GERD treatment. This article reviews the role of these newer-generation PPIs in the care of patients with GERD.

FORMULARY MANAGEMENT
Formulary management policies, developed to improve safety, efficacy, and cost-effectiveness of prescription drug usage, include multitier designs, prior authorization, and step-therapy “smart-edit” programs. These policies promote the appropriate use of preferred, less expensive (lower-tier, typically generic) drugs within a particular class prior to stepping up to non-preferred, more expensive (higher-tier, branded) drugs. When these policies are well designed and include col-

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* Dollar values have been converted to 2009 values using appropriate conversion factors.

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laborative efforts between clinical pharmacists and physicians, they can reduce the overuse of PPIs in individuals for whom their use is not indicated, thereby reducing costs without adverse medical consequences in a significant proportion of patients. An analysis of the medical records of 946 patients in an ambulatory care setting receiving PPIs without supportive medical coding revealed that 36.1% had no documented indication for PPI therapy. Total drug costs for inappropriate PPI use in this cohort were approximately $1.8 million. Well-designed formulary restrictions in this setting would likely have reduced the extent of inappropriate PPI use.

Formulary restrictions, however, have also resulted in some instances of patient and clinician dissatisfaction (and, in some cases, delayed access to treatment) and can lead to increased total health care utilization costs. Tiered payment plans, step therapies, and prior authorization requirements, as well as formularies that favor the use of over-the-counter (OTC) PPIs in place of prescription PPIs, have resulted in significant no-fill rates and increased expenditures to obtain non-preferred prescription PPI drugs. Prior authorizations can require extensive documentation before reimbursement for non-preferred brands is allowed, as well as coordination between pharmacy, clinician, and third-party administrators to obtain resolution. Handling formulary restrictions can disrupt clinician workflow and may incur indirect costs associated with a loss of provider productivity.

Formulary guidelines are implemented based on the assumption that all members of a drug class are therapeutically equivalent and that treatments with drugs that have lower acquisition costs will be as clinically effective as their more expensive counterparts. However, for some “niche” patients with GERD, such as individuals with severe erosive esophagitis, those with nocturnal symptoms, poor responders, and non-responders (Table 1), this assumption might not hold true. Indeed, newer-generation PPIs may provide better healing and symptom relief than generic PPIs and OTC formulations, which do not share the same pharmacokinetic properties and delivery systems and, therefore, might be less efficacious in some GERD populations. For these patients, improvements in clinical performance with newer branded prescription PPIs may decrease overall health care expenditures, offsetting the initial medication costs.

**UNMET NEEDS IN ACID SUPPRESSION**

PPIs suppress gastric acid by inactivating gastric proton pumps responsible for the terminal step of acid secretion. Despite their clinical efficacy, once-daily administration of conventional single-release PPIs does not always adequately control intragastric acidity over a 24-hour period in a significant proportion of GERD patients, leading to suboptimal symptom relief, particularly at night. Although the time to peak plasma concentration for most PPIs is generally less than two hours, their relatively prolonged pharmacodynamic effect is reflected in sustained inactivation of the gastric proton pumps. Pumps that are not activated by the first meal consumed after PPI administration may be activated later in the day when drug plasma levels are low, leading to breakthrough symptoms. Approximately 25% of pumps are regenerated every day, and the largest number of new proton pumps are usually synthesized overnight after a prolonged fast. Thus, the combination of previously unbound proton pumps and newly synthesized pumps in the absence of circulating PPI at the end of the dosing cycle effectively contributes to suboptimal 24-hour acid suppression and could provide a pharmacological explanation for nocturnal symptoms.

Overnight recovery of gastric acid is frequently seen with once-daily morning administration of conventional single-release PPIs and, with it, the potential for nocturnal GERD symptoms. For patients experiencing ongoing nocturnal symptoms, twice-daily dosing is often prescribed off-label, as currently recommended by both the American Gastroenterology Association and the American College of Gastroenterology. However, most patients following a twice-daily dosing regimen still experience breakthrough symptoms. The importance of timing of drug administration is often underappreciated; most PPIs are to be taken before meals, usually breakfast, to ensure that the maximum number of proton pumps will be active and subject to inhibition. Furthermore, PPI administration before a meal obviates the possibility of a food effect decreasing drug absorption or bioavailability, as seen with omeprazole, esomeprazole, and lansoprazole. Thus, noncompliance with before-meal dosing recommendations may have a negative impact on the clinical efficacy of PPI therapy. Approximately half of patients do not take their PPIs within one hour of breakfast (Figure 1). Inadequate compliance is likely the single most common cause of a poor response to PPI therapy. Patients may take the PPI in the morning, leaving it too difficult to remember to take them at different times.

**Table 1 “Niche” Patients Who Might Benefit From Branded Proton Pump Inhibitors (PPIs) For Gastroesophageal Reflux Disease (GERD)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Niche Patients Who Might Benefit From Branded PPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has persistent symptoms, with or without nocturnal symptoms, even though patient is compliant with current PPI therapy</td>
<td>From Branded Proton Pump Inhibitors (PPIs) for Gastroesophageal Reflux Disease (GERD)</td>
</tr>
<tr>
<td>2. Has persistent symptoms, with or without nocturnal symptoms, because of improper PPI administration:</td>
<td>• Doesn’t take a PPI 30 to 60 minutes before a meal</td>
</tr>
<tr>
<td>3. Has severe erosive esophagitis (Los Angeles grades C and D)</td>
<td>• Doesn’t eat breakfast (when a PPI is prescribed once daily before breakfast)</td>
</tr>
<tr>
<td>4. Has complicated GERD (i.e., Barrett’s esophagus, strictures, bleeding)</td>
<td>• Performs shift work</td>
</tr>
<tr>
<td>5. Concomitant use of medications metabolized by CYP2C19</td>
<td>• Travels or eats at irregular times</td>
</tr>
<tr>
<td>CYP2C19 = cytochrome P450 isoenzyme 2C19.</td>
<td>• Takes PPIs with other medications at mealtime because it is too difficult to remember to take them at different times</td>
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<tr>
<td></td>
<td>• Snacks late at night</td>
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<td></td>
<td>• Forgets to take a prescribed second dose before dinner when a PPI is prescribed twice daily</td>
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ing and skip breakfast; shift work may interfere with proper dosing; and some patients may take PPIs with other medications at mealtime. Late-night snacking can stimulate acid pumps just prior to recumbency, increasing the tendency for reflux. In addition, patients are not always properly advised by their physician or pharmacist regarding the correct timing of PPI administration. Taken together, all of these factors can lead to reduced PPI efficacy and continued GERD symptoms.

**SUBOPTIMAL SYMPTOM RELIEF AND ITS IMPACT ON COSTS**

Although there is no standard definition of PPI failure, up to 50% of patients with nonerosive GERD do not obtain resolution of symptoms. Persistent breakthrough symptoms, estimated to occur in 46% of GERD patients receiving daily chronic PPI therapy, can lead to patient dissatisfaction with treatment. A number of factors can lead to PPI failure, including rapid PPI metabolism, duodenogastric–esophageal reflux, non-acidic gastroesophageal reflux, visceral hypersensitivity, delayed gastric emptying, and psychological comorbidities. However, poor compliance, with or without improper dosing of PPIs, may be the most common cause of therapeutic failure. In addition, patients with more severe erosive esophagitis (Los Angeles grade C and D) experience higher PPI failure rates (20% and 30%, respectively) than those with grades A (8%) or B (15%).

Patients with frequent nocturnal heartburn symptoms have impairments in health-related quality of life, sleep, and productivity. As a result, patients with persistent daytime and/or nighttime symptoms may require off-label, twice-daily dosing (Figure 2) or supplementation with other GERD medications, such as histamine-2 receptor antagonists or antacids, in an attempt to achieve better symptom relief, driving up GERD-related medical costs. Patients with severe or persistent symptoms despite therapy may then be referred to a gastroenterologist.

Referred patients often need a greater number of office visits and undergo expensive endoscopic examinations and additional diagnostic procedures. The need for a specialist visit, endoscopy, and twice-daily dosing all contribute to direct costs associated with GERD and PPI use. Treatment strategies that control persistent daytime and nighttime symptoms by increasing compliance, by offering more flexible dosing, or by extending the duration of acid suppression, might be effective in lowering the rate of sleep disturbances, improving quality of life and patient satisfaction, and lowering costs among GERD patients.

**DRUG–DRUG INTERACTIONS AND SAFETY CONCERNS**

Long-term studies have shown that PPIs are generally well tolerated and cause few adverse events. As a class, however, PPIs are associated with an increased risk of bone fractures, *Clostridium difficile* infection, and community-acquired pneumonia, particularly when these drugs are used at high doses for long durations. In 2010, the FDA required all manufacturers of OTC and prescription (generic and branded) PPIs to revise their labels to include a warning about a possible increased risk of fractures of the hip, wrist, and spine when used at high (multiple daily) doses or long-term therapy (for one year or longer), based on the reviewed findings from published epidemiological studies using claims data.

All PPIs are metabolized by the cytochrome P450 (CYP) isoenzyme 2C19 (CYP2C19) and thus have the potential to interfere with the metabolism of other drugs upon which this enzyme acts. This potential for an interaction is not universal among all PPIs, because various PPIs are metabolized by CYP2C19 to a different extent. One specific potential drug interaction involves omeprazole’s ability to inhibit CYP2C19, which reduces the enzyme’s ability to activate clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis) from its prodrug form. This has resulted in an FDA-required warning on the clopidogrel label, because this potential drug interaction may prevent the beneficial effects of clopidogrel on clotting, potentially subjecting patients to a higher risk of cardiovascular events.

Esomeprazole, an

![Figure 1](image1.png)

![Figure 2](image2.png)
enantiomer of omeprazole, may have a similar interaction with clopidogrel; the FDA recommends avoiding the concomitant use of these two drugs. Currently, there is insufficient information for the FDA to extend this warning to other PPIs.

In vitro pharmacokinetic studies have demonstrated that omeprazole diminishes the effect of clopidogrel on platelets, although these studies have not shown a significant effect with other PPIs. Based on pharmacokinetic studies, the branded PPIs rabeprazole and dexlansoprazole MR are less dependent on CYP2C19 for their metabolism and demonstrate no clinically important interactions with CYP2C19-dependent drugs such as diazepam (Valium, Roche) and phenytoin (Dilantin, Pfizer). Thus, neither PPI would be expected to alter the pharmacokinetic profile of other drugs metabolized by CYP2C19 (such as clopidogrel), CYP2C9, CYP1A2, and perhaps CYP3A.

A recent open-label pharmacokinetic/pharmacodynamic study examined the effects of omeprazole and pantoprazole on clopidogrel in healthy adults. Both omeprazole and pantoprazole decrease platelet inhibition, but the effect of pantoprazole was significantly less than that of omeprazole. In patients undergoing coronary stenting, those receiving pantoprazole had a significantly better platelet response to clopidogrel than those receiving omeprazole. These data suggest that the CYP2C19-mediated inhibition of clopidogrel activity observed for omeprazole is drug-specific but not class-specific.

HOW NEWER-GENERATION PROTON PUMP INHIBITORS CAN FILL UNMET PATIENT NEEDS

Despite the remarkable success of PPIs in treating GERD, conventional delayed single-release PPIs are not always effective, and gaps in clinical effectiveness persist. Patients taking once-daily conventional PPIs who are poor responders or non-responders may be considered “niche” patients (see Table 1). There may be a role for the newer branded PPIs in treating these patients who exhibit unmet needs.

Use of Enantiomers and New Delivery Systems to Increase Bioavailability and Extend Time of pH Control

Two branded PPIs, esomeprazole and dexlansoprazole, are enantiomers of their parent compounds, omeprazole and lansoprazole, respectively. Omeprazole consists of two non-superimposable mirror image isomers (R- and S-enantiomers) of the same chemical compound. Esomeprazole, the S-enantiomer of omeprazole, has a more prolonged plasma concentration curve than omeprazole because it is more slowly metabolized. Administration of esomeprazole 40 mg results in a significantly higher percentage of patients experiencing at least a 12-hour period of intragastric pH above 4.0 compared with omeprazole 20 mg (P = 0.03), lansoprazole 30 mg (P = 0.02), rabeprazole 20 mg (P = 0.005), and pantoprazole 40 mg (P = 0.004).

Similarly, lansoprazole is a mixture of its R- and S-enantiomers. Dexlansoprazole, the R-enantiomer, which comprises more than 80% of circulating drug following oral administration of lansoprazole, displays lower clearance and greater systemic exposure, compared with its S-enantiomer.

The efficacy of conventional PPIs is limited in part by their drug-release kinetics. Although conventional PPI delivery systems employ single-release (immediate or delayed) formulations, dexlansoprazole MR employs dual-delayed-release technology, which liberates the drug in two discrete phases. The first drug release is in the proximal small intestine, followed by a second drug release at more distal regions of the small intestine several hours later, leading to peak plasma concentrations after one to two hours and then again four to five hours after administration. This delivery system results in an extended plasma concentration and a higher mean 24-hour intragastric pH above 4.0 beyond that of lansoprazole. Thus, dexlansoprazole MR, through its unique dosage formulation and slower clearance, provides a distinct pharmacodynamic profile, compared with the conventional single-release drug-delivery systems commonly used in the formulation of PPIs.

Rabeprazole ER, not yet approved for use by the FDA, was developed to provide a longer duration of acid suppression. Each 50-mg capsule contains a single 10-mg enteric-coated tablet and four identical 10-mg pulsatile-release tablets, which liberate medication in the small intestine and colon. This formulation demonstrated a significant increase in the percentage of time with gastric pH above 4.0 in a 24-hour period on study day 5 compared with esomeprazole 40 mg (P < 0.001) and the conventional rabeprazole delayed-release formulation (P < 0.001).

The esomeprazole/sodium bicarbonate formulation is the only immediate-release PPI that uses the bicarbonate as an immediate acid suppressant and as a buffer for omeprazole. The immediate release of omeprazole is associated with its rapid absorption and rapid onset of antisecretory effect, without compromising the duration of acid suppression. This formulation allows for rapid onset of acid suppression but does not extend the duration of suppression beyond that seen with conventional omeprazole.

Improved or Complete Symptom Relief

In a 2009 comprehensive meta-analysis of PPI efficacy, based on 16 head-to-head trials and published by the Oregon Health & Science University, there was no difference in relief of erosive esophagitis symptoms at four weeks between once-daily omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg. However, esomeprazole 40 mg, but not 20 mg, did provide a clinically significant increase in symptom relief at four weeks compared with omeprazole 20 mg, with a pooled risk difference of 8% (95% confidence interval [CI], 3–13) but not with lansoprazole 30 mg or pantoprazole 40 mg.

A 2006 meta-analysis examining 10 studies, including more than 15,000 patients with erosive esophagitis, revealed no evidence of any clinically meaningful improvement in symptom relief with esomeprazole 40 mg compared with lansoprazole 30 mg, omeprazole 20 mg, and pantoprazole 40 mg. A double-blind, randomized, active-controlled study in a primary care setting included more than 1,300 patients with GERD. The findings revealed that symptom relief was comparable with rabeprazole 20 mg, esomeprazole 40 mg, and esomeprazole 20 mg.

A small, open-label study observed 94 GERD patients experiencing persistent heartburn (mean frequency, 4.4 days/week) despite PPI use (lansoprazole 30 mg, 26.6%; omeprazole 20 mg, 12.2%; rabeprazole 20 mg, 30.4%; esomeprazole 40 mg, 22.5%; esomeprazole 20 mg, 20%).
20 mg, 71.3%; and rabeprazole 40 mg, 2.1%). The patients were switched to eight weeks of therapy with esomeprazole 40 mg. After eight weeks, the mean frequency of heartburn was reduced to one episode per week ($P < 0.0001$), corresponding to a mean reduction of 78%.59

In a multicenter, primary-care, observational Dutch study, approximately 5,000 patients with GERD who were taking omeprazole 10 to 120 mg/day, pantoprazole 20 to 80 mg/day, rabeprazole 10 to 40 mg/day, or lansoprazole 15 to 60 mg/day were switched to esomeprazole 20 to 120 mg/day. At enrollment, 84% were still experiencing symptoms, and only 21.9% were satisfied with treatment. After switching to esomeprazole, with a median of 28 days of therapy, only 26.9% of patients were still experiencing symptoms and 71.3% were more satisfied with esomeprazole than with their previous PPI.60 Use of rescue medication dropped by 62% following the switch.

In 2009, the FDA approved the newest PPI, dexlansoprazole MR. According to a life-table analysis, the 30- and 60-mg doses were superior to placebo for maintaining erosive esophagitis healing over a six-month period in 445 patients as follows: 75%, 83%, and 27% for 30 mg, 60 mg, and placebo, respectively ($P < 0.0001$).61 Most patients on active treatment remained free of heartburn during the six-month treatment period. Patients receiving dexlansoprazole MR 30 mg and 60 mg experienced a median of 96% and 91% of 24-hour heartburn-free days, respectively ($P = 0.0025$), and 99% and 96% of heartburn-free nights, respectively ($P < 0.0025$).62 In patients with symptomatic nonerosive GERD, dexlansoprazole MR provided significantly greater median percentages of 24-hour heartburn-free days (55% and 50% for 30 mg and 60 mg, respectively, vs. 18% for placebo; $P < 0.00001$) and nights without heartburn (81% and 77% for 30 mg and 60 mg, respectively, vs. 52% for placebo; $P < 0.00001$).63 More head-to-head studies are necessary to determine whether dexlansoprazole MR is clinically superior to conventional-release PPIs in providing heartburn relief and whether it can provide the same benefit to patients experiencing persistent symptoms with their current PPI regimen, as described for esomeprazole.

**Esophageal Healing in Moderate-to-Severe Erosive Esophagitis**

The newer branded PPIs esomeprazole and dexlansoprazole MR have demonstrated higher esophageal healing rates compared with other PPIs in severe cases of erosive esophagitis (Los Angeles grades C and D). In the 2006 meta-analysis described earlier,64 esomeprazole provided a statistically significant yet modest degree of improved healing primarily in patients with more severe erosive esophagitis (grades C and D). The effectiveness of esomeprazole 40 mg, compared with other PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg), was inversely proportional to baseline severity of esophagitis.65 Similarly, in the 2009 report from Oregon Health and Sciences University, esomeprazole 40 mg was more effective in healing moderate-to-severe esophagitis than omeprazole 20 mg and lansoprazole 30 mg at four and eight weeks and more effective than pantoprazole 40 mg at four weeks.66

In a multicenter, randomized blinded trial, more patients with moderate-to-severe erosive esophagitis taking esomeprazole 40 mg (82.4%) were healed by week 8 than those taking lansoprazole 30 mg (77.5%; $P = 0.007$).67 In recently published data on healing rates for erosive esophagitis grade C and D, rabeprazole ER 50 mg was noted to be as effective as (but not superior to) esomeprazole 40 mg,68 despite a greater duration of acid suppression shown in pharmacodynamic studies.

In two identically designed studies of erosive esophagitis healing, dexlansoprazole MR 60 mg was superior to lansoprazole 30 mg in healing at eight weeks in one study ($P < 0.05$) and comparable in efficacy in the second study (crude rate analysis, 85.3% vs. 79% and 86.9% vs 84.6%, respectively).69 However, a post hoc integrated analysis showed that among patients with more severe erosive esophagitis (Los Angeles grades C and D), the benefit of dexlansoprazole MR was more pronounced but did not reach statistical significance (78.8% of the dexlansoprazole MR 60-mg patients vs. 72% in the lansoprazole 30-mg patients).70

**Flexibility in Dosing**

Dosing flexibility removes adherence to strict dosing schedules as a factor for compliance. In pharmacokinetic studies, the respective bioavailabilities of dexlansoprazole MR65 and rabeprazole66 were not influenced by food intake. In addition, no relevant differences in pharmacodynamics were found between mean 24-hour intragastric pH levels after dexlansoprazole MR administration in fasted and fed states.65 The benefit of longer plasma concentrations and mean 24-hour pH levels seen with dexlansoprazole MR may provide symptom relief for patients who were not responsive to traditional PPIs that should be taken before breakfast for optimal efficacy. However, studies are still needed to show that this difference in pharmacokinetic and pharmacodynamic profiles translates to improved clinical outcomes.

In addition to a flexible dosing schedule in relation to food, some patients may benefit from alternative routes of administration. For example, patients who require a PPI and who have difficulty swallowing capsules or who have enteral tubes are limited to PPIs in which the capsule contents can be resuspended (e.g., omeprazole, esomeprazole, lansoprazole) or that are available as an oral suspension (e.g., omeprazole, esomeprazole, lansoprazole, omeprazole/sodium bicarbonate, or pantoprazole). For patients unable to tolerate oral formulations because of erosive esophagitis, intravenous (IV) delivery is available for pantoprazole, esomeprazole, and lansoprazole. To date, there are no generic versions of the oral suspensions or IV formulations.

**INTEGRATING NEWER BRANDED PROTON PUMP INHIBITORS INTO FORMULARIES**

Including newer branded PPIs on formularies may help to keep health care utilization costs in check. In 2007, after esomeprazole was removed from the formulary of one large health plan, 19.5% of patients continued with esomeprazole, 43% switched to another PPI, and 37.5% had no PPI prescription. The highest mean increase in cost occurred in patients with erosive esophagitis who switched to another PPI, compared with those who stayed with esomeprazole (the dosage was not reported). Over a six-month period, PPI patients who switched had increased overall medical expenditures ($1,838 vs. $725 for non-switchers).67 Whether similar findings would apply if such an analysis were extended to other branded PPIs is unclear.
A retrospective administrative claims database analysis revealed that reductions in utilization of health care resources and direct medical costs that occurred when GERD patients received PPI therapy were greater for compliant patients than for noncompliant patients.38 Although a newer PPI such as dexlansoprazole MR can increase initial medication costs, flexible dosing may improve patient compliance. In combination with its dual-dose release pharmacokinetic profile, this drug may provide longer durations of 24-hour acid suppression, thereby leading to improved relief of GERD and severe erosive esophagitis, as well as resolution of total 24-hour and nocturnal heartburn symptoms, particularly among niche patients. Such clinical improvements could result in improved quality of life and increased work productivity, as has been demonstrated for dexlansoprazole MR and esomeprazole.20,62,69

In the only randomized controlled trial to date that explored the cost-effectiveness of switching PPI therapies, it was determined that among patients with persistent GERD symptoms who were taking acid-suppressive therapy, primarily PPIs (omeprazole, 12.5%; pantoprazole, 20.5%; lansoprazole, 12.9%; and rabeprazole, 24.7%), switching to esomeprazole 20 mg or 40 mg resulted in an extrapolated cost of approximately $10,000 per quality-adjusted life-year (QALY) gained.70 This is well below the accepted threshold of $50,000 per QALY for cost-effectiveness. The authors state, “A strategy of identifying patients with continued reflux symptoms despite acid suppression and switching to esomeprazole is cost-effective in the short term.”70

Within a heterogeneous patient population, all PPIs might be comparable; however, for certain subsets of patients experiencing persistent GERD symptoms while taking generic PPIs, the newer branded PPIs may provide benefits, whether through improved compliance owing to flexible dosing or to an extended period of acid suppression. Although increasing the dosing of a generic PPI in patients with persistent symptoms from once daily to twice daily may be less expensive than a branded PPI taken once daily, two retrospective database claims analyses have shown that twice-daily patients are less likely to be compliant with their prescribed dosing schedule than once-daily patients.71,72 Reduced compliance could lead to continued persistence of symptoms and, eventually, increased medical costs.

We suggest that placing newer PPIs on formularies is a strategy that could be adopted by health plans for niche patients who need access to these drugs. More direct access to newer-generation PPIs may improve compliance and patient satisfaction and thus may decrease total health care utilization, resulting in fewer doctor visits and diagnostic tests. This can be accomplished by reducing formulary restrictions on newer PPIs while adjusting copayments and allowing patients to choose a higher-tier PPI, with or without a step-therapy process. By definition, if step-therapy criteria are met, patients should not need to go through a prior authorization process or be charged higher copayments for an unapproved use. Step-therapy should be the preferred coverage determination in the PPI category, because access to diagnosis and previous drug history are readily available data elements in most health plans’ electronic patient records. Although data are currently insufficient to support our suggestions, we hope that the information will serve as a basis for consideration and as a stimulus for further studies examining the inclusion of branded PPIs under appropriate patient-care circumstances.

We feel that reasonable formulary management strategies for branded PPIs (discussed next) can be optimized to achieve maximal safety, efficacy, and cost-effectiveness while maintaining appropriate access to the newer generation of branded PPIs. For example, health care plans should consider coverage of OTC PPIs only if the plans can capture claims at the point of service; it is critical to monitor for adherence, because increased usage may be associated with more severe cases of GERD, and these patients may receive greater benefit from prescription PPIs.

Health insurance plans may benefit from covering generic brands and keeping newer-generation branded PPIs on the preferred tier with a quantity limit of 30 tablets per 30-day supply for retail prescriptions or 90 tablets per 90-day supply for mail-order prescriptions to prevent inappropriate use. Health plans might also consider merging diagnostic medical data (e.g., International Classification of Disease [ICD-9-CM] codes for GERD, esophagitis, peptic ulcer, or heartburn) with pharmacy utilization data to create automated smart-edit protocols, which eliminates manual intervention and can optimize therapies.73 This would be particularly useful for patients with severe erosive esophagitis and nocturnal heartburn who continue to experience breakthrough symptoms when taking a generic PPI. Patients without a diagnosis of GERD, severe erosive esophagitis, or nocturnal heartburn should receive a maximum of only two prescriptions for PPIs (i.e., a 60-day supply). This cost would be paid annually under the pharmacy benefit unless the physician decides that there is an appropriate indication for a PPI or unless he or she has documented the patient’s response to empirical therapy. This process can ensure that patients do not self-medicate or receive PPIs chronically for inappropriate indications and that they can have access to a newer PPI for once-daily dosing before switching to a twice-daily generic PPI.

CONCLUSION

For some niche patients with inadequate responsiveness to once-daily dosing of generic PPIs or who have difficulty with before-meal dosing, the newer branded PPIs should be considered for a patient-specific trial. Although direct pharmacy costs are higher, these PPIs may provide optimal symptom control and healing rates. Management of niche patients can lead to reductions in total health care costs stemming from decreases in physician visits and diagnostic tests and also to improved quality of life and productivity.

Large database analyses, mathematical modeling, and comparative effectiveness research will be needed to directly assess the economic impact of various PPI payer utilization strategies. Specifically, properties of the newer-generation branded PPIs may warrant their continued inclusion on managed care formularies, because they may be the most effective PPIs to provide symptom relief, improved PPI adherence, and higher relief rates, which will lead to lower direct and indirect medical costs in GERD patients with nocturnal heartburn and severe erosive esophagitis as well as in patients with nonerosive GERD.
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