

# Formulary Exclusion of Esomeprazole: Impact on Healthcare Costs and Utilization

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Current healthcare costs are more than \$2.5 trillion annually in the United States and are expected to rise by a projected rate of 6.2% annually through 2018.<sup>1</sup> To control prescription utilization and expenditures, managed care organizations promote lower-cost medications within a class of pharmacologic therapies or restrict specific higher-cost medications from their formularies.<sup>2,3</sup> However, few studies have evaluated the effects formulary changes involving proton pump inhibitors (PPIs) have had on healthcare utilization and costs.

A therapeutic substitution policy was implemented in British Columbia requiring patients with acid-related diseases to switch from their currently prescribed PPI to that with the lowest monthly acquisition cost (rabeprazole).<sup>4,5</sup> Initial analysis of data from patients 66 years or older in the provincial drug benefits program suggested that the British Columbia therapeutic substitution policy resulted in substantial savings in pharmacy costs during the first 6 months.<sup>4</sup> However, a subsequent analysis of data from the entire study population found a significant and preventable increase in net healthcare costs (pharmacy costs, physician services, and hospital services) over approximately 3 years.<sup>5</sup> Similarly, findings from 2 other studies showed that formulary restriction of omeprazole led to cost increases for other medical services and increased the risk of negative outcomes in some patients, including more severe symptoms and decreased treatment satisfaction.<sup>2,6</sup>

Proton pump inhibitors are a commonly prescribed class of medications.<sup>7</sup> Similar to other PPIs,<sup>8,9</sup> esomeprazole (Nexium) is indicated for gastroesophageal reflux disease (GERD); erosive esophagitis (EE); reduction of the risk of gastric ulcer in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs); eradication of *Helicobacter pylori* in combination with other medications to reduce the risk of duodenal ulcer recurrence; and Zollinger-Ellison syndrome in adults.<sup>10</sup> Although medications within the same class often are deemed therapeutically equivalent by

## ABSTRACT

**Objectives:** To evaluate the impact on healthcare utilization and costs of exclusion of esomeprazole from the United Healthcare formulary (for most patients beginning September 1, 2006, and for all patients beginning January 1, 2007).

**Study Design:** Retrospective analysis of a provider database comparing utilization and costs before and after formulary exclusion of esomeprazole.

**Methods:** The study included 45,679 patients 18 years or older with (1) 1 or more claims for esomeprazole at an approved dose for erosive esophagitis, gastroesophageal reflux disease, or reduction of risk of gastric ulcer in patients taking nonsteroidal anti-inflammatory drugs; (2) continuous plan eligibility during the index period; and (3) 2 or more prescriptions for esomeprazole ( $\geq 60$  days of supply) during the baseline period (defined as a sliding 12-month window from March 1, 2005, to August 31, 2006).

**Results:** In the 12 months following the formulary change, 12,060 patients (26.4%) continued on esomeprazole, 26,602 (58.2%) switched to another PPI, and 7017 (15.4%) sequentially used esomeprazole and another PPI (mixed cohort). Patients who switched to another PPI after exclusion had significantly higher adjusted overall and GI-specific annual healthcare expenditures per patient per year, including medical and prescription costs, compared with patients who remained on esomeprazole.

**Conclusions:** The results suggest that formulary exclusion of esomeprazole with the intent to cut costs may actually lead to substantially higher healthcare utilization and medical and prescription costs.

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## PRACTICAL IMPLICATIONS

Retrospective analysis of a medical claims database found that excluding the proton pump inhibitor (PPI) esomeprazole from formulary had unexpected consequences:

- Patients with erosive esophagitis (EE) or gastroesophageal reflux disease (GERD) who switched to another PPI after exclusion had higher overall healthcare utilization compared with patients who remained on esomeprazole.
- Patients with EE or GERD who switched to another PPI after exclusion incurred significantly higher adjusted average total and GI-related medical costs per patient per year compared with patients who remained on esomeprazole.

a formulary plan, they may not be clinically equivalent in real-world situations. In fact, pharmacologic studies have demonstrated that treatment with esomeprazole can provide more effective acid control<sup>11-14</sup> and better maintenance of healing<sup>15-17</sup> of EE than treatment with other PPIs.

Esomeprazole was excluded from the United Healthcare formulary for most patients beginning September 1, 2006, and was excluded through United Healthcare beginning January 1, 2007, for all patients who had initially deferred the exclusion. Thereafter, most patients on esomeprazole were required to switch to another PPI if they wanted the prescription cost to be covered by United Healthcare. Patients could continue on esomeprazole only if they were with a subset of formularies that continued to make esomeprazole available in a limited fashion or if they paid the entire cost as an out-of-pocket expense. Findings from a previous analysis evaluating healthcare utilization 6 months after esomeprazole formulary exclusion showed that the costs associated with increased individual patient utilization of healthcare resources surpassed observed prescription cost savings.<sup>18</sup> In this study, prescription medication costs and healthcare utilization were assessed in a medical claims database 12 months before and 12 months after the United Healthcare formulary exclusion of esomeprazole.

## PATIENTS AND METHODS

### Study Design and Patients

This retrospective claims analysis was conducted using a study design that allowed comparison of healthcare utilization and costs during the 12 months before and after formulary exclusion of esomeprazole, and between patients who switched to another PPI and patients who remained on esomeprazole. Healthcare utilization and costs for patients who had claims for esomeprazole and another PPI (mixed cohort) after the formulary exclusion were also compared.

Patients eligible for inclusion in the study were 18 years or older; had 1 or more prescription claims for esomeprazole at an approved dose for EE, GERD, or risk reduction of NSAID-associated gastric ulcer; and had continuous plan eligibility during the index period (March 1, 2005, through December 31, 2007; **Figure 1**). (*Current Procedural Terminology, 4th edition* codes for procedures specific to the upper gastrointestinal [GI] tract are included in **eAppendix A**, available at [www.ajmc.com](http://www.ajmc.com).) Patients with a GI-related diagnosis code but no claim for esomeprazole were

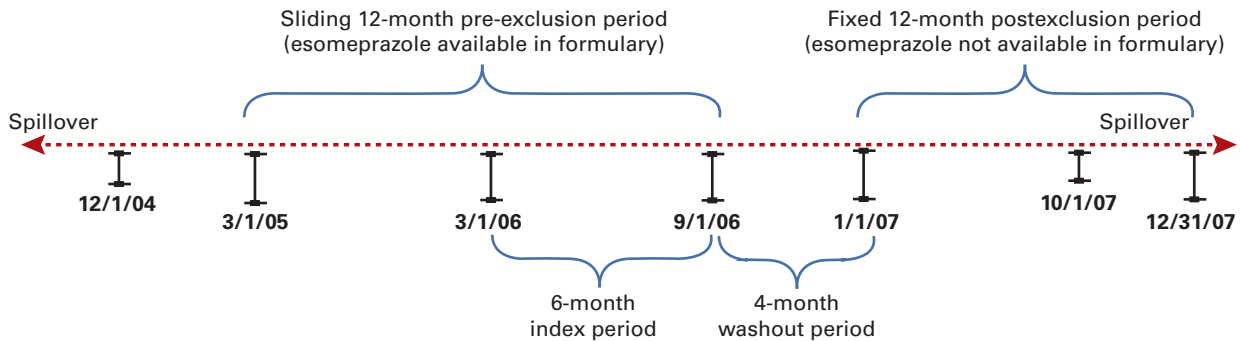
excluded. Patients with a claim for esomeprazole or any other PPI in the pre-exclusion period but no GI diagnosis code and patients with no claim for esomeprazole or any other PPI in the postindex period also were excluded. Additional inclusion criteria included 2 or more prescriptions for esomeprazole ( $\geq 60$  days of supply) during the baseline period, which was defined as a sliding 12-month window from March 1, 2005, to August 31, 2006 (Figure 1).

Patients were stratified based on their indication for using esomeprazole, as described previously. Indications for using esomeprazole were determined based on *International Classification of Diseases, 9th Revision (ICD-9)* codes or prescription claims data: EE (*ICD-9* codes 530.10-530.19), GERD (*ICD-9* codes 530.81 and 787.1), and risk reduction of NSAID-associated gastric ulcer (identified by  $\geq 1$  NSAID prescription claim and PPI prescription claim within 6 days of each other; it was assumed that these patients were taking a PPI to reduce the risk of developing NSAID-associated gastric ulcers and not for a preexisting acid-related disorder).<sup>18</sup> The types and number of visits, as well as healthcare costs, were calculated per patient per 12 months in the pre-exclusion and postexclusion periods. Data for this study were obtained from health plan enrollment and medical and pharmacy claims from the Ingenix LabRx database for the period of March 1, 2005, to December 31, 2007.

### Assessments

Healthcare utilization and costs incurred before and after the formulary exclusion of esomeprazole were assessed in patients who switched to another PPI and patients who remained on esomeprazole. Specific outcome measures were (1) total medical services and related costs and (2) upper GI-related healthcare utilization and expenditures.

**Total Medical Services.** These included inpatient and outpatient visits, emergency department (ED) visits,

Figure 1. Patient Identification<sup>a</sup>

<sup>a</sup>Spillover refers to the number of days of supply of prescription medication that a patient carried over at the beginning of the study period (added in the utilization analysis) or the unused days of supply that the patient still had at the end of the study period (excluded from the utilization analysis). Spillover was defined on a sliding time scale to allow for a full 6 months for each patient regardless of start date.

office visits, other services such as laboratory tests and ambulatory procedures, and outpatient prescriptions. Subanalyses were conducted for each patient group, including those with a diagnosis of EE or GERD and those taking PPIs for risk reduction of NSAID-associated gastric ulcers (prescription NSAID plus prescription PPI group).

**Upper GI-Related Healthcare Utilization and Expenditures.** These were defined as ambulatory visits, ED visits, or inpatient admissions associated with a diagnosis of GERD (*ICD-9* code 530.81), a diagnosis of EE (*ICD-9* codes 530.10–530.19), or an upper GI procedure (eg, *Current Procedural Terminology* code for endoscopy, assay of gastrin, motility study, gastrostomy tube, acid reflux test). Similar subanalyses were conducted by patient group (ie, those diagnosed with EE or GERD, and patients taking PPIs for risk reduction of NSAID-associated gastric ulcers [prescription NSAID plus prescription PPI group]).

### Statistical Analysis

Descriptive statistics were used to evaluate patient demographic and baseline characteristics. A comparative analysis of pre-exclusion and postexclusion differences in healthcare utilization and costs was performed with appropriate statistical tests of significance including  $\chi^2$  and *t* tests in patients who switched to another PPI and patients who remained on esomeprazole. Healthcare utilization and costs analyzed included inpatient visits, outpatient visits, ED visits, office visits, other services (eg, laboratory or diagnostic services), out-of-pocket prescription costs, prescription fills and costs, and PPI prescription fills and costs. Analyses were performed for total healthcare utilization and costs and GI-related healthcare utilization and costs.

Unadjusted healthcare utilization results are presented. Healthcare costs were analyzed using a generalized linear model with a log link and a gamma distribution,<sup>19</sup> adjusting for patient demographic and baseline characteristics (including age, sex, geographic region, plan type, baseline costs, comorbidity index, and provider specialty). Healthcare costs were analyzed by indication for using esomeprazole (EE, GERD, or risk reduction of NSAID-associated gastric ulcer). Data were analyzed and the generalized linear model was fit using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

### Patients

Overall, 45,679 patients who filled esomeprazole prescriptions during the 12 months before the formulary exclusion met inclusion criteria. Of these, 13,755 (30.1%) had a diagnosis of EE, 27,024 (59.2%) had a diagnosis of GERD, and 4900 (10.7%) were taking esomeprazole for risk reduction of NSAID-associated gastric ulcer. Demographic and baseline characteristics generally were similar among subgroups by esomeprazole indication (Table 1).

In the 12-month postexclusion period, 12,060 patients (26.4%) continued on esomeprazole, 26,602 patients (58.2%) switched to another PPI (including rabeprazole, omeprazole, lansoprazole, and pantoprazole), and 7017 patients (15.4%) received esomeprazole and another PPI (mixed cohort; Table 2). The distribution of patients on esomeprazole, another PPI, or mixed PPIs was similar across indications (Table 2).

### Healthcare Utilization

Unadjusted healthcare utilization results in patients who remained on esomeprazole compared with

**Table 1. Patient Demographics and Baseline Characteristics**

Characteristics	Total (N = 45,679)	EE (n = 13,755)	GERD (n = 27,024)	Risk Reduction of NSAID-Associated Gastric Ulcer (n = 4900)
<b>Age group, n (%)</b>				
18-34 y	2413 (5.3)	779 (5.7)	1529 (5.7)	105 (2.1)
35-44 y	7089 (15.5)	2334 (17.0)	4317 (16.0)	438 (8.9)
45-54 y	14,460 (31.7)	4498 (32.7)	8557 (31.7)	1405 (28.7)
55-64 y	15,316 (33.5)	4490 (32.6)	8877 (32.8)	1949 (39.8)
65-74 y	4159 (9.1)	1128 (8.2)	2416 (8.9)	615 (12.6)
≥75 y	2242 (4.9)	526 (3.8)	1328 (4.9)	388 (7.9)
<b>Women, n (%)</b>	24,817 (54.3)	7147 (52.0)	14,667 (54.3)	3003 (61.3)
<b>PPO health plan type, n (%)</b>	31,020 (67.9)	9540 (69.4)	18,259 (67.6)	3221 (65.7)
<b>Geographic region, n (%)</b>				
Midwest	12,279 (26.9)	3474 (25.3)	7473 (27.7)	1332 (27.2)
Northeast	4201 (9.2)	1571 (11.4)	2267 (8.4)	363 (7.4)
South	23,387 (51.2)	6993 (50.8)	13,875 (51.3)	2519 (51.4)
West	5801 (12.7)	1716 (12.5)	3403 (12.6)	682 (13.9)
<b>Baseline comorbidities, n (%)</b>				
0	29,931 (65.5)	9134 (66.4)	17,799 (65.9)	2998 (61.2)
1	11,264 (24.7)	3295 (24.0)	6651 (24.6)	1318 (26.9)
>1	4483 (9.8)	1326 (9.7)	2574 (9.5)	584 (11.9)

EE indicates erosive esophagitis; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PPO, preferred provider organization.

**Table 2. Patient Count and Distribution by Postexclusion Period Proton Pump Inhibitor Use**

Distribution	Number of Patients	% Continued on Esomeprazole	% Switched to Another PPI	% in the Mixed Cohort
Total population	45,679	26.4	58.2	15.4
EE	13,755	26.4	57.3	16.3
GERD	27,024	26.3	58.8	14.9
NSAID <sup>a</sup>	4900	27.0	57.6	15.4

EE indicates erosive esophagitis; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

<sup>a</sup>Risk reduction of NSAID-associated ulcer.

patients who switched to another PPI are shown in **Table 3**. Patients who switched to another PPI had higher healthcare utilization (ie, overall medical use, GI-specific medical use, overall prescription use, and PPI use) compared with patients who remained on esomeprazole (Table 3). Results by indication for using esomeprazole were similar (data not shown). The average number of PPI prescriptions used in the postexclusion period was higher in the patients who switched to another PPI than in the patients who remained on esomeprazole in the overall population (9.0 vs 7.7) and in subgroups by esomeprazole indication (8.9 vs 7.4 [EE]; 9.0 vs 7.7 [GERD]; 9.4 vs 8.2 [risk reduction of NSAID-associated gastric ulcer]).

### Healthcare Costs

In the total study population, patients who switched to another PPI in the postexclusion period incurred significantly higher ( $P \leq .0006$ ) adjusted average total medical and GI-related medical costs per patient per year compared with patients who remained on esomeprazole therapy (\$22,237 vs \$21,131 and \$3379 vs \$2965, respectively; **Figure 2A**). Compared with patients who remained on esomeprazole, patients who switched to another PPI also incurred significantly higher ( $P < .0001$ ) average total prescription costs (\$4398 vs \$4075) and PPI prescription costs (\$1194 vs \$1079).

Results from subgroup analyses by esomeprazole indication generally showed similar results. Patients with

**Table 3.** Differences in Pre-Exclusion and Postexclusion Healthcare Utilization for Patients Who Remained on Esomeprazole Versus Patients Who Switched to Another Proton Pump Inhibitor

Utilization	Switched to Another PPI (n = 26,602)			Remained on Esomeprazole (n = 12,060)			% Relative Change
	Pre	Post	% Change	Pre	Post	% Change	
<b>Medical utilization, per patient per year</b>							
Inpatient visits	0.267	0.277	3.7	0.245	0.233	-4.9	8.6
Outpatient and ED visits	3.392	3.224	-5.0	3.253	2.989	-8.1	3.2
Office visits	13.113	12.675	-3.3	13.265	12.419	-6.4	3.0
Other visits	3.233	3.233	0	3.266	3.064	-6.2	6.2
<b>GI-related medical utilization, per patient per year</b>							
Inpatient visits	0.111	0.106	-4.4	0.096	0.087	-9.6	5.2
Outpatient and ED visits	0.403	0.325	-19.2	0.407	0.283	-30.4	11.2
Office visits	1.427	1.193	-16.4	1.415	0.975	-31.1	14.7
Other visits	0.262	0.209	-20.3	0.268	0.190	-29.1	8.8
<b>Prescription use, per patient per year</b>							
PPI prescriptions	9.1	9.0	-0.7	8.8	7.7	-13.2	12.5
Total prescriptions	51.0	58.1	13.9	49.4	52.9	7.0	6.9

ED indicates emergency department; GI, gastrointestinal; PPI, proton pump inhibitor.

EE who switched to another PPI encountered significantly higher ( $P \leq .005$ ) average adjusted total and GI-related costs per patient per year compared with patients who continued on esomeprazole (\$20,513 vs \$18,983 and \$3286 vs \$2931, respectively; **Figure 2B**). Significantly higher ( $P < .0001$ ) average adjusted total prescription costs and PPI prescription costs were shown in patients with EE who switched to another PPI than in patients who remained on esomeprazole (\$4095 vs \$3757 and \$1198 vs \$1042, respectively) (see **eAppendix B**, available at [www.ajmc.com](http://www.ajmc.com)). Similarly, compared with GERD patients who remained on esomeprazole, patients with GERD who switched to another PPI incurred significantly higher ( $P \leq .0486$ ) average adjusted total costs (\$20,742 vs \$19,970) and GI-related costs (\$3423 vs \$2969) per patient per year (**Figure 2C**). In GERD patients, significantly higher ( $P < .0001$ ) average prescription costs and PPI prescription costs also were incurred by those who switched to another PPI compared with those who remained on esomeprazole (\$4172 vs \$3855 and \$1179 vs \$1078, respectively).

In patients taking a PPI for risk reduction of NSAID-associated gastric ulcer, average adjusted total and GI-related costs incurred by patients who switched to another PPI were numerically higher compared with those who remained on esomeprazole, but the differences were not statistically significant (\$25,233 vs \$24,348 and \$3131 vs \$2885, respectively; **Figure 2D**). Patients who switched to another PPI had numerically higher average total

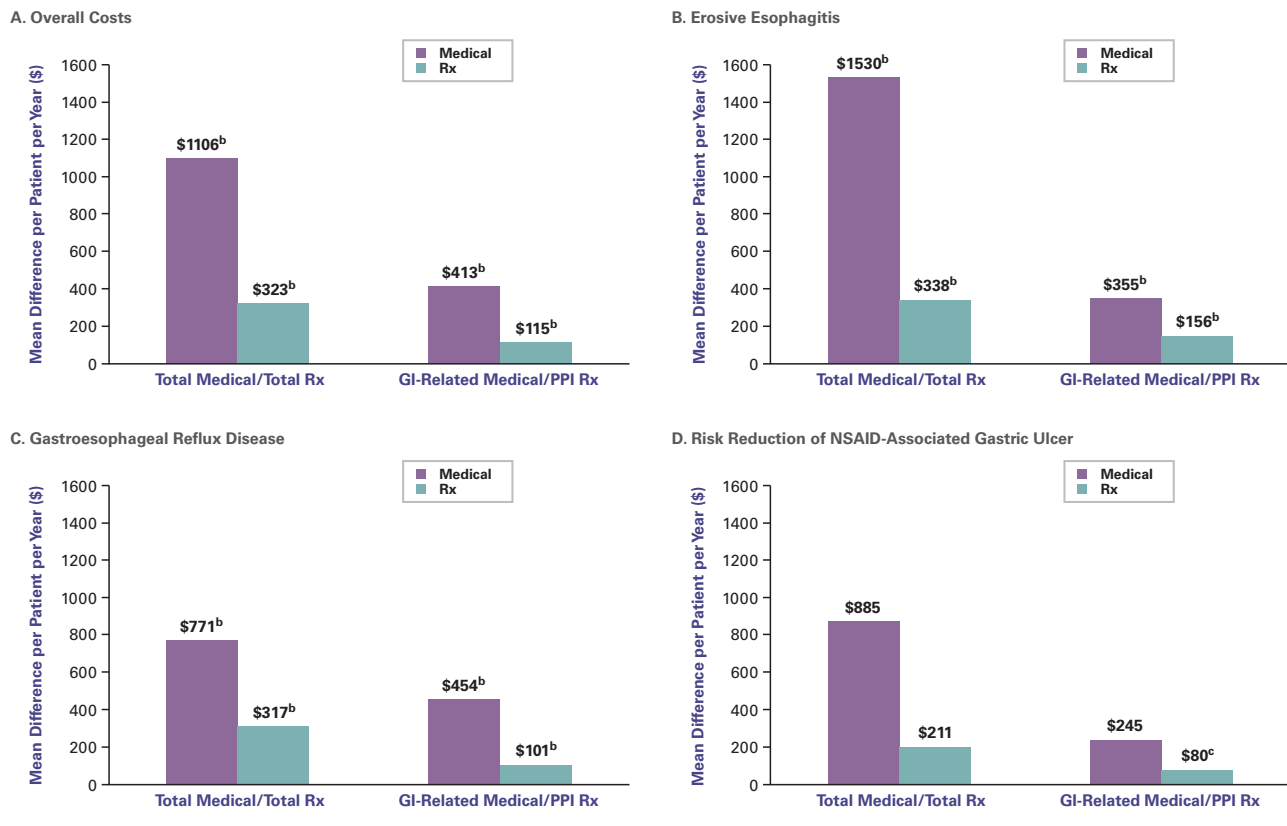
prescription costs compared with those who remained on esomeprazole (\$6010 vs \$5799). Compared with patients who remained on esomeprazole, patients who switched to another PPI incurred significantly higher ( $P = .0425$ ) average PPI prescription costs (\$1234 vs \$1154).

### Mixed Cohort Group

From the pre-exclusion to the postexclusion period, average total and average GI-specific healthcare utilization increased in the mixed PPI group and decreased in the esomeprazole group. For the mixed versus the esomeprazole group, the relative change in average total healthcare utilization was 19.2% for inpatient visits, 5.7% for outpatient and emergency visits, 5.1% for office visits, and 6.2% for other visits. Similarly, for the mixed versus the esomeprazole cohort, the relative change in average GI-specific healthcare utilization was 26.3% for inpatient visits, 21.7% for outpatient and emergency visits, 26.3% for office visits, and 14.4% for other visits. From the pre-exclusion to the postexclusion period, the percent change in average number of prescriptions was also higher in the mixed group compared with the esomeprazole group, with a relative change of 7.2% in total prescriptions and 16.7% in PPI prescriptions.

In the total study population, patients in the mixed group incurred significantly higher ( $P \leq .0002$ ) average adjusted total costs, total prescription costs, PPI prescription costs, and medical costs per patient per year compared with patients who remained on esomeprazole

**Figure 2.** Mean Differences in Adjusted<sup>a</sup> Total and GI-Related Medical and Prescription Costs Between Patients Who Switched to Another Proton Pump Inhibitor and Patients Who Continued on Esomeprazole: (A) Overall and for Patients Prescribed Esomeprazole for (B) Erosive Esophagitis, (C) Gastroesophageal Reflux Disease, and (D) Risk Reduction of NSAID-Associated Gastric Ulcer



EE indicates erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; Rx, prescription.  
<sup>a</sup>Adjusted for baseline patient characteristics (including age, sex, geographic region, plan type, baseline costs, comorbidity index, and provider specialty).

<sup>b</sup>*P* < .001.  
<sup>c</sup>*P* < .05.

therapy in the postexclusion period (\$22,793 vs \$21,131, \$4494 vs \$4075, \$1234 vs \$1079, and \$3503 vs \$2965, respectively). Compared with patients who switched to another PPI, patients in the mixed cohort group incurred significantly higher (*P* ≤ .0145) average adjusted total prescription costs and PPI prescription costs per patient per year (\$4494 vs \$4398 and \$1234 vs \$1194, respectively). However, patients in the mixed cohort group and patients who switched to another PPI incurred similar total costs and medical costs (\$22,793 vs \$22,237 and \$3503 vs \$3379, respectively).

## DISCUSSION

In a recent review of the role of comparative effectiveness research in helping to reduce healthcare costs and improve the quality of care, Brixner and Watkins noted, “When assessing the impact of cost, it is important to look beyond drug costs to the overall impact on treatment costs, including cost offsets that may occur

through improved health or decreased morbidity.”<sup>20</sup> This study examined patterns of healthcare utilization and cost implications for 12 months following the exclusion of esomeprazole from the United Healthcare formulary in patients who had been taking esomeprazole for EE, GERD, or risk reduction of NSAID-associated gastric ulcer. Findings showed that patients who switched to another PPI incurred higher healthcare utilization and significantly higher average adjusted total medical, GI-related medical, total prescription, and PPI prescription costs per patient per year compared with patients who continued on esomeprazole. These findings suggest that formulary exclusions can lead to unexpected higher overall healthcare utilization and costs.

Findings from previous pharmacologic studies suggest that esomeprazole more effectively controls acid and promotes<sup>11-14</sup> and maintains<sup>15-17</sup> healing of certain conditions (eg, EE) than other PPIs. These findings support the present findings and provide a potential explanation



for the lower healthcare utilization and costs (ie, office visits, ED visits, prescription costs) associated with using esomeprazole for EE or GERD compared with other PPIs. In addition, fewer PPI prescriptions were used in the group that remained on esomeprazole than in the group that switched to another PPI, providing another potential explanation for the lower costs associated with continued use of esomeprazole compared with switching to other PPIs.

It also is possible that this formulary exclusion led to negative health outcomes by affecting not only GI diseases, but also other comorbidities. Findings from the present study showing that patients who switched to another PPI experienced greater increases in overall medical use and expenditures than in GI-specific medical use and expenditures support this hypothesis. Gastroesophageal reflux disease is associated with several non-GI comorbidities.<sup>21</sup> The most common comorbidities associated with GERD include hypertension, hypercholesterolemia, obesity, diabetes, and depression.<sup>21</sup> Patients taking a PPI to reduce the risk of NSAID-associated gastric ulcer could be taking the NSAID for various diseases, which may also be associated with comorbidities (eg, osteoarthritis including hypertension and coronary artery disease).<sup>22</sup> As noted in the previous study assessing healthcare utilization 6 months after esomeprazole formulary exclusion, further research into the effect the formulary exclusion may have on healthcare costs and utilization associated with non-GI comorbidities is warranted.<sup>18</sup>

Analyses of the subgroups of patients with EE, GERD, and patients taking a PPI for risk reduction of NSAID-associated gastric ulcer also showed lower adjusted total and GI-related healthcare costs per patient per year in patients who remained on esomeprazole compared with those who switched to another PPI. Differences between the patients who remained on esomeprazole and those who switched to another PPI were significant in patients with EE or GERD, but not significant in the patients taking a PPI for risk reduction of NSAID-associated gastric ulcer. This may be explained by the small sample size of that particular group (n = 757 patients). Further evaluation with a larger pool of patients receiving a PPI for risk reduction of NSAID-associated gastric ulcer is needed to confirm these observations.

## Limitations

This is a retrospective analysis of medical claims data from a large national healthcare payer during the period before and after esomeprazole was excluded from the formulary. Claims data do not allow assessment of symptom

severity or any indirect costs, such as those related to a patient's ability to work or healthcare quality of life. Moreover, the changes we observed were associated in time with the formulary exclusion, but cannot be proved to be causally related. Although esomeprazole was excluded from the formulary for all members, certain patients may have been exempted (eg, if their employer petitioned to continue the treatment coverage). In addition, a limitation inherent to retrospective observational studies is that the analysis results may be confounded by variables that were not measured in the study. Another possible limitation of this study is that patients who were able to continue on esomeprazole by paying for it out of pocket might represent a more affluent group than the overall population, and thus might have better overall health or better adherence to the medication regimen compared with patients who switched to another PPI. This might bias the results toward lower costs and healthcare utilization in the self-pay group, although within-group comparison of the pre-exclusion versus postexclusion costs would control for this bias to some extent.

## CONCLUSIONS

After formulary exclusion of esomeprazole from a large US national health plan, patients in this study who switched to another PPI incurred higher overall healthcare utilization and higher healthcare costs compared with patients who remained on esomeprazole. The results of this analysis suggest that in some cases, formulary exclusions that are expected to save money can yield unexpected and substantially higher annual healthcare utilization and medical and prescription costs.

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**Authorship Information:** Concept and design (BA, JAC, MI); acquisition of data (BA, XK); analysis and interpretation of data (BA, JAC, XK, MI); drafting of the manuscript (BA); critical revision of the manuscript for important intellectual content (BA, JAC, MI); statistical analysis (BA); obtaining funding (JAC); administrative, technical, or logistic support (BA); and supervision (BA, MI).

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**eAppendix A. Current Procedural Terminology, 4th Edition (CPT-4) Codes Used to Specify Upper Gastrointestinal–Specific Procedures**

<b>CPT code</b>	<b>Description</b>	<b>CPT code</b>	<b>Description</b>	<b>CPT code</b>	<b>Description</b>
74246	Radiologic examination, gastrointestinal tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glucagon; with or without delayed films, without KUB	74249	Radiologic examination, gastrointestinal tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glucagon; with small bowel follow-through	76775	Echography, retroperitoneal (eg, renal, aorta, nodes), B-scan and/or real time with image documentation; limited
43234	Upper gastrointestinal endoscopy, simple primary examination (eg, with small diameter flexible endoscope) (separate procedure)	43239	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with biopsy, single or multiple	43243	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with injection sclerosis of esophageal and/or gastric varices
43245	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with dilation of gastric outlet for obstruction, any method	43247	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with removal of foreign body	43249	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with balloon dilation of esophagus (less than 30 mm diameter)
43251	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique	43258	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique	31505	Laryngoscopy, indirect (separate procedure); diagnostic

31512	Laryngoscopy, indirect (separate procedure); with removal of lesion	31515	Laryngoscopy direct, with or without tracheoscopy; for aspiration	31526	Laryngoscopy direct, with or without tracheoscopy; diagnostic, with operating microscope
31527	Laryngoscopy direct, with or without tracheoscopy; with insertion of obturator	31529	Laryngoscopy direct, with or without tracheoscopy; with dilatation, subsequent	31536	Laryngoscopy, direct, operative, with biopsy; with operating microscope
31541	Laryngoscopy, direct, operative, with excision of tumor and/ or stripping of vocal cords or epiglottis; with operating microscope	31561	Laryngoscopy, direct, operative, with arytenoidectomy; with operating microscope	31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope
31576	Laryngoscopy, flexible fiberoptic; with biopsy	31579	Laryngoscopy, flexible or rigid fiberoptic, with stroboscopy	91031	Upper GI diagnostic – not specified
91033	Esophagus, acid reflux test, with intraluminal pH electrode for detection of gastroesophageal reflux; prolonged recording	91035	Esoph G-E reflux test: telemetry PH electrode	91037	Esophageal function test, G-E reflux
91039	Upper GI diagnostic – not specified	43324	Esophagogastric fundoplasty (eg, Nissen, Belsey IV, Hill procedures)	76705	Echography, abdominal, B-scan and/or real time with image documentation; limited (eg, single organ, quadrant, follow-up)
78264	Gastric emptying study	31575	Laryngoscopy, flexible fiberoptic; diagnostic	790	Anesthesia for intraperitoneal procedures in upper abdomen including laparoscopy; not otherwise specified
43235	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)	43326	Esophagogastric fundoplasty; with gastroplasty (eg, Collis)	74022	Radiologic examination, abdomen; complete acute abdomen series, including supine, erect, and/ or decubitus views, upright PA chest

74240	Radiologic examination, gastrointestinal tract, upper; with or without delayed films, without KUB	43848	Revision of gastric restrictive procedure for morbid obesity (separate procedure)	500	Anesthesia for all procedures on esophagus
74246	Radiologic examination, gastrointestinal tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glucagon; with or without delayed films, without KUB	43241	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with transendoscopic tube or catheter placement	43458	Dilation of esophagus with balloon (30 mm diameter or larger) for achalasia
43200	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)	43248	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with insertion of guide wire followed by dilation of esophagus over guide wire	74010	Radiologic examination, abdomen; anteroposterior and additional oblique and cone views
43659	Laparoscopic procedure, stomach, unlisted	43259	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with endoscopic ultrasound examination	43250	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
82270	Blood, occult; feces screening, 1-3 simultaneous determinations	31525	Laryngoscopy direct, with or without tracheoscopy; diagnostic, except newborn	43244	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with band ligation of esophageal and/or gastric varices

74247	Radiologic examination, gastrointestinal tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glucagon; with or without delayed films, with KUB	31535	Laryngoscopy, direct, operative, with biopsy	31510	Laryngoscopy, indirect (separate procedure); with biopsy
43235	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)	31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic	91038	Esophageal function test, G-E reflux, prolonged
43246	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with directed placement of percutaneous gastrostomy tube	91030	Esophagus, acid perfusion (Bernstein) test for esophagitis	31540	Laryngoscopy, direct, operative, with excision of tumor and/ or stripping of vocal cords or epiglottis
43255	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with control of bleeding, any method	91036	Upper GI diagnostic – not specified	91032	Esophagus, acid reflux test, with intraluminal pH electrode for detection of gastroesophageal reflux
31513	Laryngoscopy, indirect (separate procedure); with vocal cord injection	76700	Echography, abdominal, B-scan and/or real time with image documentation; complete	43280	Laparoscopy: esophagogastric fundoplasty
31528	Laryngoscopy direct, with or without tracheoscopy; with dilatation, initial	74020	Radiologic examination, abdomen; complete, including decubitus and/or erect views	74000	Radiologic examination, abdomen; single anteroposterior view

31578	Laryngoscopy, flexible fiberoptic; with removal of lesion	45331	Sigmoidoscopy, flexible; with biopsy, single or multiple	74241	Radiologic examination, gastrointestinal tract, upper; with or without delayed films, with KUB
91034	Esophageal G-E reflux test: cath ph electrodes	43289	Laparoscopic procedure, esophagus, unlisted	43122	Partial esophagectomy, thoracoabdominal or abdominal approach, with or without proximal gastrectomy; with esophagogastrostomy, with or without pyloroplasty
91040	Esophageal balloon distention provocation study	49999	Unlisted procedure, abdomen, peritoneum and omentum	43499	Unlisted procedure, esophagus
82941	Gastrin assay			76770	Echography, retroperitoneal (eg, renal, aorta, nodes), B-scan and/or real time with image documentation; complete
740	Anesth, upper GI endoscopy	43255	Dilation of esophagus, by unguided sound or bougie, single or multiple passes	44500	Introduction of long gastrointestinal tube (eg, Miller-Abbott) (separate procedure)
43450	Dilation of esophagus, by unguided sound or bougie, single or multiple passes	43245	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with dilation of gastric outlet for obstruction, any method	43752	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with dilation of gastric outlet for obstruction, any method



**eAppendix B.** Adjusted Mean Total Prescription and PPI Prescription Costs—Overall and in Patients Taking a PPI for EE, GERD, or Risk Reduction of NSAID-Associated Gastric Ulcer—and Differences Between Esomeprazole, Mixed, and Other PPI Groups

Type of Service and GI Indications	Patient Count			Adjusted Mean From the Gamma Model, Transformed			Mix-Esomeprazole		Mix-Other PPI		Other PPI-Esomeprazole	
	Esomeprazole	Mix	Other PPI	Esomeprazole	Mix	Other PPI	Difference	<i>P</i>	Difference	<i>P</i>	Difference	<i>P</i>
<b>Total prescription costs</b>												
Overall	12,060	7017	26,602	\$4075	\$4494	\$4398	\$419	<.0001	\$96	.0128	\$323	<.0001
EE	3633	2243	7879	\$3757	\$4144	\$4095	\$388	<.0001	\$50	.4419	\$338	<.0001
GERD	7106	4017	15,901	\$3855	\$4298	\$4172	\$444	<.0001	\$127	.0096	\$317	<.0001
NSAID	1321	757	2822	\$5799	\$6023	\$6010	\$225	.1429	\$14	.9227	\$211	.0643
<b>PPI prescription costs</b>												
Overall	12,060	7017	26,602	\$1079	\$1234	\$1194	\$155	<.0001	\$40	.0145	\$115	<.0001
EE	3633	2243	7879	\$1042	\$1233	\$1198	\$191	<.0001	\$36	.2131	\$156	<.0001
GERD	7106	4017	15,901	\$1078	\$1218	\$1179	\$140	<.0001	\$39	.067	\$101	<.0001
NSAID	1321	757	2822	\$1154	\$1283	\$1234	\$129	.0165	\$49	.328	\$80	.0425

EE indicates erosive esophagitis; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.