Proton-Pump Inhibitor Utilization Associated With the Change to Nonpreferred Formulary Status for Esomeprazole in the TRICARE Formulary

Andrea Linton, MS; Thomas Bacon, PharmD, MS; and Michael Peterson, DVM, DrPH

ABSTRACT

BACKGROUND: The Department of Defense (DoD) placed the proton-pump inhibitor (PPI) esomeprazole in the third copayment tier on the TRICARE formulary on July 17, 2005. The change to nonpreferred formulary status for esomeprazole included a $13 copayment increase (from $9.00 to $22.00) for either a 30-day supply purchased from a community pharmacy or a 90-day supply purchased from the mail-order pharmacy and a $0 copayment if obtained from a military pharmacy but with a prior authorization (PA) requirement. The change to nonpreferred formulary status was designed to encourage the use of PPIs other than esomeprazole and to increase the use of the mail-order pharmacy for esomeprazole purchases.

OBJECTIVE: To quantify changes in (a) the TRICARE beneficiary utilization of esomeprazole relative to other PPIs and (b) the pharmacy settings used for filling esomeprazole prescriptions following implementation of a copayment increase and nonpreferred formulary status for esomeprazole.

METHODS: A census of outpatient pharmacy fill records for prescription acid-reducing medications (PPIs, histamine-2 blockers, misoprostol, and sucralfate) obtained by beneficiaries aged 18 years or older from January 1, 2005, through December 31, 2006, was examined. Interrupted time series regression analyses without a control group were used to compare the utilization of esomeprazole relative to other PPIs, as well as the pharmacy setting used to obtain esomeprazole, in the months before and after the formulary change. The rates of continued esomeprazole use, switching to other prescription PPIs (lansoprazole, omeprazole, pantoprazole, and rabeprazole), switching to non-PPI prescription acid-reducing drugs, and discontinued prescription acid-reducing medication use among existing esomeprazole users (i.e., beneficiaries who obtained esomeprazole as the last PPI fill before the formulary change) were calculated overall and for each pharmacy setting used prior to the formulary change.

RESULTS: Over the 24-month study period from January 1, 2005, through December 31, 2006, the total numbers of PPI fills and PPI users increased by 8.5% and 9.0%, respectively, and the number of esomeprazole users decreased by 4.6%. Of esomeprazole users, the percentages of individuals obtaining esomeprazole from military pharmacies and community pharmacies, respectively, decreased from 1.7% to 1.1% and from 89.7% to 81.7%, while the percentage of individuals obtaining esomeprazole from the mail-order pharmacy increased from 8.8% to 17.6%. Time series analyses yielded a positive, statistically significant growth in esomeprazole fills (ß1 = 0.114; P = 0.012) during the 6-month pre-intervention period (January through June 2005) and a significant reduction in August 2005 (ß2 = -5.0%; P < 0.001), the month immediately following the formulary change. During the 17-month post-intervention period (August 2005 through December 2006), no statistically significant change in trend for esomeprazole fills (ß3 = -0.0265; P = 0.534) was observed, although a small increase in the raw number of esomeprazole fills was noted. Among the 117,801 existing esomeprazole users, 86,386 (73.3%) continued using esomeprazole, 17,676 (15.0%) switched to other prescription PPIs, 679 (0.6%) used only non-PPI prescription therapy, and 13,060 (11.1%) discontinued all prescription acid-reducing pharmacotherapy after the formulary change. Significantly higher PPI switching and acid-reducing therapy discontinuation rates were observed among men aged 18-44 years and in TRICARE enrollees relative to women, those over 45 years of age, and those who used other health insurance (P < 0.001). Individuals who used military pharmacies, where a PA requirement was implemented, were more likely to change pharmacy settings to obtain esomeprazole (43.8%) than were users of community pharmacies (19.9%) or the mail-order pharmacy (22.8%). Mail-order pharmacy users were less likely to discontinue acid-reducing pharmacotherapy (4.9%) than were community (11.9%) or military (12.9%) pharmacy users (P < 0.05).

CONCLUSIONS: After adjustment for serial correlation, the formulary change was associated with a migration of approximately 5% of all PPI fills and 25% of esomeprazole fills to the preferred PPIs in the first post-intervention month. Over the 17-month post-intervention period, the trend toward increased esomeprazole use was slowed and use of the mail-order pharmacy for esomeprazole fills nearly doubled. Our observed PPI switch rate of 15.0% resembled the rate observed for another insured population that experienced a similar formulary restructuring, but was substantially lower than the rates reported for more sizeable formulary changes. Thus, the present study’s copayment differentials for third-tier medications ($19 compared with tier 1 and $13 compared with tier 2 copayments) may be less than the threshold amount required to optimize switching to preferred PPIs.

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What is already known about this subject

- Current research suggests that there are no significant differences with respect to safety and efficacy among the currently available PPI formulations. While interventions to motivate the use of preferred PPIs, such as 3-tier copayment plans, therapeutic maximum allowable cost programs, and coverage for over-the-counter PPIs, have generally resulted in cost-savings for health plans, variable rates of formulary compliance and therapy discontinuation have been reported.
- In a previous study of 3-tier copayment implementations, users of nonpreferred PPIs were more likely to switch to a preferred PPI if their copayment changed from $12 to $24 than if their copayment remained at $12 (17.6% vs. 2.1%, respectively), but were not more likely to discontinue therapy. However, nonpreferred PPI users experiencing a $2.3 copayment change from $7 to $30 were more likely to switch (35.1% vs. 1.5%) and to discontinue PPI therapy (32.0% vs. 18.9%) than were nonpreferred PPI users whose copayment remained at $15.
- A 36% PPI switch rate and a 16% acid-reducing therapy discontinuation rate were reported among publicly insured enrollees aged 66 years or older in the 12 months following a formulary change that reduced the number of covered PPIs from 4 to 1 and imposed a requirement for treatment failure with a histamine-2 blocker.
- Greater use of preferred maintenance medications in other therapeutic classes has been observed among insured populations transitioning from 2-tier to 3-tier formularies, but patients with gastroesophageal reflux disease have been reported to be less responsive to formulary changes than those with other chronic diseases.
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What this study adds

- In the first calendar month following an increase in the copayment for esomeprazole from $9 to $22 for a 30-day supply purchased from a community pharmacy or a 90-day supply purchased from the mail-order pharmacy, the percentage of PPI fills attributable to esomeprazole decreased approximately 25% and, in the 17 months following the change, use of the mail-order pharmacy doubled among esomeprazole users.
- Among the 117,801 users of esomeprazole when the formulary change was implemented, 73.3% continued using esomeprazole, 15.0% switched to a preferred PPI, 0.6% switched to non-PPI prescription medication, and 11.1% discontinued all prescription acid-reducing pharmacotherapy.
- Esomeprazole users who were enrolled in a TRICARE managed care health plan were more likely than those who used TRICARE only to obtain prescription drugs to switch to preferred PPIs (19.1% vs. 13.7%, respectively), to discontinue acid-reducing pharmacotherapy (14.7% vs. 9.9%, respectively), and to switch to a different pharmacy setting for esomeprazole fills (15.8% vs. 11.8%, respectively; all comparisons P<0.05).
- The relatively low rates of PPI switching (15.0%) and discontinuation of prescription acid-reducing medication (11.1%) suggest that the copayment differential ($13 vs. other brand PPIs, $19 vs. generic omeprazole) was below the threshold amount needed to promote switching to preferred medications.

The increasing reliance on pharmacotherapy for the management of chronic disease has significantly increased the pharmaceutical component of overall health care spending in the United States each year for more than a decade. In an effort to contain these rising costs, strategies to increase patient cost-sharing have evolved to promote the use of medications believed to be more cost-effective for the health plan. Foremost among them are multi-tiered formularies, which offer lower patient cost-shares for first-tier (generic) or second-tier (preferred brand) medications relative to nonpreferred medications placed in higher tiers. Patient response to increased cost-sharing has been the focus of numerous studies that often present inconsistent conclusions. Quasi-experimental studies of insured populations transitioned to a multi-tier formulary generally reported modest cost savings for the health plan and no adverse effect on patient compliance with critical medications, but cross-sectional studies have reported significantly greater utilization changes with increased patient cost-shares and the suggestion of an increased risk of negative patient outcomes.

Since the first proton-pump inhibitor (PPI), omeprazole, was launched in 1989, PPIs have demonstrated superior acid suppression relative to histamine-2 blockers and have been incorporated into the treatment guidelines for acid-related disorders including gastroesophageal reflux disease (GERD), Helicobacter pylori–negative peptic ulcer disease, and nonsteroidal anti-inflammatory drug-induced gastropathy. As new PPIs were introduced into the market, this class has grown into one of the top-selling medication classes in both total sales and market share. As a result, the PPI class has been a frequent target for patient cost-share increases as health plans have imposed incentive-based formularies, prior authorization (PA), and other utilization management techniques to encourage use of (a) preferred medications within the PPI class or (b) non-PPI acid-reducing medications to manage acid-related conditions.

While implementation of these measures has generally resulted in cost savings for health plans, variable rates of formulary compliance and therapy discontinuation have been reported. Huskamp et al. compared PPI utilization changes following the implementation of 2 different 3-tier copayment structures. In a plan that switched from a 2-tier ($6/$12 [generic/brand]) to a 3-tier ($6/$12/$24 [generic/preferred brand/nonpreferred brand]) formulary, users of nonpreferred PPIs, who experienced a copayment change from $12 to $24, were more likely to switch to a preferred product than were those whose copayment remained at $12 throughout the study (17.6% vs. 2.1%, respectively; P<0.001), but were no more likely to discontinue therapy (18%-19% in both groups; P=0.79). However, nonpreferred PPI users who experienced a $23 copayment change from $7 (single tier) to $30 (3-tier: $8/$15/$30) were more likely both to discontinue PPI treatment (32.0% vs. 18.9%, respectively; P<0.001) and to switch to a preferred PPI (35.1% vs. 1.5%, respectively; P<0.001). Huskamp et al. observed similar findings for users of angiotensin-converting enzyme (ACE) inhibitors and statins. Schneeweiss et al. reported a 36% switch rate and a 16% acid-reducing therapy discontinuation rate among publicly insured enrollees aged 66 years or older in the 12 months following a more restrictive formulary change from 4 to only 1 covered PPI and a histamine-2 receptor antagonist treatment failure requirement. Delate et al. reported a 92% decrease in the rate of PPI claims among Medicaid recipients in the month directly following the implementation of a PA requirement and an overall acid-reducing therapy discontinuation rate of approximately 22%.

Although the generalizability of these findings is limited by broad differences in study populations and methodologies (only one of these studies used comparison groups, while the others used time series analyses with no comparison groups), the addition of a tier or restriction to a health plan’s formulary has generally been associated with increased utilization of preferred medications in many maintenance medication classes. PPI users and patients with GERD, however, have been reported to be less responsive to formulary changes than patients diagnosed with other common chronic conditions.

Like many health plans, the Department of Defense (DoD) health plan, TRICARE, implemented formulary changes within the class of acid-reducing medications as part of an effort to
contain the rising cost of its prescription drug benefit. Initially, the TRICARE formulary used a 2-tier copayment structure to encourage use of generic over brand medications. The formulary also included financial incentives, such as reduced or $0 copayments, to promote the use of military pharmacies and the TRICARE mail-order pharmacy over community pharmacies. The DoD purchases medications under a federally mandated pricing structure that allows it to stock medications at its military pharmacies and at the mail-order pharmacy at a lower cost than the reimbursements paid to community pharmacies used by TRICARE beneficiaries.

In 2005, a third copayment tier was established, and esomeprazole (Nexium) became one of the first medications to be placed in the third (nonformulary) copayment tier. The formulary change was made by consensus vote of the DoD Pharmacy and Therapeutics Committee, following review of meta-analyses that identified no significant differences with respect to safety and efficacy among the available PPI formulations.11,12 A cost-minimization analysis undertaken to rank PPIs from most to least cost-effective (based on weighted average cost per day of treatment) found esomeprazole to be the least cost-effective PPI on the formulary. The formulary change was announced on May 31, 2005, and implemented on July 17, 2005. At the time of the formulary change, the TRICARE Web site was the main method by which drug benefit changes were communicated to beneficiaries outside of the dispensing environment. The primary objective of the change was to promote the use of generic omeprazole or other brand PPIs over esomeprazole. The secondary objective was to promote the use of the mail-order pharmacy over community pharmacies for esomeprazole purchases.

The copayment structure for acid-reducing medications before and after the formulary change is presented in Table 1. Prior to July 17, 2005, generic medications required a $3 copayment and formulary brand medications required a $9 copayment for a 30-day supply from a community pharmacy or a 90-day supply from the mail-order pharmacy. Medication dispensed at military pharmacies had a $0 copayment. Effective July 17, 2005, the copayments for esomeprazole (nonformulary) were raised from $9 to $22 for a 30-day supply in community pharmacies or a 90-day supply at the mail-order pharmacy, and PA was required to obtain esomeprazole from a military pharmacy at a $0 copayment. To obtain PA, the esomeprazole prescription had to be written by a military provider or civilian provider to whom the patient was referred by a military provider, and medical necessity had to be demonstrated by (a) evidence of contraindication to the formulary agent, (b) adverse effects or therapeutic failure with the formulary agent, or (c) previous response to esomeprazole in a patient for whom changing to the preferred medication presented unacceptable risk. The PA form, containing justification for esomeprazole use over each formulary alternative, had to be signed by the prescriber and faxed or mailed to the dispensing location.

Copayment amounts for the remaining PPIs (lansoprazole, omeprazole, pantoprazole, and rabeprazole) and other acid-reducing medications (cimetidine, famotidine, nizatidine, ranitidine, misoprostol, and sucralfate) were not affected by the formulary change. No other cost-sharing or coverage changes for acid-related disorders under the TRICARE benefit were made, nor were any brand, generic, or over-the-counter (OTC) PPIs introduced or removed from the market in the 24-month period during which we assessed utilization changes among the PPI class of drugs.

### Methods
The DoD maintains an enterprise-wide information system that captures patient demographic and prescription information for all prescriptions filled by beneficiaries using their TRICARE pharmacy benefit. A fill record is created in real time when the prescription is filled regardless of whether a military, community, or mail-order pharmacy is used. The fill records are forwarded to a central data repository for processing to remove transactions that have been reversed (e.g., prescriptions that were filled but never picked up) and are coded with an auto-generated, pseudo-patient identifier that enables researchers to link pharmacy and health care service records for the same person without the inclusion of any protected health information in the study datasets. This data repository was the source of the data used in this study.

A census of outpatient pharmacy fill records for prescription acid-reducing medications (identified by First DataBank generic code number) obtained by beneficiaries aged 18 years

<table>
<thead>
<tr>
<th>Medication</th>
<th>Military Pharmacies (All Days Supply)</th>
<th>Community Pharmacies (30-Day Supply)</th>
<th>Mail-Order Pharmacy (90-Day Supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to July 17, 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All brand PPIs⁴</td>
<td>$0.00</td>
<td>$9.00</td>
<td>$9.00</td>
</tr>
<tr>
<td>Generic PPI (omeprazole)</td>
<td>$0.00</td>
<td>$3.00</td>
<td>$3.00</td>
</tr>
<tr>
<td>Brand H2RAs/other⁶</td>
<td>$0.00</td>
<td>$9.00</td>
<td>$9.00</td>
</tr>
<tr>
<td>Generic H2RAs/other⁶</td>
<td>$0.00</td>
<td>$3.00</td>
<td>$3.00</td>
</tr>
<tr>
<td>Copayment and Formulary Change Effective July 17, 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>$0.00</td>
<td>$22.00</td>
<td>$22.00</td>
</tr>
<tr>
<td>All other medications</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

⁴Includes brand prescriptions for esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

⁵Includes prescriptions for brand and generic medications, respectively: cimetidine, famotidine, nizatidine, ranitidine, misoprostol, and sucralfate.

⁶Prior authorization and demonstration of medical necessity required.

DoD = Department of Defense; H2RAs = histamine-2 receptor antagonists; PPIs = proton-pump inhibitors.

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**Proton-Pump Inhibitor Utilization Associated With the Change to Nonpreferred Formulary Status for Esomeprazole in the TRICARE Formulary**

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**TABLE 1** Beneficiary Copayment Requirements for Acid-Reducing Medications Before and After the DoD Formulary Change on July 17, 2005

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or older during a 24-month period (January 1, 2005, through December 31, 2006) was extracted from this central repository. Approximately 0.05% of the fill records were then excluded from the dataset because they contained missing data or represented medications administered by a clinician during a clinic visit. The resulting 9,395,357 fill records were aggregated into 1,478,815 unique beneficiary records that included all acid-reducing medication prescriptions filled during the study period. In all analyses, we defined a “fill” as any prescription for a PPI filled by a beneficiary regardless of the pharmacy type used or the days supply obtained (i.e., a 30-day fill at a community pharmacy and a 90-day fill at a mail-order pharmacy each counted as 1 fill).

The raw numbers of PPI fills and beneficiaries filling prescriptions for PPIs were calculated for each study month by PPI drug and type of pharmacy used, and the percentage of change over the 24-month study period was calculated. Interrupted time series regression analyses as described by Wagner et al. were used to compare the utilization of esomeprazole relative to other PPIs as well as the types of pharmacies used to obtain esomeprazole before and after the formulary change. The 24-month study period was subdivided into pre-intervention months (January 1, 2005, through June 30, 2005) and post-intervention months (August 1, 2005, through December 31, 2006). Because the formulary change occurred on July 17th, July could not appropriately be classified as either a pre-intervention or a post-intervention month and was thus excluded from the time series analysis. Claims from July 2005 were included in calculations of medication discontinuation and switch rates.

To assess the change in utilization of esomeprazole relative to other PPIs, the numbers of esomeprazole fills, generic omeprazole fills, and other branded PPI fills (lansoprazole, brand omeprazole, pantoprazole, and rabeprazole) were plotted as a percentage of total PPI fills by month. To assess the changes in the pharmacy setting used, the percentages of users who obtained esomeprazole from each pharmacy setting were plotted by month. Regression models were used to estimate the level and slope of each pre-intervention and post-intervention period for each fill type and pharmacy setting:

\[ Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{time} \times \text{intervention} + e_t \]

where \( Y_0 = \) level at month = 0 (intercept); \( \beta_1 = \) pre-intervention slope (change in the mean number of fills or users each month from January 2005 through June 2005); \( \beta_2 = \) change in level in the month following the intervention (change in the mean monthly number of fills or users in August 2005 relative to January 2005 through June 2005); \( \beta_3 = \) change in slope following the intervention (change in the trend in the mean number of fills or users each month from August 2005 through December 2006 relative to January 2005 through June 005); and \( e_t = \) error term.

An initial plot of the error terms, \( e_t \), over time indicated the presence of positive autocorrelation between adjacent months. Autocorrelation violates the assumptions of ordinary least-squares regression analysis and has been shown to cause underestimation of error terms and overestimation of significance of effects. Thus, we used a maximum-likelihood autoregression analysis, a technique commonly applied in time series studies. Maximum-likelihood autoregression analysis produces estimates that are more likely than those derived from ordinary
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### Table 3
Raw Number and Distribution of PPI Fills by Type, Number of Beneficiaries, and Pharmacy Setting During Key Months

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Total number of PPI fills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI fills by PPI type, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>19.4</td>
<td>20.0</td>
<td>18.5</td>
<td>15.7</td>
<td>15.4</td>
<td>16.2</td>
<td>17.0</td>
<td>−12.4</td>
</tr>
<tr>
<td>Generic omeprazole</td>
<td>9.3</td>
<td>9.9</td>
<td>10.9</td>
<td>11.7</td>
<td>13.9</td>
<td>15.4</td>
<td>16.8</td>
<td>+80.6</td>
</tr>
<tr>
<td>Other brand PPI</td>
<td>71.4</td>
<td>70.1</td>
<td>70.5</td>
<td>72.7</td>
<td>70.7</td>
<td>68.4</td>
<td>66.2</td>
<td>−7.3</td>
</tr>
<tr>
<td>PPI fills by pharmacy type, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Military pharmacy</td>
<td>37.4</td>
<td>35.6</td>
<td>34.5</td>
<td>36.0</td>
<td>35.2</td>
<td>33.5</td>
<td>31.4</td>
<td>−16.0</td>
</tr>
<tr>
<td>Community pharmacy</td>
<td>52.5</td>
<td>54.2</td>
<td>55.0</td>
<td>53.7</td>
<td>53.7</td>
<td>55.3</td>
<td>56.0</td>
<td>+6.7</td>
</tr>
<tr>
<td>Mail-order pharmacy</td>
<td>10.1</td>
<td>10.2</td>
<td>10.5</td>
<td>10.2</td>
<td>11.1</td>
<td>11.2</td>
<td>12.6</td>
<td>+24.8</td>
</tr>
<tr>
<td>Total number of beneficiaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filled PPI prescription</td>
<td>303,678</td>
<td>308,745</td>
<td>298,273</td>
<td>315,510</td>
<td>303,202</td>
<td>299,061</td>
<td>331,341</td>
<td>+9.0</td>
</tr>
<tr>
<td>Filled esomeprazole prescriptiona</td>
<td>59,523</td>
<td>62,468</td>
<td>56,269</td>
<td>50,229</td>
<td>52,456</td>
<td>54,288</td>
<td>56,789</td>
<td>−4.6</td>
</tr>
<tr>
<td>Military pharmacy, %</td>
<td>1.7</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4</td>
<td>1.3</td>
<td>1.2</td>
<td>1.1</td>
<td>−35.3</td>
</tr>
<tr>
<td>Community pharmacy, %</td>
<td>89.7</td>
<td>89.4</td>
<td>89.1</td>
<td>88.1</td>
<td>84.9</td>
<td>84.3</td>
<td>81.7</td>
<td>−8.9</td>
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<tr>
<td>Mail-order pharmacy, %</td>
<td>8.8</td>
<td>9.4</td>
<td>9.9</td>
<td>10.9</td>
<td>14.1</td>
<td>14.8</td>
<td>17.6</td>
<td>+100.0</td>
</tr>
</tbody>
</table>

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The number and percentage of TRICARE beneficiaries who filled 1 or more prescriptions for an acid-reducing medication, PPI, or esomeprazole at any time during the study period are presented in Table 2 by gender, age group (at first fill), and enrollment status. Beneficiaries were categorized as “enrolled” if they were enrolled in a TRICARE managed care option similar to a health maintenance organization in the civilian health care sector. Enrollees are required to obtain all of their health care services within the TRICARE network of military and civilian providers. Enrollees consist primarily of active-duty service members and their families, but retired service members and their dependents may also enroll. Beneficiaries categorized as users of other health insurance programs consist of retired military service members, rather than health plan expenditures both before and after the formulary change. Analysis and reporting of TRICARE drug expenditures are complicated by variability among the 3 pharmacy settings in the net acquisition cost of individual medications and by regionally or locally negotiated contracts with pharmaceutical manufacturers that prohibit disclosure of price information.

All data manipulations and analyses were performed using SPSS (SPSS Inc., Chicago, IL), Base 10.0. This study was reviewed by the TRICARE Management Activity Exempt Determination Officer on February 28, 2007, and was found to be exempt under 32 CFR 219.101(b)(4).

### Results

The number and percentage of TRICARE beneficiaries who filled 1 or more prescriptions for an acid-reducing medication, PPI, or esomeprazole at any time during the study period are presented in Table 2 by gender, age group (at first fill), and enrollment status. Beneficiaries were categorized as “enrolled” if they were enrolled in a TRICARE managed care option similar to a health maintenance organization in the civilian health care sector. Enrollees are required to obtain all of their health care services within the TRICARE network of military and civilian providers. Enrollees consist primarily of active-duty service members and their families, but retired service members and their dependents may also enroll. Beneficiaries categorized as users of other health insurance programs consist of retired military service members,
their dependents, and those who use their TRICARE pharmacy benefit to obtain prescription medications but use private insurance or Medicare as the primary payer for their health care services.

Compared with acid-reducing medication users overall, esomeprazole users were disproportionately women (64.5% vs. 57.1%), aged 65 years or older (50.7% vs. 40.2%), and more likely to use other health insurance to obtain health care (74.6% vs. 55.1%). The mean [SD] age of esomeprazole users enrolled in other health insurance programs was significantly higher (67.0 [12.8] years) than that of TRICARE-enrolled beneficiaries (49.7 [13.5] years; P<0.001).

The raw number and distribution of PPI fills by PPI type and pharmacy type, the number of beneficiaries filling prescriptions for PPIs and esomeprazole, and the distribution of beneficiaries by pharmacy type for esomeprazole fills for key months throughout the study period are presented in Table 3. Over the entire study period from January 2005 through December 2006, the raw number of PPI fills increased by 8.5%. The percentage of esomeprazole fills as a proportion of PPI fills decreased from 19.4% to 17.0%. As a proportion of all PPI fills, other brand PPI fills decreased from 71.4% to 66.2% and generic omeprazole fills increased from 9.3% to 16.8%. The proportion of PPI prescriptions filled at military pharmacies decreased from 37.4% to 31.4%, while the proportion of PPI fills at community pharmacies and the mail-order pharmacy increased from 52.5% to 56.0% and from 10.1% to 12.6%, respectively.

Similar to the trend observed for the number of PPI fills, the number of beneficiaries filling prescriptions for PPIs increased by 9.0% over the study period; however, the number of esomeprazole users decreased by 4.6%. The percentage of esomeprazole users obtaining esomeprazole from community pharmacies and military pharmacies decreased from 89.7% to 81.7% and from 1.7% to 1.1% respectively, while use of the mail-order pharmacy to obtain esomeprazole increased from 8.8% to 17.6%. Comparing the calendar months directly before (June 2005) and after (August 2005) the formulary change, the percentage of esomeprazole fills as a proportion of PPI fills decreased from 20.0% to 15.7%, and the percentage of esomeprazole users who obtained esomeprazole from the mail-order pharmacy increased from 9.4% to 10.9%.

The percentages of total PPI fills for esomeprazole, generic omeprazole, and other brand PPIs by month are plotted in

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**Proton-Pump Inhibitor Utilization Associated With the Change to Nonpreferred Formulary Status for Esomeprazole in the TRICARE Formulary**

**Figure 1** Percentage of Total PPI Fills by Month and Type of PPI, January 2005 – December 2006

Other brand PPIs include lansoprazole, omeprazole (brand only), pantoprazole, rabeprazole. β1 and β2 represent pre- and post-intervention slopes; β3 represents the post-intervention change in level.

PPI = proton-pump inhibitor.
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Figure 2. Percentage of Beneficiaries Filling Prescriptions for Esomeprazole by Month and Pharmacy Type, January 2005 – December 2006

\[ \beta_1 = -0.0673 \text{ (} P = 0.457 \text{)} \]
\[ \beta_2 = -1.8\% \text{ (} P < 0.001 \text{)} \]
\[ \beta_3 = 0.292 \text{ (} P = 0.005 \text{)} \]
\[ \beta_1 = 0.126 \text{ (} P = 0.152 \text{)} \]
\[ \beta_2 = 1.9\% \text{ (} P < 0.001 \text{)} \]
\[ \beta_3 = 0.252 \text{ (} P = 0.009 \text{)} \]

< 0.001; Formulary change

\( \beta_1 \) and \( \beta_2 \) represent pre- and post-intervention slopes; \( \beta_3 \) represents the post-intervention change in level.

Figure 1. During the pre-intervention period, positive and statistically significant slopes were observed for generic omeprazole (\( \beta_1 = 0.140; P = 0.030 \)) and esomeprazole (\( \beta_1 = 0.114; P = 0.012 \)). A negative and statistically significant slope was observed for other brand PPIs (\( \beta_1 = -0.244; P < 0.001 \)). In August 2005, directly following the formulary change, statistically significant increases in the percentage of fills for generic omeprazole (\( \beta_2 = 1.5\%; P < 0.001 \)) and other branded PPIs (\( \beta_2 = 3.3\%; P < 0.001 \)) were observed, corresponding to approximately 5,000 and 11,000 fills, respectively. A statistically significant decrease in the percentage of fills for esomeprazole was observed (\( \beta_2 = -5.0\%; P < 0.001 \)), corresponding to approximately 16,700 or 25% of fills relative to June 2005. During the post-intervention period, the magnitude of the positive slope for generic omeprazole (\( \beta_3 = 0.184; P = 0.013 \)) increased significantly, and the magnitude of the negative slope for other brand PPIs (\( \beta_3 = -0.169; P = 0.003 \)) decreased significantly. A negative but nonsignificant slope for esomeprazole (\( \beta_3 = -0.0265; P = 0.534 \)) was observed.

The percentages of esomeprazole users who used a military pharmacy, community pharmacy, or the mail-order pharmacy to fill a prescription for esomeprazole by month are shown in Figure 2. During the pre-intervention period, nonsignificant slopes for the mail-order pharmacy (\( \beta_1 = 0.126; P = 0.152 \)) and community pharmacies (\( \beta_1 = -0.0673; P = 0.457 \)) were observed, and a small but statistically significant negative slope was observed for military pharmacies (\( \beta_1 = -0.0870; P < 0.001 \)). In August 2005, in the month following the formulary change, statistically significant increases in the percentage of esomeprazole users who obtained esomeprazole from a military pharmacy or the mail-order pharmacy were observed (\( \beta_2 = 0.2\%; P = 0.006 \); and \( \beta_2 = 1.9\%; P < 0.001 \), respectively), corresponding to approximately 100 and 950 users, respectively. A statistically significant decrease in the percentage of beneficiaries who obtained esomeprazole from a community pharmacy was observed (\( \beta_2 = -1.8\%; P < 0.001 \)), corresponding to approximately 900 users.

During the post-intervention period, use of the mail-order pharmacy (\( \beta_3 = 0.252; P = 0.009 \)) accelerated, use of community pharmacies (\( \beta_3 = -0.292; P = 0.005 \)) continued to decline, and a small but significant reversal of the pre-intervention trend in the use of military pharmacies (\( \beta_3 = 0.068; P < 0.001 \)) was observed, indicating a slowdown of the rate of decline of military pharmacy use that was observed in the pre-intervention period. Across the entire class of prescription PPIs, use of military pharmacies (military pharmacy users as a proportion of all PPI users) decreased (\( \beta = -0.189; P < 0.001 \)) and use of community pharmacies and the mail-order pharmacy increased (\( \beta = 0.082, P < 0.001 \); and \( \beta = 0.107, P < 0.001 \)).
A summary of utilization changes among existing esomeprazole users, that is, study subjects whose last PPI fill prior to the formulary change was for esomeprazole, is presented in Table 4. Among the total of 117,801 existing esomeprazole users, 86,386 (73.3%) continued to obtain esomeprazole, 17,676 (15.0%) switched to other prescription PPIs, 679 (0.6%) switched to non-PPI prescription acid-reducing medications, and 13,060 (11.1%) discontinued all prescription acid-reducing pharmacotherapy (i.e., did not fill any prescriptions for acid-reducing medications) after July 17, 2005. Among those who continued esomeprazole use, 10,942 (12.7%) changed the pharmacy setting(s) through which they obtained esomeprazole.

Men were significantly more likely than women to switch to a preferred PPI (18.0% and 13.3%, respectively; \( P < 0.001 \)), and individuals aged 18-44 years were more likely to discontinue all acid-reducing pharmacotherapy (25.2%) than were those aged 45-64 years (9.5%) or those aged 65 years or older (9.0%; \( P < 0.001 \)). Among age groups, the rates of switching to a preferred PPI revealed a bimodal pattern. Switch rates were higher for the youngest (18-44 years) and oldest (65 years and older) age groups (18.4% and 15.2%, respectively) than for the middle age group (45-64 years, 13.6%; \( P < 0.001 \)). TRICARE enrollees were significantly more likely than those using other health insurance plans to switch to a preferred PPI (19.1% and 13.7%, respectively; \( P < 0.001 \)), to switch to non-PPI prescription medications (0.8% and 0.5%, respectively; \( P < 0.001 \)), to discontinue all prescription acid-reducing therapy (14.7% and 9.9%, respectively; \( P < 0.001 \)), or to change pharmacy settings for obtaining esomeprazole (15.8% and 11.8%, respectively; \( P < 0.005 \)). Other smaller but statistically significant utilization changes were observed among all gender and age subgroups (\( P < 0.05 \)). Because community pharmacies were used by 101,166 (85.9%) of the 117,801 existing users to obtain their esomeprazole fills, utilization patterns were determined primarily by these users.
Among those using other prescription PPIs prior to July 17, 2005, mail-order pharmacy users (13.9% and 4.9%, respectively). The prescription PPI switch rate and acid-reducing medication discontinuation rate were highest among military pharmacy users (15.7% and 12.9%, respectively) and lowest among the mail-order pharmacy users (13.9% and 4.9%, respectively). Among those using other prescription PPIs prior to July 17, 2005, switching and acid-reducing pharmacotherapy discontinuation rates during the 17-month follow-up period were comparable with those observed for esomeprazole: generic omeprazole (5.1% and 12.7% for switching and discontinuation, respectively), brand omeprazole (14.5% and 11.0%, respectively), lansoprazole (7.8% and 16.2%, respectively), pantoprazole (5.5% and 16.5%, respectively), and rabeprazole (4.0% and 14.2%, respectively; data not shown).

Discussion
This study examined changes in PPI utilization associated with the placement of esomeprazole in the third tier of the TRICARE formulary. The DoD's primary objective was to promote the use of generic omeprazole or the other 4 brand PPIs over esomeprazole. Our time series analyses indicated that, in the 6 months prior to the formulary change, esomeprazole fills represented approximately 20% of the PPI fills with a trend of gradual, positive growth. Esomeprazole fills dropped to less than 16% of total PPI fills in the calendar month following its removal from the formulary. A roughly commensurate 1.5% increase in fills for generic omeprazole and 3.3% increase for other brand PPIs from June 2005 to August 2005 suggests that the DoD successfully migrated approximately 5% of the PPI fills, 25% of the esomeprazole fills, and 15% of existing esomeprazole users to the preferred PPIs and slowed the trend toward increased esomeprazole market share over the 17-month post-intervention period.

The DoD's secondary objective was to promote greater use of the mail-order pharmacy for esomeprazole fills. A small but significant jump in mail-order pharmacy use was observed in the month immediately following the formulary change, and a significant trend toward increased mail-order pharmacy use to obtain esomeprazole was observed over the study period. The roughly 2% increase in the mail-order pharmacy usage relative to community pharmacies during the first post-intervention month was likely a combination of existing esomeprazole users switching to the mail-order pharmacy, as well as higher rates of PPI switching or therapy discontinuation among community pharmacy users relative to mail-order pharmacy users. The formulary change may have motivated some new users (i.e., those who did not fill any prescriptions for esomeprazole prior to the formulary change) to choose the mail-order pharmacy over community pharmacies for their esomeprazole fills, but the degree to which the formulary change impacted the purchase decision cannot be validated using administrative data alone. Although a positive trend toward increased mail-order pharmacy use was observed for esomeprazole and PPIs in general, use prevalence was substantially lower for the mail-order pharmacy—less than 18% for esomeprazole and less than 13% for all PPIs—than for community pharmacies during all months in the study period. Other health plans have used similar financial incentives (i.e., offering a 90-day supply of medication for the same price as a 30-day supply purchased from a community pharmacy) to promote use of mail order pharmacies. but limited research has been done to assess the extent to which the lower out-of-pocket cost motivates a patient to voluntarily use a mail-order option over a community pharmacy.

Fewer than 2% of esomeprazole users obtained the medication from a military pharmacy during any study month, but significant utilization changes were observed among users of this setting. Following the intervention, we observed a nearly constant use of military pharmacies for esomeprazole fills, which is likely a reflection of the baseline of beneficiaries who pursued and obtained PA to fill their esomeprazole prescriptions with a $0 copayment. While the military pharmacy setting is unique to the TRICARE pharmacy benefit, utilization changes associated with the use of military pharmacies may arguably be compared with those from other low or $0 copayment plans in which a PA requirement was imposed. Delate et al. reported that approximately 50% of Medicaid enrollees who received a prescription for a PPI did not pursue PA following implementation of a PA requirement for all PPI medications. In the present study, approximately 44% of existing esomeprazole users who obtained the drug from a military pharmacy before the formulary change and who chose to continue esomeprazole use elected to obtain esomeprazole elsewhere at greater expense to themselves, presumably because they did not pursue or meet the esomeprazole PA requirement. Clearly, a PA requirement that applies to all PPIs is more restrictive than one that applies to esomeprazole exclusively, and the degree to which DoD enrollees can be compared with Medicaid recipients is questionable, but the magnitude and direction of the beneficiary response to the PA requirements appears comparable.

Consistent with other studies, we found that esomeprazole users were disproportionately female and older compared with users of PPIs overall and that these subgroups were generally less responsive to the formulary change. We also found that those who were TRICARE enrollees displayed a greater sensitivity to the formulary change in terms of significantly higher PPI switching and therapy discontinuation rates. These beneficiaries receive their care from TRICARE providers who are expected to assimilate formulary changes into their prescribing practice,
whereas non-TRICARE providers are unlikely to be aware of TRICARE formulary changes. The bimodal PPI switching pattern we observed among different age groups was reported by Nair et al., who found formulary compliance rates to be higher in the 18-to-25-year and 65-year-and-older age groups than in the 26-to-64-year age group. Our observation may be attributable to the combined influence of TRICARE enrollment, which is more common among those aged 18-44 years, and the prevalence of multiple comorbidities, which are likely to be highest among those aged 65 years or older. A prior study that examined the association between PPI switching and variables hypothesized to influence switching for well-advertised products reported lower PPI switch rates among subjects without significant comorbidities than among those with multiple comorbid conditions.

Underlying all formulary and drug policy changes is the potential risk of motivating a premature discontinuation of therapy. We found no evidence that the TRICARE formulary change was associated with an increased prescription acid-reducing medication discontinuation rate among esomeprazole users (11.1%) relative to users of the preferred PPIs (ranging from 11.0% to 16.5%) on the TRICARE formulary. For esomeprazole users, our observed therapy discontinuation rate was also lower than the stable 16% background PPI discontinuation rate among PPI users reported among publicly insured seniors by Schneeweiss et al.

Huskamp et al. evaluated utilization changes following the introduction of a 3-tier plan restructuring strategy similar to that imposed on TRICARE beneficiaries. Among nonpreferred PPI users who experienced a $12 co-payment increase (from $12 to $24), the change was associated with a higher PPI switch rate (17.6%) but was not significantly associated with the therapy discontinuation rate, which was 18%-19% in both the intervention and comparison groups. Our 15.0% switch rate from esomeprazole to preferred PPIs was lower than the 36.4% switch rate reported by Schneeweiss or the 23%-24% rate among commercially insured populations by Hall et al. under the normal course of treatment, but it was higher than the 2% PPI switch rates observed among Huskamp’s comparison groups whose 2-tier plans ($6-$7 copayment differentials) underwent no formulary change. Our switch rates among existing users of other preferred PPIs on the TRICARE formulary ranged from 4.0% to 7.8% with the exception of brand omeprazole, with a switch rate of 14.5%, similar to that observed for esomeprazole.

Although the formulary changes, target populations, and study methodologies reported in the literature varied considerably, their findings when combined with our results reinforce the notion that copayment increases in the $12-$15 range can promote switching to a preferred medication without significant increases in therapy discontinuation. Our relatively modest switch rates to preferred PPIs suggest that financial incentives greater than the $13 copayment difference between second- and third-tier medications are needed to achieve the formulary compliance observed among other populations. However, a greater switch rate to preferred medications may be achieved when applying a similar copayment restructuring strategy to other therapeutic classes. Huskamp et al. reported substantially higher switch rates and lower therapy discontinuation rates among ACE inhibitor and statin users relative to PPI users, and other studies have found variable subject responses to the same copayment restructuring for medications in different therapeutic classes.

Like other managed care payers, the DoD faces the challenge of communicating benefit changes to prescribers and beneficiaries to effectively promote formulary compliance. During the study period, formulary change notices published on the TRICARE Web site were the primary means of communicating benefit changes, and it is not clear how frequently the Web site was used for obtaining formulary information. It is unlikely that the formulary change affected prescribing practices beyond the military and DoD-contracted hospitals and clinics where providers are expected to assimilate TRICARE formulary changes into their prescribing practice. Non-TRICARE providers, who treated nearly 75% of the esomeprazole users in our study, were probably unfamiliar with the TRICARE drug benefit or the formulary status of the medications they prescribed. Many beneficiaries may not have even realized that they were using a third-tier medication unless they queried their pharmacist for other options. Since the time of the present study, the DoD has recognized the importance of advertising benefit changes and has initiated direct mailings to notify beneficiaries when the formulary status of their medications is changing.

A study that examined the impact of a letter-based notification program in a commercially insured group found that beneficiary mailings improved formulary compliance for many medications. One of the highest switch rates to a formulary alternative was associated with generic omeprazole, a finding that the authors potentially attributed to direct-to-consumer (DTC) advertising (for Prilosec) and consumer loyalty for the OTC product with the same name. Our study was conducted concurrently with an extensive marketing campaign, in which more spending was dedicated to DTC advertising for esomeprazole than was spent for any other prescription medication in 2005. Exposure to DTC advertising has been associated with increased prescribing and utilization of the advertised medication, as well as higher rates of switching to the advertised product. The $22 copayment for a 30-day supply of esomeprazole may be inadequate to motivate beneficiaries to investigate less-familiar alternatives, even if they can save up to $19 by doing so. These findings suggest that formulary changes involving less well-advertised brands may achieve a higher rate of conversion to preferred medication than was observed in this study.
Limitations
Foremost among the study limitations is the absence of a comparison group. Although a comparison group would have strengthened the validity of our findings, the unique nature of the TRICARE benefit complicated the identification of a suitable comparison group. Ideally, esomeprazole utilization among military pharmacy users should be compared against that of a managed care population with low or $0 copayment transitioning to a PA requirement, while utilization among users of community pharmacies and the mail-order pharmacy is probably best compared with that of other large insured populations transitioning from a 2-tier to a 3-tier formulary. A suitable comparison group would have assisted in controlling for other potentially confounding effects of intensive DTC advertising, direct-to-physician promotions, changes in Medicare or other health plans used by numerous study subjects, and patient-specific or other factors beyond the control of the TRICARE planners. However, the strengths of this study include the uniform prescription drug benefit and the absence of other changes—such as modifications to the TRICARE benefit design or introduction of new PPI drugs—that could have affected the treatment of acid-related disorders among the study population during the study period. Despite the absence of a suitable comparison group, the direction and magnitude of our utilization changes suggest that TRICARE beneficiary response is comparable with that of other populations when exposed to similar formulary changes.

Second, although we found no evidence of increased pharmacotherapy discontinuation rates, we did not examine clinical data to assess whether patients who discontinued or switched PPI therapy had any related increase in other health care service utilization. However, previous research reported no impact on the utilization of medical services in a 12- or 30-month period following implementation of a 3-tier formulary and copayment increase. Additionally, the extent to which the formulary change was associated with changes in patients’ adherence to pre-intervention dosing levels, symptoms, or overall quality of life cannot be assessed using our methodology.

Third, costs for dataset extraction and analyses limited our study period to 24 months. The use of a 6-month pre-intervention period likely limited our statistical power to detect significant differences in pre-intervention and post-intervention trends but had little effect on our calculated rates of PPI switching and medication discontinuation. These rates could have been underestimated, however, if beneficiaries elected to switch medications or pharmacy settings in June 2005 in anticipation of the upcoming formulary change. Anticipatory stockpiling during June 2005 may also have resulted in a biased estimation of the immediate effects of the formulary change if beneficiaries obtained esomeprazole fills early to avoid the higher copayment later. Post-intervention trends and the nature of acid-related conditions do not suggest the presence of seasonal effects.

Finally, the absence of data about nonprescription medication usage may have inflated our acid-reducing therapy discontinuation rates if some users elected to switch to nonprescription medications only. This behavior would more likely be seen among users of military pharmacies where many OTC medications, including omeprazole OTC, are available to DoD beneficiaries at no cost. The TRICARE benefit, however, provides no coverage for OTC medications at community pharmacies, where the beneficiaries’ cost to purchase OTC medications would exceed a PPI prescription copayment if the OTC medication was used daily. Prior studies reported significant switch rates from prescription PPIs to omeprazole OTC when the OTC medication was available at a lower member cost-share. No such financial incentive is available under TRICARE; thus, it is difficult to assess the extent to which omeprazole OTC utilization may have impacted our findings.

Conclusions
Moving esomeprazole to the third tier of the TRICARE formulary and changing the copayment from $9 to $22 for a 30-day supply obtained at a community pharmacy were associated with a 25% reduction in the number of esomeprazole fills in the calendar month following the change, slowdown of the trend toward increased esomeprazole use, and acceleration in the use of the mail-order pharmacy for esomeprazole fills in the post-intervention period. The significantly lower sensitivity to the formulary change that was seen among individuals who used TRICARE only for their prescription fills but obtained their health care through other plans highlights the challenge of improving formulary compliance without prescriber involvement, particularly when the nonpreferred medication is highly advertised. In the case of the PPI class or other medication classes in which multiple therapeutic equivalents are available at different costs, health plans attempting to transition users to preferred medications should consider larger third-tier copayments; more robust interventions, such as a PA requirement for third-tier medications; step therapy (if applicable); mandatory use of a mail-order pharmacy for third-tier medications; or complete removal of the nonpreferred medication from coverage.
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Authors

ANDREA LINTON, MS, is Senior Research Associate, Office of the Assistant Secretary of Defense, Health Affairs (OASD(HA)), TRICARE Management Activity (TMA), Health Programs Analysis and Evaluation (HPAS-E); THOMAS BACON, PharmD, MS, is Director of Utilization Management, OASD(HA)/TMA Pharmaceutical Operations Directorate; MICHAEL PETERSON, DVM, DrPH, is Director, OASD(HA)/TMA/HPAS-E.

AUTHOR CORRESPONDENCE: Andrea Linton, MS, Senior Research Associate, Office of the Assistant Secretary of Defense, Health Affairs, TRICARE Management Activity, Health Programs Analysis and Evaluation, 5111 Leesburg Pike, Ste. 810, Falls Church, VA 22041. Tel.: 202.207.5833; Fax: 703.681.3682; E-mail: andrea.linton.ctr@tma.osd.mil

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Linton did the majority of work in study design and concept, data collection and interpretation, and writing and revision of the manuscript. Peterson contributed to data collection but not data interpretation. Bacon contributed to data interpretation but not data collection.

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DISCLAIMER

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