The Role of Pharmacoeconomics in Formulary Management: Triptan Case Study for Migraine

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ABSTRACT

The use of pharmacoeconomic (PE) evaluations for formulary decision-making has become increasingly common. When a new drug is being considered for inclusion on a formulary, the drug is compared with other available alternatives with respect to efficacy and effectiveness, safety, and cost. The 5-hydroxytryptamine agonists, also known as triptans, are being used to a greater extent as first-line abortive therapies for patients with migraine headache.

Triptans offer several advantages over previous antimigraine therapies. The seven currently available triptans offer clear evidence of improved clinical and economic (cost-saving) outcomes compared with other abortive migraine therapies, such as ergotamine alkaloids; however, the clinical and economic benefits of triptans are less clear.

In this article, we describe a triptan case study that introduces a systematic methodology to help formulary decision-makers in evaluating the cost-effectiveness of drugs within a category by relying on readily available data.

Key Words: formulary, triptans, migraine, pharmacoeconomics, managed care

OVERVIEW

In today’s increasingly cost-conscious environment, payers of health care are beginning to look at economic analyses for decisions on purchasing, contracting, and accepting new pharmaceuticals for inclusion on formularies. As a result, drug manufacturers are being required to demonstrate both the economic value and the clinical benefits of their products.

A formulary (preferred drug list) assists health care providers in evaluating, appraising, and selecting drugs. One function of drug formularies is to allow health care providers to exert partial control over spending without compromising the health of patients.

Pharmacoeconomics is a tool that helps decision-makers evaluate the costs and clinical, economic, and humanistic outcomes of different therapies within the same class or across therapeutic classes. Although the Food and Drug Administration (FDA) does not require an economic analysis for drug approval, most pharmaceutical companies conduct economic evaluations in order to stay competitive in the health care market.

From an industry’s perspective, PE models are especially important for differentiating “me too” (follow-on) drugs, gaining market share, and determining acceptance on a health system’s formulary. From the perspective of a managed care organization (MCO), such evidence provides a quantitative method of predicting the cost and outcomes of adding a new drug to an established therapeutic class, and it justifies the access or restriction of a drug to its constituencies (i.e., state insurance commissioner, providers, and beneficiaries).

Four types of PE analyses are used to assess the resource use and outcomes of pharmaceutical products. The calculated value of the product should include the cost of the entire treatment (i.e., the drug’s acquisition price, the cost of treating side effects, and the cost of treating relapses or additional resources); these resources are always valued in terms of monetary units. The resources may include:

- direct medical costs (e.g., payments for obtaining the drug)
- direct nonmedical costs (e.g., transportation to the pharmacy)
- indirect costs (e.g., lost earnings during the illness)
- the intangible costs of pain and suffering

The type of costs used in the analysis depends on the perspective of the study. From the standpoint of a pharmacy and therapeutics (P&T) committee, direct medical costs are usually the only type of expenses that are taken into consideration in a PE analysis.

The PE analyses differ according to how outcomes are evaluated. Each method is based on a different set of assumptions and provides a quantitative snapshot of the product’s value.

A cost-minimization analysis assumes equivalence in patient outcomes and thus may be used for comparing a generic drug with its equivalent brand-name drug or for comparing treatments that are considered therapeutically equivalent.

If outcomes cannot be assumed to be equivalent, a cost-effectiveness analysis would be more appropriate. The results of this type of analysis are expressed in terms of cost per outcome.

The other two types of PE analyses can be thought of as a “specialized” form of cost-effectiveness analysis, wherein costs are valued in monetary units and outcomes are valued either as quality-adjusted life years (QALY), such as in a cost-utility analysis, or as monetary units, such as in a cost–benefit analysis.

MCOs have started to recognize the value of PE evaluation, which enables them to compare total costs and associated outcomes of two or more competing therapies. Migraine therapy is presented as an example of the clinical and economic issues involved when a more expensive and effective treatment than the standard treatment becomes available on the market.

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Part of the study results were presented as a poster at the 16th annual meeting and showcase of the Academy of Managed Care Pharmacy, held in San Francisco, California, April 1–3, 2004.
The purpose of this case study was to introduce a systematic methodology for evaluating the available triptans as possible migraine treatments and to assist P&T committee members in the recommendation process. The following sections describe an example of the application of PE principles for adding triptans to a formulary. We now present a brief introduction of the epidemiological and economic impact of migraine headache, followed by a thorough review of all PE studies pertinent to this case study.

**Epidemiology and Economic Impact of Migraine**

Migraine is a disorder that affects approximately 28 million Americans. The number of migraineurs increased from 23.6 million in 1989 to 27.9 million in 1999, commensurate with the growth of the U.S. population. The prevalence peaks between ages 25 and 55. More women than men are affected.

Thus, migraine is a highly prevalent condition that affects individuals during their most productive years. Because of this high prevalence during the age range when an individual contributes most to the society, the indirect costs of migraine are greater than the direct cost of migraine therapies. A study in 1999 showed that migraine contributed to $13 billion of missed work or reduced productivity annually.

Migraine also has become a significant economic burden in managed care as well as in Medicaid populations. Thus, migraine represents a significant financial cost for individuals, employers, and health systems.

**Which Triptan for Migraine?**

The newer class of migraine medications include the 5-hydroxytryptamine (5-HT₁) agonists, or triptans, which provide a defined and targeted treatment compared with earlier analgesics. Placebo-controlled trials have demonstrated the superiority of all seven available triptans over placebo.

Although all of the products in this drug class are safe and efficacious, important pharmacokinetic differences exist between them, such as variations in onset and duration.

For example, frovatriptan succinate (Frova®, Elan) has a half-life of 26 hours, whereas the range for all other triptans is two to six hours. No comprehensive head-to-head studies have been performed to completely illustrate all the differences between the agents. Clinical outcomes such as rate of onset, rate of recurrence, adverse drug effects (ADEs), and patients’ preferences should be considered first during triptan selection. After clinical considerations are met, PE analyses may be performed to determine the preferred triptan for a formulary.

More data about the pharmacoeconomics of triptans, however, are now available in the literature. A total of 12 PE studies on five triptans have been published, although no PE evidence was found to support frovatriptan or eletriptan hydrobromide (Relpax®, Pfizer). One reason might be the recent approval of the latter triptans in the U.S. market. Eight studies evaluated the use of sumatriptan succinate (Imitrex®, Cerenex) before and after the drug’s introduction in a patient population, and the comparator drug was not explicitly identified.

The remaining four studies used head-to-head comparisons of the triptans. One study compared almotriptan malate (Axert®, Ortho-McNeil) with rizatriptan (Maxalt®, Merck), sumatriptan, zolmitriptan, (Zomig®, AstraZeneca), and naratriptan HCl (Amerge®, GlaxoSmithKline). Three studies evaluated the cost-effectiveness of almotriptan versus sumatriptan.

All of the available head-to-head PE analyses demonstrate the economic value of almotriptan based on different sets of assumptions. Reeder and colleagues conducted a cost-effectiveness analysis comparing the cost to attain sustained freedom from pain in 100 patients who used almotriptan, rizatriptan, sumatriptan, zolmitriptan, and naratriptan. The investigators used sustained pain-free rates and ADE rates from a published meta-analysis to calculate the number needed to treat migraine in triptan users with and without ADEs. This model demonstrated that other triptans cost between 1.5 and 2.8 times more than almotriptan to achieve 100 sustained pain-free patients with or without ADEs.

Three other studies examined the association between chest pain and the use of oral almotriptan or sumatriptan. Mannix and associates developed a decision-analysis model comparing the direct medical cost of managing chest symptoms after the first dose of either almotriptan or sumatriptan. The model assumed that 0.3% of almotriptan-treated patients and 2.2% of sumatriptan-treated patients would report chest pain, as observed in a previous clinical trial. Using this model, the investigators found that a saving of $1.42 per migraine treatment was associated with symptoms of chest pain when patients used almotriptan.

Wang et al. created another economic model with the same rates of chest pain to estimate the annual cost savings per 1,000 patients who received almotriptan instead of sumatriptan. This model predicted $11,215 in direct medical cost savings annually per 1,000 patients receiving almotriptan instead of sumatriptan because of the lower incidence of chest pain associated with almotriptan. The authors projected annual savings from using almotriptan treatment to be $17 million for 86 million covered lives. They also used the same model to project cost savings for a health plan with one million covered lives.

It is evident from the existing literature that a rigorous head-to-head PE study is warranted to include all of the available triptans. The lack of additional comparative trial data may be the result of the disparity between the methods used to evaluate outcomes. For example, one study estimated the cost of attaining sustained freedom from pain in 100 patients, whereas another study included costs associated with the management of chest symptoms. This problem is also compounded by the different clinical outcome measures (i.e., the definition of “success”) that add to the complexity of making appropriate comparisons. Previous studies have considered a two- or four-hour reduction in migraine severity or no recurrence of headache in 24 hours to be a measure of success. The only consistent outcome measure performed by the manufacturers is a two-hour efficacy rate; however, there are no two-hour data for frovatriptan.

The lack of comparative PE studies that include all agents in a particular drug class and the use of different clinical outcome measures among PE studies are common occurrences. Consequently, P&T committee members are faced with either making a decision based on incomplete PE data for the cate-
gory or ignoring the limited PE data that exist for some agents within the category. The approach that we describe next should assist formulary decision-makers in dealing with imperfect PE information when the clinical use of the agent has been justified.

COST-EFFICACY ANALYSES

A simple cost-efficacy analysis can be conducted to assess the value of an agent in a drug class, such as a triptan, using data available from an MCO. The drug acquisition cost data for the MCO and the efficacy rates from phase 3 clinical trials can be used to determine the cost-efficacy ratio. This type of analysis can be undertaken when head-to-head effectiveness rates are unavailable.

For example, the analysis might use the average wholesale price (AWP) per unit dose and the efficacy of decrease in migraine pain from “moderate/severe” to “none/mild” within two hours of ingesting a triptan:

\[
\text{cost efficacy} = \frac{\text{AWP or acquisition cost}}{\text{efficacy}}
\]

Table 1 summarizes the cost-efficacy ratios for the 12 available triptans in the U.S. market. The products are categorized according to their various dosage forms because a P&T committee might consider having each dosage form available on the formulary.

In a comparison of two-hour efficacy, zolmitriptan was the clear favorite (dominant) agent between the two available nasal sprays because it was less expensive and its efficacy rate was higher than that of sumatriptan.

Among the oral agents, rizatriptan had the lowest average cost-efficacy ratio and frovatriptan had the highest.

Of the two disintegrating tablets, zolmitriptan exhibited the lower cost-efficacious ratio compared with rizatriptan.

Although sumatriptan injection was the least cost-efficacious triptan treatment available because of its increased efficacy and a lack of any other competitors, its inclusion on formularies might be warranted for use in special populations who are unable to take oral medications or who are willing to pay an additional co-payment for longer migraine relief.

Incremental cost-efficacy (ICE) analyses were performed to determine the additional cost per additional gain in efficacy. This type of analysis becomes more relevant in comparisons of the oral agents to determine the increased value among the seven available agents with increasing AWPs. Because increased AWPs did not always correlate with greater efficacy (e.g., oral sumatriptan or frovatriptan), it is intuitive to include only those agents that provided greater efficacy rates with greater cost. The underlying reason for performing an ICE is to determine the additional cost spent for the additional outcome gained:

\[
\text{incremental cost efficacy} = \frac{(\text{cost of drug A} - \text{cost of drug B})}{(\text{efficacy of drug A} - \text{efficacy of drug B})}
\]

In this example, eletriptan was the reference treatment because it was the least costly oral triptan. Sumatriptan and frovatriptan were less efficacious and more expensive than eletriptan and were therefore not included in the ICE analysis. The ICE ratios for the other four agents in relation to eletriptan ranged from a low of approximately $20 to a high of $52 for each successfully aborted migraine headache (Figure 1).

A one-way sensitivity analysis was conducted on the cost-efficacy estimates for oral agents by individually varying the AWP and the efficacy rates. Among the seven oral treatments,

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name, Company</th>
<th>Dosage Form</th>
<th>AWP</th>
<th>Efficacy†</th>
<th>CE‡</th>
<th>ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizatriptan</td>
<td>Maxalt®, Merck</td>
<td>Oral tabs</td>
<td>$18.80</td>
<td>64.75%</td>
<td>$29.03</td>
<td>$20.84</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig®, AstraZeneca</td>
<td>Oral tabs</td>
<td>$18.72</td>
<td>63.15%</td>
<td>$29.64</td>
<td>$24.63</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax®, Pfizer</td>
<td>Oral tabs</td>
<td>$17.07</td>
<td>56.45%</td>
<td>$30.23</td>
<td>Reference</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Axert®, Ortho-McNeil</td>
<td>Oral tabs</td>
<td>$18.44</td>
<td>60.00%</td>
<td>$30.73</td>
<td>$38.60</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Amerge®, GlaxoSmithKline</td>
<td>Oral tabs</td>
<td>$18.84</td>
<td>59.30%</td>
<td>$31.77</td>
<td>$62.11</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imitrex®, Cerenex</td>
<td>Oral tabs</td>
<td>$19.56</td>
<td>52.53%</td>
<td>$37.22</td>
<td>—</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova®, Elan</td>
<td>Oral tabs</td>
<td>$17.40</td>
<td>41.60%</td>
<td>$41.83</td>
<td>—</td>
</tr>
<tr>
<td>Zolmitriptan ZMT</td>
<td>Zomig® ZMT</td>
<td>Disintegrating tabs</td>
<td>$17.35</td>
<td>63.00%</td>
<td>$27.53</td>
<td>Reference</td>
</tr>
<tr>
<td>Rizatriptan MLT</td>
<td>Maxalt® MLT</td>
<td>Disintegrating tabs</td>
<td>$18.80</td>
<td>66.90%</td>
<td>$28.10</td>
<td>$38.18</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig®</td>
<td>Nasal spray</td>
<td>$25.85</td>
<td>69.00%</td>
<td>$37.46</td>
<td>Dominant</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imitrex®</td>
<td>Nasal spray</td>
<td>$27.14</td>
<td>53.10%</td>
<td>$51.11</td>
<td>—</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imitrex® Injection</td>
<td>$63.40</td>
<td>81.40%</td>
<td>$77.89</td>
<td>No competitor</td>
<td></td>
</tr>
</tbody>
</table>

* Efficacy measures were weighted and derived from package inserts and based on phase 3 clinical trial results.
† Reduction in migraine severity from moderate or severe pain to mild or no pain in two hours except for naratriptan HCl, for which the reduction was measured only at the end of four hours.
‡ Cost per efficacy ratio = cost ($) per migraine headache cured in two hours (“cured” was defined as a reduction in migraine severity to mild or no pain).

AWP = 2004 average wholesale price ($ per unit dose); ICE = incremental cost efficacy.
the AWP ranged from a low of $0.61 to a high of $5.28. The breakpoint AWP is the threshold point at and below which the respective oral triptan had the smallest cost-efficacy ratio (Table 2).

For example, frovatriptan would have the lowest cost-efficacy ratio if its AWP were $5.32 or below compared with other oral agents on the market. The efficacy for each therapy was derived from the average efficacies reported in the phase 3 clinical trials. A range for each efficacy could be identified from the phase 3 studies that demonstrated the lowest and the highest efficacy values. Cost-efficacy ratios could then be calculated by varying efficacy estimates within this range.

A sensitivity analysis based on the lowest and highest efficacy rates was conducted to determine its influence on the cost-efficacy ratio. Table 3 and Figure 2 show the results when efficacy rates varied between the lowest and highest values reported in the package inserts, holding the cost of the drug constant. It is interesting that, except for frovatriptan, all ranges of cost-efficacy ratios overlapped between the oral treatments. Although the idea has not been statistically tested, a P&T committee member could conclude that there might not be a true difference between the various cost-efficacy ratios.

**RESULTS AND DISCUSSION**

The use of PE principles to determine formulary inclusion is an attempt to quantify the cost of different therapies per outcome. Pharmacoeconomic evaluations should be conducted only after questions regarding a therapy’s efficacy, safety, and availability have been addressed. Differences in demographics, socioeconomic status, and burden of illness do affect patients’ responses to and choices of therapy and thus influence clinicians’ prescribing strategies. PE results, therefore, might not be valuable when therapeutic choices are made at the level of the individual.

The case study presented in this article examined the two-hour efficacy rate, which is a critical endpoint for the FDA’s approval. The clinical efficacy endpoint could be adjusted on

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results from a One-Way Sensitivity Analysis on Average Wholesale Price (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
<td><strong>AWP (Robust Range)</strong></td>
</tr>
<tr>
<td><strong>Oral Tablets</strong></td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>$18.80 ($18.80–$19.58)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>$18.72 ($18.34–$19.40)</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>$17.07 ($16.73–$17.34)</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>$18.44 ($18.14–$19.06)</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>$18.84 ($18.22–$22.08)</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>$19.56 ($16.69–$21.97)</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>$17.40 ($15.49–$17.40)</td>
</tr>
<tr>
<td><strong>Disintegrating Tablets</strong></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan ZMT</td>
<td>$17.35 ($17.35–$17.70)</td>
</tr>
<tr>
<td>Rizatriptan MLT</td>
<td>$18.80 ($18.43–$18.80)</td>
</tr>
<tr>
<td><strong>Nasal Sprays</strong></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>$25.85 ($25.85–$35.26)</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>$27.14 ($19.89–$27.14)</td>
</tr>
<tr>
<td><strong>Injection</strong></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>$63.40</td>
</tr>
</tbody>
</table>

*Within this range, the drug maintains its base case rank order, as shown in Table 1. † Cost of the drug at which the respective triptan has the lowest cost-efficacy ratio.
the basis of a decision-maker’s perspective and practice.

Although efficacy rates for this study were derived from FDA-reported package inserts, certain limitations must be considered. Clinical efficacy is defined as the clinical outcomes from phase 3 placebo-controlled, randomized clinical trials, whereas clinical effectiveness is defined as the clinical outcomes from real-world trials. Usually, clinical efficacy is greater than clinical effectiveness because of a higher compliance rate, strict inclusion and exclusion criteria, and protocol-driven practice in phase 3 trials compared with a real-world setting. Therefore, the cost-efficacy ratios may be inflated among all the agents.

We should keep in mind the difference between “efficacy” and “effectiveness” when evaluating PE studies. Ideally, effectiveness rates derived from real-world experience should be used in PE analyses, but if effectiveness data are lacking, efficacy rates available in package inserts or published clinical trial studies may be substituted.

The final results of any cost-effectiveness study depend on the selection of the outcome under evaluation, and they may vary when other outcomes are considered. For instance, it should not be surprising if the cost-efficacy rank order (see Table 1) completely changes because the two-hour efficacy rates are replaced by a 24-hour efficacy outcome.

If efficacy rates are similar (i.e., if they are clinically not significant) or if they are statistically not significant (e.g., as with the two-hour efficacy rates for oral rizatriptan and zolmitriptan), a P&T committee might conduct a cost-minimization analysis or may choose to place a triptan on the formulary based entirely on the best price offered by the manufacturer.
Despite its limitations, a cost-efficacy ratio provides a useful method of determining the optimal price among the agents. An ICE analysis quantifies the value gained from additional dollars spent for a therapeutic agent. Results from sensitivity analyses showed that the cost-efficacy ratios were highly sensitive to the cost and clinical efficacies of the drug. A formulary review committee may elect to take the most conservative approach and use the lowest efficacy to make the decision because clinical efficacies are generally higher than real-world clinical effectiveness rates.

In terms of cost, the base case scenario showed that frovatriptan had the highest cost-efficacy ratio; however, this ratio would be the lowest if the drug acquisition price decreased from $17.40 to $12.08. The clinical benefit from this longer-acting agent should also be evaluated in patients who are helped by the longer half-life of this medication. This methodology may be used to negotiate the net cost to the plan (i.e., the drug acquisition price minus discounts or rebates) from the manufacturer in exchange for preferred formulary placement. Conversely, an MCO would be able to use a cost-efficacy analysis to determine the appropriate formulary tier for each agent in a category.

CONCLUSION

We have described how PE evaluations can be used to evaluate triptans for inclusion on a formulary. A simple analysis of cost-efficacy ratios can assist decision-makers in the selection process when comparative PE or effectiveness data are lacking.

REFERENCES