

Health Matters June 2007; Volume 2, Issue 1

Issues Raised on Avandia Safety by Deanna Daum and Trevor Hillman

In May 2007, the Food and Drug Administration (FDA) issued an alert on Avandia (rosiglitazone). This alert was issued in response to concerns that have been raised as to the safety of rosiglitazone in relation to increased risk of cardiac complications. These risks were detailed in an article published in the New England Journal of Medicine (NEJM) as a meta-analysis of 42 trials. 116 phase II, III, and IV trials were originally considered for inclusion into the analysis. This meta-analysis reviewed studies that utilized an experimental group receiving rosiglitazone, with a duration of treatment 24 weeks or more, and availability of outcome data of myocardial infarction or death due to a cardiovascular event(s). The total number of patients assigned to rosiglitazone was 15,560 with 12,283 assigned to control groups. In the rosiglitazone group, as compared to the control group, the odds ratio for myocardial infarction was 1.43 (95% [CI], 1.03 to 1.98; $p=0.03$). Only summary data was available, so time-to-event data was not obtainable. In addition, the data did not allow for discernment of

whether or not one person had more than one event.¹

The NEJM study states that rosiglitazone is associated with an increased risk of myocardial infarction and death due to cardiovascular related events.¹ The prescribing information of rosiglitazone warns of possible cardiac failure and other cardiac effects. It includes those patients with NYHA Class 1 and 2 congestive heart failure but does not include classes 3 and 4 cardiac status as they were excluded from the studies. The labeling clearly indicates that patients on rosiglitazone should be monitored and the drug should be discontinued if any deterioration in cardiac function is noted.²

Currently this issue is being further investigated by both the FDA and GlaxoSmithKline. GlaxoSmithKline is currently conducting a study: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD trial). The study is currently being conducted in over 300 centers and will take 6 years to complete. The study will be completed in 2009. There were 7000 subjects eligible for this open-label study.³ An unplanned interim evaluation of their RECORD study conducted by an independent safety and monitoring board is allowing the study to continue. This suggests the risks do not outweigh the benefits of the current study.⁴ The interim analysis of the ongoing trial was inconclusive on the overall risk of death or hospitalization from cardiovascular events (1.08; 95% [CI] 0.81 to 1.31). The interim analysis has little statistical power at the current time due to the relatively few number of patients that had completed the study (419 of 4485 enrolled) and an average of 3.75 years of the 6 year study being completed.⁵ The RECORD study when completed may provide a more robust analysis of cardiovascular outcomes of rosiglitazone in com-

parison to the meta-analysis that was recently published, although both studies do have weaknesses.

The FDA is aware of the potential safety issues of rosiglitazone and is currently reevaluating the findings of the 42 clinical studies regarding rosiglitazone and cardiac complications.⁶ Other published and unpublished data has shown contradictory evidence to the meta-analysis. The statistical methods used in the meta-analysis cited in the NEJM article have been disputed by experts leading to further questions regarding the validity of this analysis. Most experts agree that patients on rosiglitazone should continue with their current treatment at this time.⁷ Health care professionals should consider the possibility of ischemic events and congestive heart failure when making therapeutic treatment decisions.⁸

References:

- ¹Nissen SE, Wolski. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;336. Published ahead of print at www.nejm.org May, 21 2007 (DOI: 10.1056/NEJMoa072761).
- ²Glaxo Smith Kline. Avandia® prescribing information. Research Triangle Park, NC:2007 April.
- ³Home, P.D., S.J. Pocock, H. Beck-Nielsen, R. Gomis, M. Hanefeld, H. Dargie, et al. (2005). Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. *Diabetologia* 48, 1726-1735.
- ⁴Krall R. Cardiovascular safety of rosiglitazone. *The Lancet* 2007 May 30; letters to the editor.
- ⁵Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes -- an interim analysis. *N Engl J Med*. 2007.
- ⁶New safety information on diabetes drug rosiglitazone, Consumer Update. The Food and Drug Administration, Rockville (MD); May 25, 2007.
- ⁷Avandia (rosiglitazone) and the risk of myocardial infarction. Pharmacist's Letter/Prescriber's Letter 2007;23 (6):230670
- ⁸FDA Issues Safety Alert on Avandia. <http://www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm> (Accessed June 5, 2007)

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Aspirin Dose for the Prevention of CVD by Cody Kuszak

A systematic review was published in the Journal of the American Medical Association (JAMA) on May 9, 2007 regarding the correct dosage of aspirin to use in the prevention of cardiovascular disease (CVD). There has been much debate and many studies done over the years with the hope of coming to a conclusion on the appropriate long-term daily dose of aspirin. Currently more than 50 million US adults regularly take aspirin for the prevention of CVD.

The authors performed a systematic review of peer-reviewed publications over a 12 month period ending in September 2006. The trials evaluated included eight randomized controlled trials and three observational studies totaling over 10,000 patients with doses of aspirin ranging from 30 mg/d to 1500 mg/d. The majority of the cases reviewed were for secondary prevention of CVD rather than primary prevention. Of the trials reviewed, there was no significant benefit demonstrated with higher doses. The majority of the trials, in fact, showed a lower rate of CVD events in patients on the lower dose aspirin regimens.¹

The authors believed the best comparison included a trial containing 3131 patients randomized to receive either 283 mg/d or 30 mg/d of aspirin post TIA or stroke. Patients were followed-up after a mean of 2.6 years. The combination of end points evaluated consisted of vascular death, MI, and stroke. The results proved to be insignificant between the 2 groups (14.7% for 30 mg/d vs 15.2% for 283 mg/d; hazard ratio, 0.91; 95% confidence interval [CI], 0.76-1.09).² An analysis of 11 clinical trials containing 5228 patients randomized to aspirin ranging from 50 mg/d to 1500 mg/d or placebo following a TIA or stroke was also done. The results showed to be equally effective between the aspirin dose ranges.³ Continuing this trend, the Antithrombotic Trialists' Collaboration which consisted of more than 60 aspirin trials also found no relation between dose and efficacy.⁴ The greatest risk reduction in the analysis was found in the trials that used aspirin 75 mg/d to 150 mg/d.

Many studies have also looked at adverse effects between higher doses and lower doses of aspirin. According to the UK-TIA trial, there was nearly twice the risk of gastrointestinal bleeding of those patients taking 1200 mg/d vs the patients taking 300 mg/d.⁵ In the Dutch-TIA trial, a trend toward less bleeding was noted in the 30 mg/d group vs the 283 mg/d group.² Even more support was found when a meta-analysis of 31 clinical trials involving more than 192,000 patients related a significantly lower mean rate of bleeding in patients receiving less than 100 mg/d compared to patients taking more than 200 mg/d.⁶

Should the dose of aspirin be the same for all patients? Most of the data shows that efficacy does not increase with higher doses, but risks for bleeding does increase. Many small studies found variability in the individual response to aspirin. These studies looked at diabetic patients as well as differences between men and women. One meta-analysis of 6 trials found that there was a significant reduction in MI among men but no effect was found concerning stroke rate. The opposite was true for women. There was a significant reduction in stroke rate but no effect on MI.⁷ Larger-scale trials are still needed in the area of patient variability before we can answer this question clearly.

Aspirin is used by millions of individuals everyday. Overall, the trials included in the literature analysis revealed that higher dose aspirin was similarly efficacious to lower dose. Although not all trials analyzed used the same dosage range, the difference between higher-dose and lower-dose aspirin was found in the safety profile. The results illustrated that it was the lower doses that resulted in a lower risk of bleeding. Currently the clinical data supports the use of low-dose aspirin ranging from 75 mg/d to 81 mg/d. The question that still needs to be answered is whether or not every patient should be given the same dose of aspirin. Larger clinical studies are needed before this question can be answered.

References:

1. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin Dose for the Prevention of Cardiovascular Disease. *JAMA*. 2007;297:2018-2024.
2. Dutch TIA Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after transient ischemic attack or minor ischemic stroke. *N Engl J Med*. 1991; 325:1261-1266.
3. Johnson ES, Lanes S, Wentworth C, Satterfield M, Abebe B, Dicker L. A meta-regression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med*. 1999;159:1248-1253.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324:141]. *BMJ*. 2002;324:71-86.
5. Lattery J, Warlow CP, Shorrock CJ, Langman MJ. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin: analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut*. 1995;37:509-511.
6. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 21 randomized controlled trials. *Am J Cardiol*. 2005;95:1218-1222.
7. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295: 306-313.

AHA Guidelines for Infective Endocarditis Prophylaxis by Julie Capper

The American Heart Association (AHA) has been making recommendations on the prevention of infective endocarditis (IE) for more than 50 years.¹ The last guideline for prevention of infective endocarditis was published by AHA in 1997. Many organizations, societies and published studies have questioned the current guideline usage of prophylactic antibiotics for patients undergoing dental, gastrointestinal and genitourinary tract procedures. There have been several recommendations for the AHA to revise the 1997 guidelines. Members from the Rheumatic fever, Endocarditis, and Kawasaki Disease Committee of the AHA Council on Cardiovascular Disease in the Young and a national group of experts on infective endocarditis reviewed the data published on the prevention of infective endocarditis and made several recommendations for revision.

There are several reasons for the revision of the infective endocarditis prophylaxis guidelines:²

- It has been shown that IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU tract procedures.
- Prophylaxis may prevent a very small number of cases of IE, if any, in individuals who undergo a dental, GI tract or GU tract procedures.
- The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.
- Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.



There are several cardiac conditions associated with the highest risk of adverse outcomes from endocarditis for which prophylaxis with dental procedures is recommended. Prophylaxis with antibiotics should be recommended with dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa only for patients with underlying cardiac conditions stated below:²

- Prosthetic cardiac valve
- Previous IE
- Congenital heart defect (CHD)
 - Unrepaired cyanotic CHD, including palliative shunts and conduits.
 - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
 - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization).
- Cardiac transplantation recipients who develop cardiac valvulopathy.

For the patients who still need prophylaxis, the recommended regimen remains the same: amoxicillin 2 g for adults 30 to 60 minutes before dental procedures or clindamycin, azithromycin, or clarithromycin for patients allergic to penicillin.¹ For complete dosage guidelines please refer to the American Heart Association Statement on 2007 Guidelines for Prevention of Infective Endocarditis.

The new guidelines do not recommend that antibiotic prophylaxis should be used for GU or GI tract procedures. Prophylaxis is not recommended for other common procedures such as ear or body piercing, tattooing, vaginal delivery and hysterectomy.²

References:

1. 2007 AHA guidelines for infective endocarditis (IE) prophylaxis. Pharmacist's Letter/Prescriber's Letter 2007;23(6):230601.
2. Wilson W, Taubert K, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A Guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. www.circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095. (Accessed June 4, 2007).

New Generic Equivalents Available in 2007 by Jennifer Petersen

In the past year, numerous brand name products have been replaced on the shelves of pharmacies across the country with generic equivalents. Drug companies such as Pfizer, Sanofi-Aventis, Abbott, and GlaxoSmithKline are taking quite a hit as their once top-selling drugs are now being marketed as the generic equivalent at a reduced price to patients. Zoloft® (sertraline) and Norvasc® (amlodipine), which are both manufactured by Pfizer, Ambien® (zolpidem), which is manufactured by Sanofi-Aventis, Omnicef® (cefdinir), manufactured by Abbott, and Zofran® (ondansetron), which is manufactured by GlaxoSmithKline, are now all FDA-approved as generic products. Other prevalent prescription drugs that have patents expiring in 2007 are the antihistamine Zyrtec® (cetirizine) and the anti-migraine medication, Imitrex® (sumatriptan).¹

Norvasc®, a calcium channel blocker used to treat high blood pressure and chest pain, was the 9th highest selling brand name drug in 2006 with retail sales totaling more than \$2 billion.² Ambien®, a sedative hypnotic drug used for the treatment of insomnia, was the 13th highest selling brand name drug in 2006 with sales reaching \$1.9 billion.²

Zoloft®, an SSRI used to treat major depressive disorder and some anxiety disorders, was the 15th highest-selling brand-name drug in 2006 in the United States, with retail sales totaling close to \$1.7 billion.² Omnicef® (cefdinir), a cephalosporin antibiotic, and Zofran® (ondansetron), an anti-emetic agent, had retail sales reaching approximately \$700 million and \$600 million in 2006, respectively.²

To be approved as a generic drug, all products must go through the same FDA-approved process of making sure that the active ingredient, dosage form, strength, and conditions of use are equal to the brand name drug counterpart.³ The generic form must also have the same amount and rate of absorption as compared to the brand name drug, also known as bioequivalence.³ When a generic equivalent is approved, typically the first company to produce the generic receives exclusivity to market the equivalent product for six months. Following completion of this exclusivity period, other manufacturers may also produce the generic product. This competition will cause prices to decrease further, and is often when the most significant price reductions for generic medications are realized.

Brand name medications coming off patent in 2007 are valued at \$27 billion and in 2008 those coming off patent are valued at \$29 billion.⁴ In 2006, the average retail price of a brand name prescription was approximately \$111.02 and the average generic price was approximately \$32.23.⁴ Generic medications now account for around 63% of all prescriptions dispensed in the United States.⁴ With increased savings in cost and FDA approval in therapeutic equivalence and efficacy, most patients are looking at the use of generic products as a benefit in all aspects.

Information on currently available generic medications can be accessed through the [Creighton Drug Information website](#). Click on “generic alternatives chart” on the left hand side.

References:

1. Upcoming Patent Expirations, 2007-2009. Available at: <http://www.gphaonline.org/AM/Template.cfm?Section=Resources1&TEMPLATE=/CM/HTMLDisplay.cfm&CONTENTID=1597>. Accessed June 4, 2007.
2. Top 200 Brand-Name Drugs By Retail Dollars in 2006. Available at: <http://www.drugtopics.com/drugtopics/data/articlestandard/drugtopics/072007/405100/article.pdf6>. Accessed June 5, 2007.
3. New Critical Path Report Highlights Research Needed to Foster Generic Drug Development Available at: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01626.html>. Accessed June 4, 2007.
4. Generic Pharmaceutical Association Industry Statistics. Available at: <http://www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm>.

Drug Representatives Work to Sway Physician Choices by Laura Hansen

A recent article in the Public Library of Science (PLoS) Medicine journal shed some light on the tactics used by the people hired by drug companies to market their drugs.¹ A former Eli Lilly & Company drug representative gives an inside look as he explains the methods he was instructed to use in order to be successful at his job and influence physician prescribing as much as possible.

Drug representatives are hired for their outgoing personality and are trained to evaluate the character, practice style, and preferences of physicians. They use this information to tailor their message in an attempt to form a bond that will cause the physician to feel obligated to prescribe their drug. The goal is for physicians to view representatives as friends, although representatives view such relationships as business transactions.

After assessing the physician's personality, drug representatives put them into categories based on their receptiveness to the drug information provided, and a specific technique is followed in order to maximally change the prescribing behavior of the physician. Skeptical physicians are provided with abundant statistics and other drug-related information, while high-prescribers that seem easily-swayed are given things such as golf bags or silk ties. Even though some doctors may refuse to see representatives because they do not want to be persuaded, the representatives continue to seek out other employees of that particular physician's staff in order to find a way to influence the prescriber. Furthermore, almost every physician will agree to obtain samples, which has been proven to sway prescribing patterns.

Drug reps, cont. from page 4 Although physicians may believe the drug companies will not know who is prescribing their drugs, prescriptions are tracked so that the drug representatives are able to see the specific drugs physicians are prescribing and their change of prescribing habits over time. After viewing this information, drug representatives can modify their tactics.

Along with the gifts and samples physicians are given, they are also provided with an abundance of information. Even though a majority of physicians consider drug representatives their main source of new drug information, only 9% agree that it is “very accurate”. In fact, a study done in 1995 found that 11% of the facts provided by pharmaceutical representatives were inaccurate, with all of the erroneous information supporting the use of the drug.² Obviously, this false information could change a physician’s perspective on the medications they are prescribing.

All of these factors play a role in the drug the physician chooses to prescribe. Currently, there is approximately one drug representative for every 2.5 doctors.¹ Drug representatives seem to make ‘wining and dining’ an art form, and will continue to perfect their strategies until they reach their ultimate goal: to get physicians to prescribe their drug as much as possible.

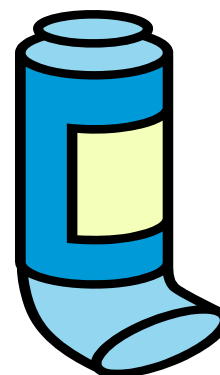
References:

1. Fugh-Berman A, Ahari S. Following the script: How drug reps make friends and influence doctors. *PLoS Medicine*. 2007;4:e150 OP.
2. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical sales representatives. *JAMA*. 1995;273:1296-1298.

UHC Changes Respiratory Drug Class Coverage

United Healthcare (UHC) has recently made changes to the tier placement of their asthma controlling inhaler category, based on a review of clinical, economic, and pharmacoeconomic data. This category of medications includes inhaled corticosteroids (ICS), long-acting beta-agonists (LABA) and one combination product. The new tiered placement for this category of medications is included in this article, and became effective 5/1/2007. In the UHC system, Tier 1 is the lowest copayment level and Tier 3 is the highest copayment level.

| Medication | Current Tier Placement |
|---------------------------|------------------------|
| Asmanex (ICS) | Tier 1 |
| Foradil (LABA) | Tier 1 |
| Pulmicort Flexhaler (ICS) | Tier 1 |
| QVAR (ICS) | Tier 1 |
| Advair (ICS/LABA) | Tier 3 |
| Azmecort (ICS) | Tier 3 |
| Flovent (ICS) | Tier 3 |
| Serevent (LABA) | Tier 3 |



Rationale provided by the UHC Prescription Drug List Management Committee included evidence suggesting some asthma patients are inappropriately managed (either under- or over-treated). Additionally, there is concern that the combination product Advair is being prescribed for indications not supported by clinical evidence, as it should not be considered a first-line treatment for mild asthma. Evidence also suggests that moving medications to a lower tier with lower costs may improve medication compliance.



Health Matters June 2007; Volume 2, Issue 1

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