



STATE MEDICAID P&T COMMITTEE MEETING  
 FRIDAY, October 19, 2007  
 7:00 a.m. to 8:30 a.m.  
 Cannon Health Building  
 Room 132



## MINUTES

**Committee Members Present:**

**Lowry Bushnell, M.D.**  
**Karen Gunning, Pharm. D.**  
**Raymond Ward, M.D.**  
**Koby Taylor, Pharm D.**

**Kort DeLost, R.Ph.**  
**Jerome Wohleb, Pharm D.**  
**Duane Parke, R.Ph.**  
**Thomas Miller, M.D.**

**Board Members Excused:**

**David Harris, M.D.**

**Dept. of Health/Div. of Health Care Financing Staff Present:**

**RaeDell Ashley**  
**Jennifer Zeleny**

**Lisa Hulbert**

**Other Individuals Present:**

Chris Beckwith, U of U	Nash Haleem, Takeda	Jim Hambacher, Abbott
Barbara Boner, Novartis	Mark Germann, Novartis	Matt Johnson, Takeda
Craig Boody, Lilly	Erika Brumleve, GSK	Deborah Griffis, GSK
Ben Focht, Amylin	Reed Murdoch, Wyeth	Brett Brewer, EMD Serono
Craig Southwick, GSK	John Vu, U of U	Mike Cobble, M.D.
Wayne Roberts, GSK	David Browning, GSK	Ed Drea, GSK
Dan Heincy, Merck	Don Perry, BMS	Eliot Brinton
Penny Atwood, Boehringer-Ingelheim	Lisa Sanchy Trask, Takeda	Jennifer Blake, SLC VA

Meeting conducted by: Karen Gunning, PharmD., Chairperson.

1. Minutes for September 2007 were reviewed. Dr. Ward made a motion to approve the minutes. The motion was seconded by Dr. Taylor. The motion passed with a unanimous vote by Dr. Ward, Dr. Taylor, Dr. Bushnell, Dr. Gunning, Dr. Wohleb, Dr. Miller Kort DeLost, and Duane Parke.
2. DUR Board Update: There is no update this month.
3. Election of P&T Committee Co-chair Person: Duane Parke addressed the Committee. Duane

has been directed to get a P&T Committee co-chair person. Since a pharmacist is the current chairperson, the co-chair needs to be a physician.

Dr. Harris nominated Dr. Ward by email submission. Dr. Bushnell seconded the nomination. Dr. Miller nominated Dr. Bushnell. Dr. Ward and Dr. Bushnell accepted nominations.

Dr. Ward asked what the responsibilities are. The responsibility is to conduct the meeting in the absence of the chairperson.

Dr. Taylor, Dr. Bushnell, Dr. Miller, and Dr. Gunning and Dr. Ward voted for Dr. Ward. Dr. Wohleb, Kort DeLost, and Duane Parke voted for Dr. Bushnell.

Dr. Ward was elected co-chairperson.

4. Antidiabetic Agents, Oral: Karen Gunning addressed the Committee. There are some agents that are the only agents in their class. These do not lend themselves well to a PDL discussion and will not be discussed during the P&T Committee meeting today.

Chris Beckwith addressed the Committee. As Karen Gunning stated, there are some agents that are unique in their class. These include agents such as acarbose, miglitol, sitagliptin, and metformin. They will not be discussed. The agents that will be discussed are the thiazolidinedions - there are two agents in that class, pioglitazone and rosiglitazone. Of the older oral hypoglycemic agents, they include chlorpropamide, glimepiride, glipizide, glyburide, micronized glyburide, tolazamide, tolbutemide, nateglinide, and repaglinide.

The base document for the thiazolidinedions was prepared by the Oregon Health Sciences Center. The Oregon documents set out key clinical questions for each class to help decide what are the clinical differences for the agents in that class. They conduct searches of the medical literature, both the Cochran Database, Medline Database, and other search databases to identify trials that address those questions. Once they identify the trials, they select the studies. In this case, both the documents from Oregon included studies that were conducted in adults with Type II Diabetes. The thiazolidinedione study also included patients that were being treated for prediabetes or metabolic syndrome to answer other key clinical questions. The included studies had to address primary outcomes of interest. For glycemic control, they had to address either hemoglobin A1C or fasting blood glucose, time to progression to insulin therapy, progression or occurrence of microvascular disease or macrovascular disease in diabetes, other complications of diabetes, mortality, and quality of life. For the thiazolidinediones study, they also had to have a sample size of 10 participants in the studies in order to have sufficient evidence to be included. In one stage of the search for the thiazolidinediones, they included a meta analysis of the key clinical outcomes to try and determine the differences between the agents. They included 87 randomized trials that compared the effectiveness of pioglitazone and rosiglitazone and 42 studies that addressed safety and tolerability.

The first key question was whether in patients with Type II Diabetes these agents differ in their ability to control hemoglobin A1C either when used as monotherapy or when added to or substituted for other oral hypoglycemic agents. Their conclusion was that pioglitazone equals rosiglitazone on both of these questions. For monotherapy, the difference in A1C between pioglitazone and rosiglitazone was -.24%, but the confidence interval for that difference did cross zero, so the difference was deemed statistically insignificant. For

combination therapy with other agents, the difference in hemoglobin A1C, which was reported as pioglitazone minus rosiglitazone was .21%. Again, this was not statistically significant.

The second key clinical question was whether the thiazolidinediones differed in their ability to prevent macrovascular and microvascular complications. There were only two studies that were included that evaluated this endpoint, and they did not provide enough data to actually determine whether there is a difference between the agents.

The third question is for patients with prediabetes or metabolic syndrome, do they differ from one another in improving weight control. There was not enough data to assess this. In many studies, they appeared weight-neutral or they caused slight weight gain, but the studies do vary in their endpoints.

For patients with prediabetes or metabolic syndrome, do they differ from one another in delaying the onset of clinical diabetes? Again, not enough data to determine whether or not there is a difference in the incidence of diabetes among these patients during treatment.

For patients with prediabetes or metabolic syndrome, do they differ in their ability to reverse or slow progression of cardiac risk factors, such as lipids, obesity, or elevated blood pressure? Again, there are not enough data to determine whether they differ in this. There are no data on assessing comparative effects on blood pressure. Both drugs have shown mixed effects on lipid levels.

For patients with Type II Diabetes, prediabetes, or metabolic syndrome, do they differ in safety or adverse effects, such as congestive heart failure, pulmonary edema, weight gain, liver toxicity, or hypoglycemia. There were only two head-to-head efficacy trials that evaluated this. There were no differences in the drugs for weight change, liver function tests, effects on creatinine kinase, blood pressure, heart rate, hemoglobin, hematocrit, hypoglycemic episodes, edema, or congestive heart failure. Total withdrawals and withdrawals due to adverse events were similar for both drugs. In looking at the indirect evidence from placebo controlled trials, the two agents appear similar for overall withdrawals, withdrawals due to adverse effects, edema, weight gain, and hypoglycemia.

How did they compare to sulfonoureas in serious hypoglycemic events, functional status, and quality of life? These comparisons have shown that comparing pioglitazone to sulfonoureas, there may be fewer hypoglycemic events with pioglitazone. Comparisons of rosiglitazone to sulfonoureas showed variable outcomes. In some cases with rosiglitazone, there were more hypoglycemic events with rosiglitazone or with combination therapy with rosiglitazone than with sulfonourea monotherapy. There have been other trials that have shown that hypoglycemia is similar with both groups.

The last clinical question - are there subgroups of patients based on demographics where there are differences between the agents. These would be things, such as racial groups, age, gender, obesity, other comorbidities, or history of hypoglycemic episodes in the past. Only two publications have examined subgroups of age. Most of the studies were conducted in Western populations with Caucasian patients, so it is difficult to draw any conclusions. In patients that were less than or greater than 70 years, there were no differences between the agents or between the age groups in blood pressure control or adverse events. The only one that defined a difference was a study that compared pioglitazone plus sulfonourea with

insulin, and hypoglycemia was higher in the elderly patients than in the younger age group.

Cardiovascular risk for these agents will be addressed after a review of the OHSU document on oral hypoglycemics.

For this Cochran review, they included studies that evaluated sulfonoureas and the short-acting secretagogos repaglinide and nateglinide. For this review, they were not able to do a meta-analysis because there were not enough trials. They prepared a table of the results instead. There were 12 trials that were included, and 5 of those were from the United Kingdom Prospective Diabetes study, which is the largest head-to-head trial ever done with these agents. That one made several comparisons. The ones of interest here are chlorpropamide versus glyburide or glipizide and metformin or sulfonourea versus conventional treatment, although this does not define conventional treatment.

The first key clinical question was for adult patients, do oral agents differ in the ability to reduce hemoglobin A1C? Overall, from the UK Prospective Diabetes study, there is a small absolute change in hemoglobin A1C with these drugs. The change occurs after about eight weeks, but diminishes with time from then on. The study found that chlorpropamide is equal in efficacy to either glyburide or glipizide for up to 5 years. Other trials that were conducted comparing these agents included studies of chlorpropamide, glyburide, glipizide, glimepiride, and repaglinide. There are no comparative studies for tolazamide, tolbutamide, or nateglinide, so it is hard to assess comparative efficacy for those agents. Because of that lack, they also included a systematic review evaluating the efficacy of oral hypoglycemic drugs compared to placebo in order to find some indirect comparison between the agents. This found no difference in effectiveness within the class of oral sulfonoureas or within the class of oral secretagogos when comparing the agents within each class.

The second question for adults with Type II Diabetes, do they differ in progression of occurrence of clinically relevant outcomes such as macrovascular or microvascular disease. There is only the UKPDS Study available. In that study, the glyburide was more effective than chlorpropamide - this is the only comparison. There is a long-term trial with repaglinide that evaluated simply treatment satisfaction and quality of life. It did improve treatment satisfaction, but had no impact on well-being or health status.

For adult patients, do these agents differ in safety or adverse events? Again the UKPDS study has the most data available. In that one, chlorpropamide caused more side effects than glyburide or glipizide overall, except that hypoglycemia was more common with the glyburide and glipizide. One systematic review evaluated these agents. This one found no significant differences in lipid profiles associated with any of the drugs that were included in this report. There are no comparative studies evaluating drug interactions, although drug interaction does differ between the agents.

Are there subgroups of patients where one of these is more effective or associated with fewer side-effects. With demographics, there is no evidence that any one of these agents has any advantage in effectiveness in any racial group, although there is not a lot of data to assess that. In obesity, one of the trials in the UK group analyzed metformin as one of the comparator groups. They found that patients who got metformin had a significantly lower risk of any diabetes endpoint over anyone who got sulfonoureas or insulin. In renal insufficiency, the only information that is available is for repaglinide. There is a recommended dosage adjustment in patients with renal failure or renal insufficiency.

However, one trial evaluated patients with renal insufficiency and found no difference in glycemic control, adverse events, hypoglycemia, or death in patients with normal or impaired renal function.

The next question that had come up was a comparison between the thiazolidinediones and the other oral hypoglycemics. Since these reviews came out from Oregon, the Oral Hypoglycemics had come out in May 2005 and the Thiazolidinediones was May 2006. In May of this year, the FDA put out a cardiovascular warning based on an early release of a New England Journal of Medicine article discussing risks of heart failure and myocardial infarction with rosiglitazone. Since that time, there have been other articles published that evaluated this risk. For that reason, the P&T Committee felt that the University Drug Information Center needed to do a more in-depth analysis of some of the adverse events. The University's approach was similar to Oregon's, except that they did not do a meta-analysis. For cardiovascular risk, they included only trials or meta-analysis. No observational trials were included. For fracture risk or other adverse events, the University did include some observational studies but utilized mainly clinical trials. The thiazolidinediones are very similar as far as labeling and warnings, even with the new information and alerts that came out this year. After the alert that came out with May, the product labeling for both agents was changed to include a black box warning for heart failure and cardiovascular events. They also both have precautions for the risk of fracture and for the risk of macular edema that were recently added this past year.

When comparing the thiazolidinediones with metformin or sulfonoureas, weight gain and edema tend to be less common with metformin than with the thiazolidinediones. With the thiazolidinediones, hypoglycemia tends to be less common than with sulfonoureas. Gastrointestinal disorders tend to be more common with metformin. This data is from direct head-to-head efficacy trials rather than meta-analyses. Weight gain occurs in the majority of clinical trials. During monotherapy, thiazolidinediones and sulfonoureas tend to increase body weight up to 5kg, whereas metformin tends to decrease body weight as much as 3kg. Of the trials that did report statistical comparisons between the agents, metformin causes statistically significantly less weight gain than pioglitazone in 2 trials, and less weight gain than rosiglitazone in 1 trial. Glyburide caused significantly less weight gain than pioglitazone or rosiglitazone in 1 trial each. These trials were variable in their outcomes.

Comparing risk of cardiovascular toxicity, compared with metformin, sulfonoureas, or insulin, thiazolidinediones may increase the risk of heart failure. That risk is 1.5-2.3% with thiazolidinediones versus up to about 1.8% with controls. However, cardiovascular mortality is not significantly increased. In the available published trials, risk of heart failure appears similar for pioglitazone with 2.3% versus rosiglitazone at up to 1.7%. Because of these new publications that came out, the FDA did strengthen the warnings on both drugs. Looking at these agents, the evidence that is available suggests that they both have similar safety in this regard. There were actually 3 meta-analyses that came out besides the one that the FDA was responding to. These showed that heart failure events were more common with thiazolidinediones than with controls; however, cardiovascular mortality was similar. That is the consistent theme, whether the meta-analysis evaluated pioglitazone, rosiglitazone, or both agents together. There were meta-analyses that were conducted between the two agents, and those studies found no risk between the agents.

As far as comparative effects on lipids, which is a surrogate marker of cardiovascular risk, pioglitazone consistently improves HDLs and triglycerides compared with insulin or

sulfonoureas. Rosiglitazone has HDL and triglycerides similar to other agents. Both thiazolidinedions worsened total cholesterol and LDLs more than metformin or sulfonoureas. Blood pressure changes are similar between the thiazolidinedions and metformin. There were 3 trials that reported differences in blood pressure changes between thiazolidinedions and sulfonoureas; however, they were very small numbers and it is not likely that these small changes would make a clinical difference.

Fracture risk was the other warning that came out recently. A long-term observational trial and analysis of the safety databases found that in women risk of fractures is higher - about 9% with thiazolidinedions versus metformin, which is about 5%, or sulfonoureas, which is about 3.5%. That was statistically significant. In men, there is no statistically significant difference.

Peripheral edema is more common with thiazolidinedions, up to 29%, compared to other oral hypoglycemic agents. Metformin is up to 7% and sulfonoureas is up to 14%. With the thiazolidinedions, peripheral edema may lead to discontinuation in up to 10% of the patients who experience this side-effect.

There are no data to assess the comparative risk of macular edema. It is a rare side-effect of either agent.

Pharmacodynamic interactions are similar between all of these drug classes. With metformin, there is an increased risk of lactic acidosis if it is given with contrast media, with other agents that are eliminated by renal tubular secretion, or with anticholinergic agents. Drugs that either inhibit or induce cytochrome P450 metabolism can effect both the thiazolidinedions and sulfonoureas. Combining sulfonoureas with fluoroquinolone antibiotics may increase the risk of hypoglycemia.

Recommendations for use in special populations differ between these patients. Metformin is contraindicated for renal dysfunction and for use in patients who are requiring therapy for heart failure. The thiazolidinedions are contraindicated in patients with class 3 or class 4 heart failure. This has recently been changed to a black box warning. Dosage adjustments for sulfonoureas need to be made in patients with some organ dysfunction. The risk of some adverse events differs between these classes; the impact of the cardiovascular mortality studies still is not clear, because each meta-analysis had some flaws and new information is still coming out. The bottom line is that both agents can increase the risk of heart failure, but do not increase the risk of cardiovascular mortality.

The University prepared a table that shows the available combination agents, just to show what is available. There are many combinations available for oral antidiabetics. These combinations will allow patients to take one tablet instead of several tablets once they are stabilized on a particular dose.

The Committee asked Dr. Beckwith if she anticipated any new information coming out for this class. New meta-analyses are coming out all the time. Two of the studies that were included in the University's study were also included in the meta-analyses that were conducted, so there is some crossover. The meta-analyses are drawing conclusions from studies that have already drawn conclusions on other data, so it is sometimes difficult to draw conclusions because so many data get lumped together and get re-analyzed in different ways.

The Committee asked if there data indicated any pluses or minuses between TZD's or metformin based on the data that were analyzed by the University. For a patient who is obese, metformin may minimize weight gain and, sometimes, actually cause weight loss. Long-term there are no outcome studies with metformin. Other agents do have long-term outcome studies. The UKPDS study followed patients for up to ten years. It did find differences in glycemic control between glyburide and chlorpropamide, but there is not enough data to assess the differences in these older agents for differences such as macrovascular complications.

Dr. Nash Haleem, Regional Scientific Manager from Takeda addressed the Committee about the Actos family of products. Recently, the Actos family of products labeling was updated to include the increased risk of fracture in women who are taking Actos. Also, there is the Black Box Warning regarding the risk of heart failure. As was mentioned, the information in the previous PI was placed in the Black Box to be more prominent, so that physicians would really pay attention to it. When it comes to cardiovascular safety, it is important to differentiate between congestive heart failure and ischemic events. Ischemic events are more damaging, causing irreversible damage to the heart. Regarding the cardiovascular events, there are 3 different studies that address that. The one that is actually not mentioned is in the August issue of Pharmacoepidemiology and Drug Safety. Dr. Garrett and colleagues published an observational study from the Ingenix database to determine the risk of hospitalization for MI in Type II Diabetic patients who are receiving Actos in comparison to those who are taking rosiglitazone. There was a total of 29,911 patients eligible for analysis, 14,807 patients in the pioglitazone group and 13,108 patients in the rosiglitazone group. The author concluded the pioglitazone compared to rosiglitazone is associated with a significantly (22%) relative risk reduction of hospitalization for MI of patients with Type II Diabetes. Another which is mentioned, a meta-analysis of the Actos clinical trial database, published in the journal on September 12, by Lenkov, et al. The study objective was to evaluate the effect of pioglitazone on systemic cardiovascular events. The meta-analysis included 19 trials representing 16,390 patients. The author concluded that pioglitazone is associated with significantly (18%) lower risk of death from MI and stroke. Although, without an association of increased mortality, serious heart failure was more reported with the pioglitazone group. The gold standard in evidence-based medicine is the retrospective study. The Proactive study was a prospective randomized placebo controlled clinical trial. This study included 5,238 patients with Type II diabetes and a history of macrovascular disease. The study showed that there was no increase in mortality or macrovascular events with the Actos. The prescribing information for the Actos family of products was updated by the FDA to include this reassuring safety data, making Actos the only TZD with safety data from a cardiovascular outcomes study in its label. Also, three years ago, there was a head-to-head study to compare the lipid effects of pioglitazone and rosiglitazone. It was over 700 patients, and the pioglitazone had a more favorable effect on lipids and triglycerides. There was a huge difference in increasing LDL, the quality of the particles was impacted as well. Given the strength and consistency of the Actos data, as demonstrated by Proactive, the meta-analyses, and head-to-head studies, Takeda remains confident in the Actos safety profile regarding the risk of macrovascular events. The P&T Committee is asked to make Actos available to the Utah Medicaid clients.

Deboarh Griffis, PharmD., Regional Medical Scientist of GSK addressed the Committee regarding the Avandia franchise. Since their availability in 1997, there has been speculation that the TZD's may decrease cardiovascular risk. In studies, the TZD's reduce hyperlipidemia, hyperinsulinemia, blood pressure, microalbuminuria, and markers of

inflammation, improve endothelial function, have a net positive impact on lipids, and their mechanism of action is associated with improvement in several vascular biological processes that control arterogenesis. The TZDs have been tested in acute injury models and have demonstrated a reduction in the risk of stent occlusion, and have likewise demonstrated favorable effects in models of arterogenic progression. This class of drugs has, therefore, been widely anticipated to deliver positive macrovascular outcomes despite the inability of other oral antidiabetic agents to do so. To date, however, no TZD trial has delivered significant macrovascular benefit, including the Proactive. Earlier this year, Nissen and Woosky reported a meta-analysis of 42 clinical trials, including 40 small trials combined with 2 larger landmark trials. This analysis resulted in controversy by concluding that treatment with Avandia was associated with significant and greater relative risk of Myocardial Infarction as compared to placebo or other comparator antidiabetic agents. Neither the 40 small trials combined nor the two landmark trials showed an increased risk of MI or cardiovascular death. Only when these data were meta-analyzed together did the authors show an increase in the relative risk. The evaluation was conducted using aggregate, unadjudicated, and heterogeneous data using a methodology that the author concedes has significant limitations. Further, the actual rate of MI was slightly less in Avandia than in the comparators at 0.6% versus 0.66% respectively. A recent publication by academicians at UCLs reviewed Nissen and Woosky's paper in detail, and have highlighted limitations of the analysis, including possible misclassification of events, significant variability in inclusion and exclusion criteria, dosing regimens differing among the trials, use of aggregate level data, failure to report search methodology, inclusion of populations of patients that are not diabetic, utilizing statistical methods that allowed for exclusion of trials where no events occurred, and low overall event rates in the trials. These authors concluded that available data established neither an increase nor a decrease in MI or death from cardiovascular disease among diabetic patients receiving Avandia. With the exception of known heart failure risks, results or interim results from three long-term prospective trials have not revealed significant ischemic risk among Avandia-treated patients. Furthermore, several evaluations of real world medical claims, including two independent analyses from Wellpoint and Tricare that were presented at a recent FDA advisory committee revealed no increase in ischemic risk in TZD exposed patients and no greater risk in Avandia versus Actos treated patients. Committee members are encouraged to look at the Takeda-sponsored analyses that were referred to by Dr. Haleem. Finally, Avandia is currently being studied in several large long-term cardiovascular trials that are under way. These include GSK's Record and Advantage studies, the Veteran's Affairs trial, the NIH's Accord trial, and the Bary 2D studies sponsored by the National Heart Blood and Lung Institute and The National Institute of Diabetes Digestive and Kidney Diseases. Importantly, these studies represent patients across the spectrum of diabetes and cardiovascular disease, with patients in some studies so far advanced as to be candidates for revascularization. Independent monitoring committees review the safety data regularly, and each of these trials continue to be underway. Avandia is the most widely studied oral antidiabetic marketed today. It is the only TZD with landmark data from large prospective trials, which illustrates the long-term safety and efficacy of the  $\alpha$  mechanism in diabetics and prediabetics alike. It is the only TZD that provides long-term safety and efficacy comparisons head-to-head with other oral antidiabetic agents. A diabetes progression trial or ADOPT was an international multi-center randomized double-blind placebo-controlled trial involving over 4,000 patients with a median follow-up of 4 years. ADOPT was conducted to evaluate the durability of glycemic control in recently diagnosed Type II Diabetic patients receiving Avandia, metformin, or glyburide monotherapy. The primary outcome was time to monotherapy failure. The cumulative incidence of monotherapy failure at 5 years was 15% for Avandia, 21% for metformin, and

34% with glyburide. This represents a significant 32% and 63% relative risk reduction with Avandia over metformin and glyburide respectively. Statistical analysis of ischemic events suggests that the risk of MI, cardiovascular death, stroke, and major adverse cardiovascular events in patients exposed to Avandia is similar to those exposed to metformin or sulfonoureas. There was a significantly higher incidence of limb fractures observed among women in this trial, and those have been noted in the product labeling. The ADA and the American Association of Clinical Endocrinologists acknowledge that glycemic control is the key helping minimize the complications associated with Type II Diabetes. The ADOPT trial clearly provides evidence that Avandia is an important agent to aid physicians in maintaining long-term glycemic control. The Avandia franchise not only provides with intuitive and easy-to-use fixed dose combinations in Avandamet and Avandaryl, but also provides broader product labeling for use with other oral antidiabetic agents. Studies have shown that these have increased patient compliance and may reduce patient costs.

Duane Parke asked Dr. Griffis to elaborate on lipid profiles. This has been a point of competition in the class for some time. The data started originally from comparisons retrospective studies in clinical practice where it was difficult to analyze lipid assessments, because there were no controls for things such as statin use. Only one trial, to date, has studied the lipid profiles of the agents head-to-head, and that was the study that was referenced by Dr. Haleem. It was a large study, and both drugs were seen going in a similar direction. Both drugs increased LDL, HDL, changes in particle size, and triglycerides. There were some modest differences in triglycerides. There have been large studies that have evaluated the effects of large drops in triglycerides, and this has been shown to not be effective with respect to cardiovascular disease, particularly when patients are being appropriately managed.

Dr. Haleem responded that in the Proactive study, patients that were being given statin therapy were eliminated to ensure that there is no statin effect. There was a second study, called the Compliment study. In this study, patients that were on a statin and rosiglitazone for at least 90 days were converted to pioglitazone plus the same statin. A remarkable decrease in triglycerides was observed.

Dr. Griffis asked the Committee to review this paper, since there was a one-way switch of patients from rosiglitazone to pioglitazone, but the reverse was not studied so no comparison could be made.

Dr. Mike Cobble, family practice physician, addressed the Committee. Dr. Cobble was not representing any company. His interest in cardiovascular care and diabetes is driven by family history of diabetes and cardiovascular disease. Diabetes is an epidemic. The United States has seen an explosion in cases of diabetes in the last 10 years. Much of this is due to food and lifestyle choices. He wanted to address some of the recent controversy and discuss the UKPDS study, which as produced some excellent data. The big thing in diabetes care is always maintaining access to care, affordability of care, and monitoring the safety and efficacy of the products that are being used. The current guidelines are to start with metformin and therapeutic lifestyle changes when someone is diagnosed with diabetes, and then add insulin, an SU or a TZD if they are not at goal after 3 months. The ADA and the ACE have not made a distinction on the TZDs - they would continue to use either Avandia or Actos. Dr. Nissen's article that has created a lot of controversy was comparing 86 deaths in the Avandia group of 16,000 patients versus 72 heart attacks in 12,000 comparator patients. This is a heart attack incidence of only 170 heart attacks in 28,000 patients with a

14 heart attack difference. This actually gives a balance of favor to the rosiglitazone group. The way Dr. Nissen breaks down the number, this is a 43% increase between 72 and 86, but he does not count the extra 4,000 patients. George Diamond re-evaluated the data and showed no statistical difference using an appropriate statistical analysis. Now Dr. Nissen has re-published some sponsor data from Takeda using their 19 studies showing no evidence of an issue. Dr. Singh has presented data in JAMA using the 3 large outcomes studies of Avandia, all of which showed no mortality or morbidity issues, yet he includes one small heart failure study that makes the meta-analysis look like a 40% increased risk of MI. Including the same pioglitazone heart failure data without the rosiglitazone heart failure data, it would come to the same conclusion about pioglitazone with a 41% increase in a very small number of patients. Dr. Nesto in the Lancet recently looked at the number needed to harm for heart failure, MI, or death with a TZD. The number needed to harm with a TZD is 106 patients for CHF. This is not myocardial damage. In these cases, CHF is just edema or peripheral fluid retention. The number needed to harm with amlodipine was 40; the number needed to harm with insulin is about 43; the number needed to harm with SUs or metformin is about 100 as well. The incidence of mortality for this study was rosiglitazone 0.93 and pioglitazone was 1.01; both of those crossed the line. UKPDS showed a 40% reduction in morbidity and mortality for metformin; however that was not statistically significantly different from insulin or sulfonoureas but significantly better than conventional care. Looking at the people were on an SU and then added metformin 6 years later, there was an 86% increase in mortality using SU and metformin together. This shows how complicated diabetes is and how difficult it is to do a meta-analysis with a small number of patients. Without 80,000 to 100,000 patients, the conclusions that are reached can be very incorrect. Proactive in the pioglitazone research study on a very high risk group of patients showed a relative risk reduction in heart attack, stroke, and death of 16% with a number needed to treat of 45 and a number needed to harm of 89. In the Record study with rosiglitazone, there was no increase in the risk of heart attack or death with a number needed to harm of 89. In the Dream study, the number needed to treat to prevent diabetes was 5-7 people and the number needed to harm with fluid retention was 250. In the Adopt study, looking at SU and metformin and Avandia for 5 years, there was no evidence that one was any different from the other, other than the TZD preserved beta cell function for 60 months, SU for 33, and metformin 45 months with 15% failure on rosiglitazone, 21% on metformin, and 35% on SU.

Dr. Casey Stelter from Layton, UT provided comment by way of a letter. Formal evidence is not yet adequate to negate the use of TZDs as a class, or Avandia, specifically, in the collective patient population. He has a significant number of Medicaid patients on Avandia that continue to do well.

Dr. Vernon Liu from Sandy, UT provided comment by way of a letter. He asks that Medicaid continues to allow patients to have access to Avandia and Actos on the PDL.

Karen Gunning pointed out that the concerns expressed in both letters are addressed by the current override system that is available to prescribers.

Dr. Dana Clarke addressed the Committee. He teaches at the Diabetes Center. The TZDs, as a class have been exceptionally valuable to the armamentarium. Because of continued success in their use in the clinical arena, Dr. Clarke asks the Committee to retain the use of both agents on the PDL.

Karen Gunning stated that it appears from some of the meta-analyses that there are subgroups

of patients that may have more of the negative effects or adverse effects. She asked if there is a way of predicting that. Dr. Clarke said that the predictors are as stated. With individuals who have a history of any congestive heart failure, one needs to be especially careful. This includes people with a history of MI or plural MIs. In individuals who have inordinate sodium intake, understanding the mechanism whereby TZDs can lead to edema or weight gain or congestive heart failure.

Karen Gunning asked Dr. Clarke if he could compare the efficacy of the two agents. Dr. Clarke stated that he believed that the two TZDs were equal to each other. Comparing TZDs to other agents, however, the TZDs are equivalent as monotherapy.

Dr. Cobble wanted to address a pharmacoepidemiology study that was brought up. It is an important study to look at that had 50,000 patients on rosi and pio. Looking at that, it is important to compare the baseline drugs that the patients were on, because in the pio group had 10-30% more access to agents such as ACEs, ARBs, beta blockers, diuretics, statins. It was a better treated population. Karen Gunning pointed out that these problems were why the University does not include this study in its analysis.

Karen Gunning asked if the Proactive trial has been published. Dr. Haleem stated that it is published about 1&1/2 years ago in the Lancet. Dr. Beckwith stated that they did not include this trial because there were other trials available with active comparators, and this was placebo-controlled. Dr. Haleem stated that the placebo group in this study was actually being treated with the standard of care. Dr. Beckwith clarified that they did not include the trial because it lacked an active hypoglycemic comparator.

Dr. Brinton addressed the Committee. It looks as if the summary provided for the meeting did not adequately address active atherosclerotic coronary events versus generically cardiac events. Those two are different, specifically because of the occurrence of congestive heart failure which is one thing, versus the cardiac death from heart attack, stroke, etc. There is a hierarchy of validity or value of available data. At the top would be randomized clinical trials, although there can be issues with those trials. The Proactive trial and the Record trial, despite the issues that they may have, are the best trials available with regard to cardiovascular atherosclerotic risk. Proactive has been faulted in that there was no active comparator and in that their primary endpoint was not statistically significantly improved. However, for the secondary endpoint, which is a traditional primary endpoint, there was a statistically significantly better outcome. Granted, one has to consider how it would have been different had there been an active comparator. The Record study is very different because of its 2X2X2 design. This study does have a drawback of the interim analysis is underpowered to show difference. Also, the study design may have been predisposed to show a different answer. This study, in terms of interim analysis available shows a lack of trend in either direction. This is important because that negates the argument against the power question. If there is a lack of trend, this suggests that there is no increase. He is perplexed to understand why the FDA voted to indicate that there is an increase, because the single best piece of evidence shows that there is no increase. Then it goes into meta-analyses and observational data. In his opinion, the data shows that rosiglitazone is no different than other agents in terms of coronary atherosclerosis. There are some caveats with that - maybe it is a little higher with insulin, maybe it has to do with sodium retention that is seen with both insulin and TZDs that predisposes to coronary events. There are certain settings in which rosiglitazone may have somewhat of an adverse effect, but across the board it probably has the same effect on cardiovascular events as do nearly all of the other antidiabetic drugs.

This is generally fairly neutral. In contrast, there is reasonable evidence that pioglitazone may be somewhat beneficial, although the evidence is not very strong. The question today is if one or both of the TZDs should be on the PDL. Dr. Brinton asks that both be included on the PDL, since this is advantageous to the patient and the clinician. If only one can be chosen, pioglitazone may have some advantages.

Dr. Ward felt that the information that the P&T Committee received from the Drug Information Center was well summarized, and that it is not possible to say that one of the thiazolidinediones is any more effective than the other. Even though there is a cloud hanging over the class with the Black Box Warning, the class continues to be valuable. This class fits nicely into a category of drugs that is similar and that the decision on the drug class should be made on cost.

Dr. Miller seconded the motion.

The motion passed with a unanimous vote by Dr. Ward, Dr. Taylor, Dr. Bushnell, Dr. Gunning, Dr. Miller Kort DeLost, and Duane Parke.

Karen Gunning stated that the issues that Dr. Brinton and Dr. Cobble brought up may be a good discussion for the DUR Board. The questions of patient appropriateness and of patients who are at risk for harm are the purview of the DUR Board. The Board may wish to create evaluation questions to address this.

Dr. Mark Germann, Senior Regional Account Manager with Novartis, addressed the Committee. Starlix is an agent that effects a normal physiological insulin release in response to a meal. Normal patients have a biphasic post-prandial glucose spike, usually occurring within 10 minutes. Most patients are in the post-meal state for 50% of the day. Adding 3 established high-prevalence of glucose spikes of A1C of 7 and above being 99% of the patients. Those patients below 7 about 40% had post prandial hypoglycemia. The World Health Organization does recognize post prandial glucose measurement as important criteria for Type II Diabetes. Starlix is approved as an add-on to metformin for those patients that are not at their A1C goal. It does offer a dual approach in terms of attacking post prandial glucose. It offers a one dose with no dose titration. The recommendation is to take it 1-30 minutes before a meal. It acts very quickly; it increases insulin about 20 minutes after ingestion. Peak plasma concentrations are reached in an hour and normal insulin state is reached within 4 hours of dose. There are no dose adjustments required for this medication based on age, race, gender, mild to severe renal insufficiency. Most common adverse events are hypoglycemia, upper respiratory infection, and diarrhea. The UKPDS trial indicates clearly that controlling HB A1C leads to significant reduction in stroke and MI. Starlix contributes a novel approach in controlling post prandial glucose spikes. The P&T Committee is asked to place Starlix on the PDL.

Dr. Cobble stated that there is one comparative evidence-based study comparing sulfonoureas versus the secretagog class in vascular biomarker studies looking at atherosclerosis. Sulfonoureas did not show any atherosclerosis benefit, but meal secretagogos did show atherosclerotic regression.

Duane Parke commented on the utilization data that was provided to the Committee. If there is a generic available, the brand name of that drug has an automatic Prior Authorization requirement placed on it.

Dr. Brinton stated that there are two very different classes of secretagogos. One is the older sulfonoureas and the other is the newer nateglinide class. The one greatest advantage of the nateglinide class is the lower incidence of hypoglycemic events. That is a fairly major problem with the sulfonoureas. Having availability of at least one agents in the nateglinide class is very useful for that reason.

Dr. Ward stated that as far as outcome studies, there is nothing to say that this class is clearly superior, even though this group is more heterogeneous than the two thiazolidinedions. He recommends that the department make the choice based on cost, bearing in mind that the clinician has continued access to all agents with the "Medically Necessary - Dispense As Written" override.

Karen Gunning stated that from a safety standpoint, the drugs do not cause a lot of differential adverse events, but there are patients in which one would chose gilpizide versus glyburide based on underlying hepatic or renal dysfunction. She asked if the generic drugs would all be included on the PDL. This issue has not yet raised its head. Therefore, the Committee is only considering the branded agents, Prandin and Starlix, in the motion.

Dr. Ward did not see a need to explicitly include those agents on the PDL. There are no significant differences in safety or efficacy. In the few instances where he would feel that it is appropriate to go the extra mile and write "Medically Necessary - Dispense As Written" he would be willing to do so. The Department should choose agents in the older oral hypoglycemic classes based on cost.

Dr. Bushnell seconded the motion.

The motion passed with a unanimous vote by Dr. Ward, Dr. Taylor, Dr. Bushnell, Dr. Gunning, Dr. Miller Kort DeLost, and Duane Parke.

Karen Gunning also recommended that the DUR Board review utilization in this class to perhaps add hard edits on quantity limitations, and preventing the use of secretagogos with sulfonoureas.

5. Projected Future Action: Long-acting Opiate analgesics will be addressed next month. After that, the Committee will go through the antihypertensive classes class-by-class. The Committee is asked to indicate any specific needs to the Drug Information Center.

Duane Parke stated that the DUR Board has already imposed some hard quantity limits on monthly use for opiates.

Karen Gunning asked the Drug Information Center to provide any evidence available to support the use of combinations of opioid analgesics.

Next Meeting Set for Friday, November 16, 2007.  
Meeting Adjourned.

Minutes prepared by Jennifer Zeleny