



Washington State Health Care Authority  
**Prescription Drug Program**  
P.O. Box 91132 • Seattle, Washington 98111-9232  
206-521-2027 • FAX 206-521-2001 • TTY 360-923-2701 • [www.rx.wa.gov](http://www.rx.wa.gov)

UNOFFICIAL TRANSCRIPT\*  
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

December 17, 2008  
Marriott Hotel Seatac WA  
9:00am – 4:00pm

**Committee members in Attendance:**

Angelo Ballasiotes, Pharm D  
Carol Cordy, MD (Vice Chair)  
Barak Gaster, MD  
Jason Iltz, Pharm D  
Janet Kelly, Pharm D  
T. Vyn Reese, M.D.  
Kenneth Wiscomb, PA-C  
Robert Bray, MD

**Committee members on conference call:**

Patti Varley, ARNP

**Committee members absent:**

Alvin Goo, Pharm D

Jeff Graham: Jeff Graham. Healthcare Authority.  
Barak Gaster: Barak Gaster. General internist at the University of Washington.  
Carol Cordy: Carol Cordy, family physician in Seattle.  
Vyn Reese: Vyn Reese, internist and chair.  
Angelo Ballasiotes: Angelo Ballasiotes, pharmacist from Yakima.  
Robert Bray: Robert Bray, part of the committee.  
Regina Chacon: Regina Chacon, Healthcare Authority.  
Donna Sullivan: Donna Sullivan with the public employees health plans.  
Adele Robins: Adele Robins, pharmacy student, Healthcare Authority.

---

\* For copies of the official audio taped record of this meeting,  
please contact Regina Chacon at (206)521-2027 [pdp@hca.wa.gov](mailto:pdp@hca.wa.gov).

Duane Thurman: Duane Thurman, Healthcare Authority.

Ray Hanley: Ray Hanley, Healthcare Authority.

Jeff Thompson: Jeff Thompson, Medicaid.

Vyn Reese: There are also several announcements. Go ahead Jeff.

Duane Thurman: Oh we should introduce who's on the phone.

Jeff Graham: Could the members on the phone.

Patti Varley: Patti Varley, P&T committee member.

Siri Childs: Siri Childs, Medicaid.

Duane Thurman: Just remember to speak into the mic so we can hear people on the phone and we're recording the meeting so that if we need a record, identify yourself please.

Vyn Reese: Okay, now you can do your announcements.

Jeff Graham: We'd like to say that we have two members that have been reappointed to the P&T committee for three year terms. That's Carol Cordy and Patti Varley. The other announcement is we are attempting to end this meeting at one o'clock today and not have the DUR meeting. So it would help to move right along with it. Our first presenter is calling in from Austria, I hope he calls in very soon. Generally he's right on time.

Vyn Reese: Jeff, one question, are we going to do the combination drugs after lunch, or are we going to...

Jeff Graham: It will be at 12 o'clock.

Vyn Reese: So we're going to stop at 12.

Jeff Graham: No, no, no we're going to do them at 12 and be done by one.

Vyn Reese: Got it, okay.

Jeff Graham: Hopefully. Or 1:15.

Vyn Reese: Is the presenter for the first item on the agenda on the phone?

Jeff Graham: Gerald are you there? Let's give him a minute or so.

Woman: He was there already.

Jeff Graham: Was he?

Woman: Yea.

Jeff Graham: You talked to him?

Woman: He responded.

Gerald Gartlehner: Hello?

Jeff Graham: Oh there you are, good. Speak up.

Gerald Gartlehner: Yea, sorry, I had the microphone muted.

Vyn Reese: The first slide is up. This is Gerald Gartlehner.

Jeff Graham: So the first slide is up Gerald. So whenever you're ready, go ahead.

Gerald Gartlehner: Okay. So welcome. My presentation today is about the fourth update of our review on second-generation antidepressants. On slide two, we are just summarizing the included medications. We have not added any new medications for this update. Slide three and four summarize our indications of interest. We have added two new indications for this update. These were seasonal affective disorder and subsyndromal depression, also called minor depression. And then on slide four, nothing has changed for pediatric indications, the only indication of interest for us is still major depressive disorder in children.

So then, on slide five, it's a summary of the result of this update. Overall, we have included 91 new studies. Among those, 33 head to head trials. And as you see, it was a very large update and because it was so large and also because of the time restrictions here, we'll only describe new evidence. If it has changed any of our conclusions or if it is entirely new evidence on the comparison where we have had no evidence so far. In our report, all the new studies are then described in detail anyway.

So slide six, major depressive disorder in adults, overall we have included 19 new head to head trials. One of these studies was our own report for the [inaudible] Organization Act on second-generation antidepressants. In this report, we did a very comprehensive, systematic review on second-generation antidepressants and we used a statistical technique called network meta-analysis to compare each of the 66 possible comparisons among second-generation antidepressants. Findings of this report and also of the other new studies have not changed any of our conclusions. We are still saying that there are no substantial differences in efficacy between second-generation antidepressants for the treatment of MDD in adults.

Then, on slide seven, dysthymia we did not find any new studies on dysthymia.

Slide eight, subsyndromal depression. Subsyndromal depression was one of the new indications that we have added. Right now, none of the antidepressants is approved specifically for minor depression. We did not find any head to head [inaudible]. The only head to head evidence that we found was a non-randomized single blinded trial that lasted one year, which actually did not meet our formal inclusion criteria, but we are briefly describing it because it is the only head to head evidence. This study compared Citalopram with Sertraline in patients with late life subsyndromal depression and no significant differences in efficacy could be detected at any point in time.

So then slide nine. In addition to the head to head trial we found two placebo controlled studies, one was a fair 12 week trial that showed significantly greater improvements with Fluoxetine than with placebo. The second study was actually a primary care-based effectiveness trial that determined the effectiveness of paroxetine behavioral therapy and placebo in patients with dysthymia or minor depression. Overall, interestingly, paroxetine was not more efficacious than placebo.

Then slide ten, seasonal affective disorder. Seasonal affective disorder is the second new indication that we have added. Currently only bupropion has FDA approval for treatment of seasonal affective disorder. Again, we did not find any head to head studies and as with all the other indications, we viewed FDA approval as evidence for the general efficacy. So in the report, we do not elaborate on the bupropion studies any more. In addition, we found two studies on drugs that have not been FDA approved yet, one on Fluoxetine and one on Sertraline. Fluoxetine did not show any difference in clinical response compared with like therapy, while Sertraline had significantly higher response rates than placebo.

Slide 11, major depressive disorder in pediatric patients. We added six new studies that basically confirmed what we already knew. Fluoxetine appears to be the only drug with a favorable risk-benefit profile. Four new studies on escitalopram and paroxetine did not show that they were more efficacious than placebo.

Next slide, slide 12, generalized anxiety disorder. For GAD we found three new head to head trials. Two of these studies showed similar treatment effectiveness between paroxetine and venlafaxine and between duloxetine and venlafaxine. The third trial then was a head to head trial that compared a fixed dose of escitalopram, ten mg of escitalopram with 20 mg of paroxetine and results actually showed statistically more responders with escitalopram. However, we could not really assess the clinical significance of this finding, because the response rates were not recorded in the publication, they just provided the p value.

Then, slide 13, obsessive compulsive disorder. We found two new studies for OCD. A 24 week head to head trial did not find any differences between paroxetine and escitalopram and a meta-analysis of placebo

controlled trials indicated that [inaudible] actually were similar among second-generation antidepressants.

Slide 14, for panic disorder, we included two new fixed dose trials comparing venlafaxine ER with paroxetine. One study did not show any differences, the other one compared a high dose of venlafaxine with a medium dose of paroxetine and found a greater response rate of venlafaxine, but the external validity is probably low of this trial.

Slide 15, post-traumatic stress disorder. We found one head to head trial that compared venlafaxine ER with Sertraline. This was a 12 week placebo controlled RCT and at the study end point response rates were numerically higher for venlafaxine, but in all of the other primary outcome measures the efficacy and venlafaxine and Sertraline was very similar. Two additional placebo controlled trials did not find any differences in efficacy between Fluoxetine and placebo and a third study confirmed the general efficacy of venlafaxine.

Slide 16, social anxiety disorder. For social anxiety disorder we did not find any new head to head evidence. We have included two new placebo controlled trials. One showed a greater efficacy of Fluoxetine than placebo. The other one could not detect any differences in efficacy between nefazodone and placebo. And then finally, a fair meta-analysis found that SSRIs as a class are more efficacious than placebo for the treatment of social anxiety disorder.

Slide 17, we did not find any new evidence for premenstrual dysphoric disorder.

Slide 18, for adverse events we have added 16 new studies and overall these studies did not change any of our conclusions. Only one study that we thought was interesting was an analysis of FDA data, which confirmed that bupropion actually has a higher risk of seizures. So far, the evidence on the risk of seizures for bupropion was mixed, but this is possibly the best evidence we have so far.

Then, slide 19, subgroups. For subgroups we have added 28 new studies, although these studies did not change any of our conclusions. Most of them were placebo controlled trials and subgroups or patients with certain comorbidities. They basically provide indirect evidence at best. Details about these studies are summarized in the report, but as I said, they did not change any of our conclusions.

Slide 20, as you know, there is one new second-generation antidepressant that has been approved for the treatment of MDD in adults by the FDA. It is desvenlafaxine or Pristiq and we have not included desvenlafaxine in this update yet. Desvenlafaxine is a serotonin-norepinephrine reuptake inhibitor and it is the major active metabolite of venlafaxine XR, which will lose patent protection soon. The approval of desvenlafaxine is based

on four placebo controlled trials and a quick search of Medline actually found no head to head trials of desvenlafaxine with any of the other second-generation antidepressants.

This is my last slide, so if you have any questions, please go ahead.

Patti Varley: This is Patti Varley. I'm curious, there was no evidence at all in children with anxiety or OCD, is that correct?

Gerald Gartlehner: This is not, we were not looking for this indication for children. The only indication of interest for us is children with major depressive disorder.

Vyn Reese: Any other questions from the committee?

Barak Gaster: This is Barak Gaster. Could we go back to slide 12? Could you just, what does the NR stand for there? Is that not released? Data not released?

Gerald Gartlehner: Could you please repeat the question? I could not hear you.

Barak Gaster: That's okay. This is Barak Gaster. On slide 12, when you reviewed the three head to head trials on generalized anxiety disorder and you mentioned that there was one trial that suggested that maybe the escitalopram was slightly better than the paroxetine, but that the data was not completely there? Does NR in that slide stand for not released?

Gerald Gartlehner: No, that means not reported.

Barak Gaster: Not reported.

Gerald Gartlehner: The publication simply did not give us any estimate of how many responders in one group compared with how many responders in the other group. All the data was a statistically significant difference.

Barak Gaster: Without saying what the difference was?

Gerald Gartlehner: Exactly, yea.

Vyn Reese: Any other questions? Can you just stay on the line while we hear from our stakeholders?

Gerald Gartlehner: Sure.

Vyn Reese: The first stakeholder is Dr. Julia Seabolt of Upstate Pharma.

Jeff Graham: Vyn? This is Jeff Graham. Would you announce about the three minutes and...

Vyn Reese: Oh yes, Jeff is going to be, Jeff Graham is the timer. You've got three minutes to speak and please watch the time.

Julia Seabolt:

Hi, my name is Julia Seabolt. I'm a senior MSL with UCB and Upstate Pharma. Today I'm here to talk to you about venlafaxine extended release tablets that has been FDA approved as a bioequivalence to Effexor XR. This evaluation was based on four pharmacokinetic studies that were conducted and the conclusion at the end of the four studies is that it was bioequivalent and the indication for treatment is major depression and social anxiety disorder.

Some of the clinical advantages is that venlafaxine extended release tablet has a known chemical entity, venlafaxine hydrochloride, which we are familiar with the safety and the efficacy and the FDA approved that based on the FDA used the efficacy and the safety data based on the NDA, based on Effexor XR. So the clinical advantage is you have a known product, but the doses that are available in venlafaxine extended release tablets is a 37.5, 75, 150, and a new 225 tablet that is available. So therefore, for patients who are currently under the clinical burden of taking three to two Effexor XRs in order to make a 225 mg tablet, they can now move down to a single, small tablet of 225. So anytime, as a clinical pharmacist for ten years that you can decrease the pill burden or the frequency of medication, usually provides the patient better improvement with adherence and therefore improves treatment outcomes in addition to quality of life and decreases health costs. And I will be glad to answer any questions.

Vyn Reese:

Thank you. Any questions from the committee? Thank you very much. The next stakeholder is Jenny Blackham from Eli Lilly.

Jenny Blackham:

Good morning. My name is Jenny Blackham. Can you guys hear me? I'm with the medical division with Eli Lilly and company. Cymbalta is a selective serotonin-norepinephrine reuptake inhibitor indicated for the acute maintenance treatment of major depressive disorder, MDD, the acute treatment of generalized anxiety disorder, GAD, and the management of diabetic peripheral neuropathic pain, DPNP, and the management of fibromyalgia.

Efficacy for depression. Remission should be the goal of antidepressant therapy. It is important to treat patients with full remission, as patients have felt to achieve remission have a higher risk of relapse. Cymbalta has demonstrated remission rates of 43 to 44% compared to 16 and 29% of placebo. Cymbalta demonstrated a rapid onset as early as one to two weeks and sustained efficacy across a wide range of depressive symptoms in clinical trials. Depressed patients in lingering painful physical symptoms have a higher risk of relapse and the time to remission is longer. Cymbalta has demonstrated efficacy in treating patients with painful physical symptoms associated with depression with significant improvement in overall pain severity as early as two weeks. Efficacy in pain may be important, because the disease states demonstrate that depressed patients with lingering painful physical symptoms are

associated with greater total medical healthcare costs than depressed patients without pain.

GAD efficacy was established in a one nine week fixed dose and a two ten week fixed dose trials in adult. DPNP efficacy. Cymbalta 60 mg once and twice daily had significant greater improvement in average pain severity compared to placebo. Efficacy for fibromyalgia was established in two randomized, double blinded, placebo controlled, fixed dose studies in adults meeting the American College of Rheumatology criteria for fibromyalgia. Treatment for Cymbalta 60 or 120 daily statistically significantly improved the end point mean pain score from baseline and increased the portion of patients with at least a 50% reduction in pain score from baseline. Pain reduction was observed in patients both with and without depression, however the degree of pain reduction was greater in patients with comorbidity depression.

The safety and tolerability. Cymbalta carries the antidepressant box warning for increased suicide in children, adolescents, and adults. Cymbalta is not approved for the use in pediatric patients. The most common seen adverse events on Cymbalta treated patients were nausea, dry mouth...

Jeff Graham: You have 15 seconds to finish.

Jenny Blackham: Okay. Increased sweating and decreased appetite. Full prescribing and safety information is available in the Cymbalta package insert. In conclusion, Cymbalta is a balanced, potent, dual acting antidepressant that offers higher remission as well as broad, rapid relief of both emotional and physical symptoms of depression. It also offers reduction in GAD, DPNP, fibromyalgia symptoms, and...

Jeff Graham: You're over your time, please finish.

Vyn Reese: Thank you. Are there any questions from the committee? Okay, the next stakeholder is Pablo Proaño, M.D.

Pablo Proaño: Thank you for inviting me here and allowing me to speak. I'm Pablo Proaño. I'm a psychiatrist, board certified psychiatrist that has been in private practice in the Seattle area for the last 21 years and I'd like to urge the committee to consider some of the clinical data that I've had over the last five or six years from using Lexapro as an excellent medication. In my practice and in the practice of American psychiatrists in the United States is the most prescribed antidepressant, anti-anxiety medication by experts in this field. As I see it, there are four primary reasons why it's superior to the other choices, SSRIs, the SNRIs, Effexor XR, Cymbalta. I'd like to highlight briefly here in the next couple of minutes those four reasons that I see.

Number one, safety. It's the only SSRI that does not have any significant drug/drug interaction potential. This is especially important with a couple of medications that I use in my practice and a variety of places use pain medications, narcotics are dangerous in my opinion to prescribe with things like paroxetine and Fluoxetine. Without getting into a lot of detail, they tend to block the activation of those medications and can lead to higher use of those medications, because Fluoxetine and paroxetine to a lesser extent Cymbalta or desvenlafaxine, I'm sorry, Cymbalta or duloxetine. It blocks the activation of those medications. Also, all other SSRIs are between 92-98% protein bound. Lexapro is 66% protein bound, which makes it a safer medication with highly protein bound drugs such as Coumadin or Warfarin. With those other drugs, you can lead to higher [inaudible] times, higher potential for bleeding, for abnormal bleeding.

Second highlight point is that tolerability is far superior to the other medications in this class and that leads to better drug adherence. Depression is a chronic illness and the vast majority of the time people need to stay on these medications indefinitely to minimize the risk of recurrence of the illness and potential suicide, which in this state is the fourth leading cause of death.

Thirdly, it's the only SSRI that has demonstrated separation from placebo within seven days. There is no other SSRI or SNRI that has demonstrated that. And again, looking at the risk of suicide, quicker response, quicker wellness healing of this illness, getting a person well sooner is sometimes a matter of life or death.

Last, but not least, efficacy. I'm not sure which studies this physician reviewed, but there are at least 11 head to head studies specifically with Lexapro and all of the other SSRIs, Cymbalta, and Effexor XR. Nine out of the 11 have showed superior response and remission with Lexapro. These are eight to 24 week studies. In a meta-analysis done, published in the journal of psychiatry and neuroscience in May of 2006 there was up to a threefold, threefold, higher response remission prediction of success with Lexapro versus all of the other SSRIs and Effexor XR based on a meta-analysis of all of these head to head studies, especially in...

Jeff Graham: You're [inaudible].

Pablo Proaño: Thank you.

Vyn Reese: Thank you. Are there questions from the committee? Dr. Gartlehner do you have any thoughts about the speakers' presentation. Are you still there?

Gerald Gartlehner: No I don't.

Vyn Reese: I couldn't hear you. Hello?

Gerald Gartlehner: Hello?

Vyn Reese: Dr. Gartlehner are you still there?

Gerald Gartlehner: Can you hear me?

Vyn Reese: Yes, barely.

Gerald Gartlehner: I'm still.

Vyn Reese: Okay, do you have any thoughts about this last speaker's presentation.

Gerald Gartlehner: No I don't. Can you hear me better now?

Jeff Graham: Yes we can hear you.

Vyn Reese: Yea, okay, thank you. Now I'll open it up for discussion of the committee and eventually for a motion.

Man: I just finally wanted to make a motion to add, of course, Lexapro in my clinical experience to the DSHS formulary. Thank you.

Vyn Reese: Patti Varley, I have a question for you. Are you still on the phone? Hello Patti?

Patti Varley: Is that for me?

Vyn Reese: Yea, I have a question for you. What do you use in children if Fluoxetine doesn't work or there are side effects for major depression.

Patti Varley: What do I use? I use, I tend to use Zoloft or Sertraline.

Vyn Reese: Okay, so you still use one of the other drugs?

Patti Varley: Yea.

Vyn Reese: That's what I thought you would say.

Patti Varley: If you want, the rest of the story is that typically if they don't do well on that I look at family history of response. And so if there are family members, especially first generation; parents, siblings, aunts, or uncles who have good response to a particular agent and didn't to the others, that would direct me.

Vyn Reese: Okay, thank you. Any other discussion or questions on the committee's part? Bob Bray, you crafted the motion in April of 2006. Do you want to read, look at that for this review?

Bob Bray: Sure, just the discussion first is that it would be my opinion from the information we've received from this update that the past motion would still be appropriate and I would propose that we repeat the same motion.

Jeff Graham: I had only one problem with the motion last time. For transiently, Sertraline wasn't on the list of drugs. And antidepressants are pretty much like anti-psychotics in that if a patient's responding well to one, it's often difficult to change them to a different one. I know Sertraline is back on the list now, is that correct? The PDL? Generic Sertraline? Okay. Why was it off, was there a problem obtaining it or what happened with that?

Woman: The reason why it was never added to the Preferred Drug List is that the product that was selected was the brand name Zoloft. For Uniform Medical Plan and the Etna Public Employees Plan the generic was covered under Tier 1, but for Medicaid because the generic product wasn't considered in our cost analysis, it was not included.

Vyn Reese: So it would be nice if something like that came up again that we could cover a generic drug in that, especially in this class. It's very important. Bob's made a motion. Is there a second?

Ken Wiscomb: I'll second again.

Vyn Reese: Sertraline has already been added. The question was is Sertraline now on the PDL and it is, right, correct? Is that right?

Group: Yes.

Vyn Reese: So it has already been added. It was just transiently off. So the motion has been made and seconded. All those in favor say, "I."

Group: I.

Vyn Reese: Opposed same sign. The motion is passed. Next item on the agenda is the scan on drugs to treat Alzheimer's disease.

Jeff Graham: We're putting up your slides no Gerald, so just wait a minute.

Vyn Reese: Okay, we're ready now. Dr. Gartlehner do you want to go ahead and start. The first Alzheimer drug slide is up.

Gerald Gartlehner: Okay, well I have to apologize, I never got the slides. I'm actually substituting for Van Schoenes, or Rick Hanson who both could not make this call today and I actually did not know that there are any slides. So I can just verbally summarize the scan for you without the slides and I apologize for that.

Jeff Graham: Gerald we can also tell you what it says on the slides. How would that be?

Vyn Reese:

I can just read each slide to you so you can, and then you can comment on in. Just say, slide one, update number two, preliminary scan report number two, May, 2008. The date of the last update was June, 2006. That's all it says on the first slide. The scope and key questions. Number one, how do donepezil, galantamine, rivastigmine, tacrine, and memantine or combinations of these drugs (i.e., acetylcholinesterase inhibitor plus memantine) compare in their efficacy or effectiveness for stabilizing symptoms and treating behavioral disturbances in patients with AD?

Next slide, number three, part number two. How do donepezil, galantamine, rivastigmine, tacrine, and memantine (or combinations of these drugs) compare in their time to effect and in the time required to assess the clinical response?

Bullet three. What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine tacrine, and memantine (or combinations of these drugs)?

Next slide. Bullet four. Does efficacy, effectiveness, or adverse events of donepezil, galantamine, rivastigmine, tacrine, or memantine differ in subgroups of patients with (1) different demographic profiles (age, race, or gender), (2) Parkinsonian features or vascular dementia, or (3) use of other commonly prescribed drugs?

Next slide. Inclusion criteria. Populations. Study participants with Alzheimer's disease. Study with numbers greater than 100. Interventions, five different treatments are currently available in the United States, donepezil, galantamine, rivastigmine, tacrine, memantine. Duration of trial 12 weeks or greater.

Effectiveness outcomes. Stabilizing or slowing the rate of decline health outcome measures: Activities of daily living, instrumental activities of daily living, level of care changes, quality of life, behavioral symptoms; aggression, agitation, psychosis, or mood disorders.

Continued. Next bullet stabilizing or slowing the rate of decline in intermediate outcome measures. Cognition, global assessment, discontinuation effects, temporary or permanent changes in behavioral symptoms; functional capacity, or cognition as a result of discontinuing treatment. Next bullet reducing caregiver burden. Next bullet hospitalizations or nursing home placement. And lastly, mortality.

Safety outcomes. Looking at overall adverse effect reports, withdrawals because of adverse effects, serious adverse event reports, adverse events due to discontinuation, specific adverse events including: gastrointestinal symptoms, hepatotoxicity, or weight loss.

Literature search. To identify relevant citations we searched Medline from March 2005 through May 14<sup>th</sup>, 2008 using terms for included drugs and

indications and limits for humans, English language, and randomized control trials or controlled clinical trials. We also searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were reported into an electronic database and duplicate citations were removed.

Results. Overview. Searches resulted in 133 citations. Of these there are 16 new potentially relevant RCTs in appendix A. No new drugs and no new safety alerts.

So that's all the slides. Is that basically it, no new data and no new safety concerns?

Gerald Gartlehner: Yea, okay. Yea, I have briefly reviewed the 16 new abstracts before the call, and basically they are all placebo controlled studies. We still do not have any head to head trials on comparing any of the two drugs and this was also one of the results of the last update. The only head to head evidence that we had were open label head to head comparison. We did not have any double blinded trials and this can again suggest that there are still no double blind head to head trials comparing these drugs.

Most of the placebo controlled trials, which means most of these 16 studies are on memantine and rivastigmine and apparently rivastigmine is available now as a skin patch and I think four or five studies are just on the efficacy and safety of the rivastigmine skin patch compared with placebo. So from my point of view, it does not look as if any of these new studies would lead to any changes in our conclusions.

Vyn Reese: Okay, thank you. Any questions at this point? I'll take a motion to accept the scan.

Bob Bray: So moved, Bob Bray.

Vyn Reese: And a second?

Jason Iltz: And a second, this is Jason.

Vyn Reese: All those in favor say, "I."

Group: I.

Vyn Reese: Opposed same sign. The scan is accepted. There are no stakeholders on this particular topic. Do you want to speak? Go ahead. Go ahead and go to the microphone. I didn't get it. The first stakeholder is Dr. Fred Amberger of Novartis.

Fred Amberger: Good morning, I'm Fred Amberger. I'm a scientific director with Novartis...

Vyn Reese: Just a second, I'm not sure your mic is hooked up.

Fred Amberger: Does this help. Okay. I'm Dr. Fred Amberger. I'm a scientific director with the Novartis Pharmaceuticals. I'm going to speak to you this morning relative to Exelon patch. Exelon patch is a reversible cholinesterase inhibitor that's used for transdermal administration.

At steady state [inaudible] levels are approximately 60 to 80% of peak levels. Fluctuation between the c min and the c max is lower for Exelon patch than for the oral formulation. Exelon patch 9.5 mg/24 hours exhibited exposure that was approximately the same as that provided by an oral dose of six mg twice daily. Exelon patch is indicated for the treatment of mild to moderate dementia of the Alzheimer's type and also mild to moderate dementia associated with Parkinson's disease. The effectiveness of Exelon patch as a treatment of mild to moderate Alzheimer's disease is demonstrated by the results of a randomized double blind, placebo controlled, double dummy clinical investigation. In the ideal study, 1195 patients were randomized to either Exelon patch 9.5 mg, Exelon patch 17.4 mg, Exelon capsules six mg twice daily, or placebo. All treatments were statistically significantly superior to placebo in the [inaudible] cog scale. Exelon patch 9.5 mg and Exelon capsules were statistically significantly superior to placebo in the ADCS CGIC score.

In this controlled clinical trial, 7% of patients treated with Exelon patch 9.5 mg developed nausea, as compared to 23% of patients who received the Exelon capsules and 5% of those that received placebo. In the same clinical trial, 6% of patients treated with Exelon patch 9.5 mg developed vomiting, as compared to 17% of patients who received the Exelon capsule and 3% of those who received placebo. Exelon patch is for transdermal administration given as once daily dosing. Initial dose is 4.6 mg/24 hours. If the dose is well tolerated after a minimum of four weeks, the dose should be increased to Exelon patch 9.5 mg, which is a recommended effective dose. The maximum recommended dose is 9.5 mg. Higher doses confer no appreciable additional benefit and are associated with significant increases in the incidence of adverse events. So thank you very much for considering Exelon patch. Are there questions that I can answer for you?

Vyn Reese: Thank you. Any questions from the committee? The next speaker is Dr. Tony Ranno from Pfizer.

Tony Ranno: Thank you for allowing me this opportunity to provide testimony on behalf of Aricept. My name is Tony Ranno. I'm a pharmacist and medical outcomes specialist with Pfizer. Aricept is the only Alzheimer's disease drug approved for mild, moderate, and severe stages of Alzheimer's disease and is the only Alzheimer's disease drug that allows a patient with mild to moderate Alzheimer's disease to initiate treatment at an effective dose, the five mg dose. In addition, only one titration step is required to reach the maximum therapeutic dose of ten mg.

According to the Washington state prescription drug data for the second half of 2007, this obtained from the public CMS website. 89% of prescriptions written for acetylcholinesterase inhibitors were for Aricept, 6% for rivastigmine, and 5% for galantamine. When we include memantine in this analysis, the breakdown is Aricept 67%, memantine 25%, rivastigmine 5%, and galantamine 4%. In the state of Washington, two thirds of Aricept prescriptions are for the maximum therapeutic dose of ten mg. This rate of using the maximum therapeutic dose appears to be about two to three times that seen for other acetylcholinesterase inhibitors. My points here are in mild to moderate Alzheimer's disease, Aricept is unique in the class, and that the starting dose is an effective dose.

Second, in Washington, the majority of Aricept prescriptions are at the maximum therapeutic dose and treatment with other acetyl cholinergic esterase inhibitors reaches the labeled maximum therapeutic dose for Alzheimer's disease much less often. Information along with the other information you have at your disposal allows you to conclude that Aricept should remain a preferred product on the Washington PDL. Thank you.

Vyn Reese:

Thank you. Questions from the committee? Thank you very much. Next speaker is Narinder Duggal from Novartis.

Narinder Duggal:

Thank you for allowing me to speak on the motion. My name is Dr. Narinder Duggal. I am an internist and a pharmacologist. I am a clinical professor at the University of Washington. I have a very large practice in Poulsbo, Washington. I have 250 nursing home patients, so I wanted to speak on rivastigmine is used in my practice both from a clinical perspective and emotional and a family perspective as well as a pharmacological perspective. I am an expert in drug therapy and pharmacology and an internist and a pharmacist.

Now, first of all from the epidemiological perspective I think no one in this room can deny that this disease and any disease that will break Medicare, this disease can do that. The caregiver burden and the number of resources that we are using right now is astronomical. In a nursing home setting or an assisted living setting, each time a patient loses an activity of daily living and as a result to that the care burden becomes higher, the cost to the country as well as to the payers and the family increases. So any time you have a drug that can not only improve cognitive stability but activities of daily living and behavior modification in terms of their paranoid ideations, that's a benefit. Unfortunately, with the FDA standards at the current time, they're not allowing us to look at the drugs from an ADL and a behavior perspective, but that's what the family sees. It is very hard from point A to point B to recognize an individual getting smarter, that's very difficult. But it is very easy to see the patient become more independent, and can live their lives more independently as long as possible. That is the biggest reason to use these drugs in terms of chemical properties.

The second issue in terms of pharmacology. It is clear that rivastigmine in the oral form is the most anticholinergic mediated drug out of the cost. That's why it has the nausea and the vomiting. It is an extension of the pharmacological property of that drug that gives it side effect. And now in a patch form, the side effect profile comes back to a profile that is very similar to other drugs in the class. It decreases pill burden. Just last week I had a family member who came in, the husband was almost in tears in my office because his wife won't take her pills. Putting a patch on is so easy to do for family members that they don't have to worry about the pill burden or the paranoid ideations that sometimes occur with this disease process. So rivastigmine has a huge place at play.

In terms of nursing home settings, they have more individuals that aren't registered nurses, a patch delivery system can be given by a nurse assistant, as opposed to a nurse, whereas pills have to be given by nurses. That's another advantage in terms of the clinical setting that is not seen with the pill form, but a patch form can be delivered easily for that individual.

Finally, the issues of caregiver burnout. I think we have to realize this disease is not just about the index patient case. It's about the entire family. Families break down when their loved ones start to lose their memory. All of us here who use our minds as our major tool in terms of our functionality. When that loses, you lose everything that person has. If we have drugs that can maintain cognition, independence, activities of daily living as well as behavior that is an important aspect.

Furthermore, most of the drugs that we use in behavior, there is no drug at the current time that is FDA indicated for behavior in Alzheimer's, which is another mistake at the FDA. This disease has never been a disease just of memory. It's a disease of behavior, memory, and activities of daily living. And so we have to recognize that this drug, when it comes on board, we can get away from using other drugs like [inaudible] psychotics, which are contraindicated in this population, unfortunately, but they're still used, and benzodiazepines.

So as we use these medications, it has a number of advantages for the individual. I think that this group should reconsider that rivastigmine is a clear pharmacologically advantaged drug in terms of its delivery system, it has the most anticholinergic properties, it has abutocholinesterase and acetylcholinesterase activity and it's a medication that we still need to have at our disposal. Thank you very much.

Vyn Reese:

Thank you. Any questions from the committee?

Man:

Sir, can you let us know whether or not you're sponsored by the manufacturer or have you been sponsored by the manufacturer in the past?

Narinder Duggal: Sure, I've been sponsored by everybody actually. I speak for Pfizer, I speak for Novartis, I speak for a number of companies, but I speak for everyone, I speak for no one. I am an expert in drug therapy and I teach doctors and pharmacists how to use drugs all over the country and all over the world, actually.

Man: Thank you.

Woman: [inaudible].

Vyn Reese: Did you have some comment on the phone? Okay, any discussion on the committee? There is, it's nice to have a topical patch as a delivery system. That's my one thought on this, because when patients get very negative they won't take their meds, and it can be a real problem. So that's my one thought, I'll throw that out to the committee and just see what other people think about this.

Patti Varley: This is Patty Varley, would you consider that first line or if they were unable to be compliant with oral medication?

Vyn Reese: I would say it's second line clearly, most patients can take oral meds, but as the disease progresses, many will have difficulty getting medication into them, so it would be a second line type drug to use. It certainly wouldn't be my first choice. There are a lot of problems with patches too. People get contact dermatitis to them and they get, there's all sorts of problems with patches themselves. But certainly in patients who won't take PO well, PO drugs, it's an advantage.

Jeff Graham: This is Jeff Graham. Vyn I think we could probably let Dr. Gartlehner go now. Gerald if you're still there, thanks a lot.

Vyn Reese: Dr. Gartlehner are you still there?

Gerald Gartlehner: Okay, thank you.

Vyn Reese: Okay, thank you.

Barak Gaster: This is Barak Gaster. We're not actually motioning today about safety and efficacy. We're only motioning about accepting the scan, is that correct?

Vyn Reese: We're going to be... reiterate our motion, basically that we did before. This is the prior motion.

Jeff Graham: The first motion would be to accept the scan.

Vyn Reese: We already did accept the scan.

Duane Thurman: This is Duane. The process is that we accept the scan so that you're comfortable with that being an adequate update and then you move on to reiterating your previous motion or making changes to it.

Vyn Reese: The only new piece of data that I see in the scan was the new patch. Any other people on the committee have thoughts about that?

Jason Iltz: This is Jason. Vyn I think it is nice to have something like that at some point, but again, excuse me I realize that this is a PDL, so I'm comfortable with Patti's comment saying are there some first line options on here that we can utilize, and then if we need to through DAW and some of these other mechanisms, certainly those things are available. I think the same point can be made for one of the current drugs on the PDL, which is memantine. Also has a solution available that's not currently on. So I'm assuming that that drug could also be written for or through some sort of expedited prior auth if that was a needed choice that it could be chosen as well. I think there are some mechanisms in place for those things.

Vyn Reese: Any other thoughts? Okay, I'll take a motion if there is no other discussion for this, for our prior motion.

Barak Gaster: This is Barak Gaster. I would move that, to accept the previous motion of October 18, 2006 as written.

Duane Thurman: Excuse me, this is Duane Thurman. Have you accepted the scan as adequate?

Vyn Reese: Yea, we did at the beginning.

Duane Thurman: Sorry.

Barak Gaster: Should I read it or are we going to say we accept it as written.

Woman: I just put it up there so you could read it.

Vyn Reese: Do we need a second.

Carol Cordy: This is Carol Cordy. I'll second it.

Vyn Reese: All those in favor say, "I."

Group: I.

Vyn Reese: Opposed same sign. We now have a short break and let's plan on being back we're going to do a 15 minute break, I know we're in a hurry to get...

Jeff Graham: Actually, I could have the next person on the line right now if you want to give me two minutes.

Vyn Reese: You want to do a five minute break? Let's do a five minute break. We'll resume the meeting in five minutes.

Vyn Reese: Okay, I'd like to reconvene the meeting and is Susan Carson on the line?

Susan Carson: Yes.

Vyn Reese: Okay, you're going to be doing the scan on drugs to treat hepatitis C. The first slide is up.

Susan Carson: Okay, thank you. Okay, so this scan was completed in May of 2008 and the last full report, the original report was completed in May, 2007. So in our key questions, we included adults with chronic hepatitis C infection and just briefly our methods, we searched Medline only from the date of the last searches through April, 2008 and we limited our searches to randomized control trials meeting inclusion criteria. As usual, we also searched the FDA and Health Canada websites for new safety information, new drugs, or any new indications. And so our searches resulted in 84 citations and of those, 20 were potentially relevant after review of the abstracts. Page three of your scan summarizes the, oh no that's not page three. Sorry, page four of the scan summarizes the characteristics of the potentially relevant trials and the abstracts are included in your appendix.

So, of the trials we found, three compared peg interferon alfa-2a or peg interferon alfa-2b to nonpegylated interferon alfa-2a. And then two trials looked at peg interferon alfa-2a or peg interferon alfa-2a plus ribavirin to a control group that received no treatment. And then 14 trials compare different regimens, different doses or duration of the same pegylated interferon. So, no new head to head trials, which is the information that we would most want to see comparing peg interferon alfa-2a with peg interferon alfa-2b. The only head to head trial that we knew about is the Ideal trial, which had not been published at the time of this scan. There was some preliminary information out. That trial compared to the two pegylated interferons to each other and found no difference between the two. But again, I don't have the full publication and the abstract wasn't available at the time of the scan.

But also in the Ideal trial as we mentioned in our report, this was limited to patients with genotype one, hepatitis C infection and also the doses of the two ribavirin in the two groups were different, so as we said in our report, the Ideal study is probably not going to answer all of the questions about the comparative effectiveness of these two drugs.

Moving on, no new drugs were identified in the class, no new indications, and we found no new safety alerts from FDA or Health Canada. And that's basically the information we have.

Vyn Reese: Thank you very much. I will take a motion to approve the scan, or accept the scan.

Kenneth Wiscomb: This is Ken Wiscomb, I'll move that we accept the scan.

Bob Bray: I'll second it.

Vyn Reese: All those in favor say, "I."

Group: I.

Vyn Reese: Opposed, same sign. The scan is accepted. Is there any stakeholder input on this drug class? Why don't you just go ahead and go to the microphone and introduce yourself and say who you're affiliated with if you have an affiliation.

Isaac Lloyd: Hi good morning, my name is Isaac Lloyd. I am with Schering-Plough, medical science liaison. Should I go ahead and just get started?

Vyn Reese: Yea, go ahead.

Isaac Lloyd: Okay, first of all, I would like to point out a recent unique indication for PEG-Intron. As of last Friday, December 12<sup>th</sup>, PEG-Intron is the first and only approved peg interferon for combination with ribavirin for previously untreated children ages [inaudible] with chronic hepatitis C. PEG-Intron is dosed in children by body surface area at 60 mcg/m<sup>2</sup>/week with 15 mg/kg/day of ribavirin in two divided doses.

Currently there are no published head to head studies comparing pegylated interferons, however it is important for the committee to know the results of the Ideal study, which compares two pegylated interferons. It has been presented at [inaudible] 2008 and available for abstract form. Here are the top line results. The Ideal trial is a perspective study with over 3,000 U.S. genotype one patients, the most difficult to treat, revealed the following: sustained virological response rates were observed for the three treatment regimens. For the intention to treat group was PEG-Intron 1.5 at 40%, PEG-Intron 1.0 at 38%, Pegasys at 41%, or 38%, 41%. However, there were lower percentages of patients on PEG-Intron 1.5 treatment arms that relapsed after the end of treatment. Just 24% for PEG-Intron 1.5, 20% for 1.0, and 32% for the Pegasys.

There was an analysis done at a 52% of patients that received identical dosages of ribavirin and these are the results. They have similar SVR rates, PEG-Intron 1.5 was 40%, 1.0 was 38%, and Pegasys was 38%. In addition, a lower percentage of patients in the PEG-Intron treatment arms relapsed after the end of treatment in comparison to the Pegasys treatment arms. 22% for 1.5, 20% for 1.0, and 35% for Pegasys. In addition, a unique property for PEG-Intron is it is a weight based dose product. Since 1960, the average weight for both U.S. men and women has increased by

almost 25 pounds. According to the Washington State behavioral risk factor surveillance system from 2006 indicated 36% of Washington adults is overweight with approximately 24% being obese. Patients weighing more than 165 pounds have lower SVR rates when flat dosed interferon based therapy is administered. On the other hand, PEG-Intron offers individualized weight based dosing given at 1.5 mcg/kg/week. In published studies, weight based PEG-Intron with ribavirin demonstrated similar response rates regardless of weight.

Lastly, I'd just like to talk about the in charge service, which is a free service of Schering-Plough for patients considering interferon treatment for hepatitis C available to all Medicaid patients in multiple languages. Each patient will be treated with a nurse counselor, in addition the in charge is the only toll free 24 hours a day seven days a week service to speak with a live nurse. I would just like to ask the P&T committee because some of these unique properties to add PEG-Intron on the formulary to the Washington State Medicaid. Thank you.

Vyn Reese:

Thank you. And any questions? One statement, we can't really comment on studies that only are in abstract form, they haven't been reviewed yet in a published form. So we have to refrain from entering that data into the discussion today, okay until it has actually been published. I look forward to seeing it published. Any other questions? Any discussion? There's another stakeholder? Go ahead, if there's anybody else hop up and talk. Please introduce yourself and your affiliation.

Vandana Slatter:

Good morning, my name is Dr. Vandana Slatter, Pharm D. On behalf of Roche Medical I thank you for the opportunity to address the clinical benefits of Pegasys, Peginterferon alfa-2a in patients with chronic viral hepatitis C. In 2008, cirrhosis due to chronic hep-C virus is the leading specific indication for liver transplantation in the United States. Pegasys continues to be the most prescribed interferon for hepatitis C treatment in the United States and in Washington State, for five main reasons.

First, Pegasys alone or in combination with ribavirin continues to have the broadest range... Can you hear me? I'm going to hold it. Pegasys alone or in combination with ribavirin continues to have the broadest range of FDA indications including the following unique to Pegasys: cirrhotic patients with compensated liver disease SVR 47%, HIV infected patients SVR 40%, and as monotherapy in patients with chronic hepatitis B. Second, a wealth of clinical data supports the Pegasys label. For example, Pegasys Copegus therapy has achieved the highest reported registration trial or SVRs in patients overall, 63% and in those most difficult to treat, 52% in genotype one 41-47% in genotype one high viral load. SVR is the most important clinical outcome of HCV treatment.

Utilizing the Pegasys package insert's definition of SVR for Pegasys HCV registration trials, relapse rates for 48 weeks of full dose Pegasys Copegus combination therapy are 19-20%. Eight key studies with Pegasys have

been published in the New England Journal of Medicine, demonstrating the strength of the data supporting this drug. Third, Pegasys offers demonstrated durability of response and tolerability. Greater than 99% of patients who achieve SVR following treatment with Pegasys alone or with ribavirin maintain HCV RNA negativity for a mean of 4.7 years, and this study is ongoing. Safety is detailed in the Pegasys Copegus package inserts, which were updated in June of 2007.

Fourth, Pegasys is easy to use. Due to its pharmacokinetic profile, specifically, a small volume of distribution, Pegasys does not need to be dosed by weight; it is administered as one standard dose for all patients and its packages are ready-to-use prefilled syringe. We know that fat is inherently resistant to interferon, but that is different than weight. Small volume distribution, it is distributed to the spleen, the kidneys, and the blood versus just the tissue, which is a broader volume of distribution.

Fifth, Roche's commitment to optimizing therapy for HCV patients including research to improve response rates and advanced HCV therapy and difficult to treat populations, such as cirrhotics, prior treatment non-responders, racial and ethnic minorities, genotype one, high viral load, and HIV HCV co-infected patients. Clinically, Pegassist, a comprehensive support program, is also available 24/7 in patients and providers to help manage Hepatitis therapy. In closing, Pegasys has demonstrated unsurpassed efficacy and safety in patients with chronic Hepatitis C, Hepatitis C HIV co-infection, and chronic Hepatitis B. Roche, therefore, respectfully requests that Pegasys be available on your preferred drug list. Thank you. Any questions?

Vyn Reese: Are there any other stake holders that wish to speak? Discussion from the committee on this issue?

Barak Gaster: This is Barak Gaster. I have a question for Susan Carson. Are you still on the line?

Susan Carson: I am.

Barak Gaster: I was just looking at the appendix and the one head-to-head trial there which reported "early vial response only."

Susan Carson: Right.

Barak Gaster: And so this was peginterferon alfa-2a versus peginterferon alfa-2b.

Susan Carson: Yeah.

Barak Gaster: And so it looked like the only difference was that the patients treated with the peginterferon alfa-2b had a higher rate of discontinuation for safety reasons.

Susan Carson: Uh-huh.

Barak Gaster: 6% versus 1%. Do you have a sense for what those safety issues are?

Susan Carson: You know, I don't because we don't look at the full text of these appendices. We had a couple of head-to-head trials in the report that reported early viral response that aren't really included. They weren't outcomes that we had decided to include, but we did mention them just for your information, but the main outcome in our report really was sustained viral response. I would have to check the report to see if those other trials had safety information. I don't have that off the top of my head, but that would probably be a better place to get the information you would need than just this abstract, since we don't have the full information.

Vyn Reese: Are there any other questions or discussion? Take a motion to basically reiterate our prior decision. It was Bob Bray who did the previous motion.

Robert Bray: I would move that we repeat the same motion.

Vyn Reese: And second?

Janet Kelly: Janet Kelly, I second that.

Vyn Reese: All those in favor say "I."

Group: I.

Vyn Reese: Opposed same sign. It's passed. The next item on the agenda is the drug class review and update on TZDs.

Susan Carson: I am trying to get in touch with Susan Norris, like send her a email, and I'll try to call now when I hang up, but I don't know if she will be available earlier than 11:00. You know, her schedule might not allow it, so I don't know, should I tell her just to call in at 11:00 if I don't, or assume that she will call in at 11:00 at the scheduled time, if I don't get in touch with her?

Vyn Reese: Susan, I have asked Catherine Clark to try to track her down too.

Susan Carson: Oh, you did, okay.

Vyn Reese: So I think that Catherine is doing that right now.

Susan Carson: Alright. Great.

Vyn Reese: Thank you.

Susan Carson: Okay, so I am free to go.

Vyn Reese: Yes, you are free to go.

Susan Carson: Thank you. Bye.

Vyn Reese: So we are sort of stuck, apparently.

Jeff Graham: Well, I think we could do the combination, but I think you probably should probably have the TZD before it.

Vyn Reese: You can't do the combinations without the TZD first, so we are trying to move our agenda along, and now we've sort of outfoxed ourselves.

Woman: Could we ask that any speakers on the Hepatitis C please sign in on the sheet that is out in the foyer, if you didn't sign in previously?

Jeff Graham: I think [inaudible].

Vyn Reese: Okay, I would like members of the committee to stay in the room, but I think we are going to have a little bit of a delay now as we try to find the next presenter, so we are going to be temporarily adjourned, but just to the room. This is Doctor Reese, chair of the committee. We have the first slide up, and we would like to start the drug class review.

Susan Norris: Drug class review, TZDs?

Vyn Reese: On the TZDs, right.

Susan Norris: And who is my audience, please?

Vyn Reese: This is the Washington State P & T Committee.

Susan Norris: Okay, and a roomful of people?

Vyn Reese: You got it.

Susan Norris: Okay. Okay, I'll just start talking then. My collaborators are listed there in the first slide. Go on to the second slide. This review I'm presenting is a update from the original TZD report. There were some changes in scope here with this update. We originally had only looked at comparisons of pioglitazone versus rosiglitazone in this update of the participating organizations of DERP asked us to expand us to look at active control of comparisons of TZDs to other oral hypoglycemic agents, and basically to update the comparative effectiveness review of oral hypoglycemic agents that AHRQ had performed that was published in annals of internal medicine of 2007. To be consistent with that AHRQ report, we expanded our study designs for comparative effectiveness reviews to include cohort studies. Previously we were doing that to RCTs.

On the third slide are our updated key questions. The first focus is on the effect of both active control and placebo control studies on an A1c, and the second focuses on the macro- and microvascular outcomes. The third question on pre-diabetes and the effect of TZDs on the incidence of type 2 diabetes. Fourth is our usual adverse events question, and the fifth is examination of population subgroups.

On slide four is the overview of our evidence, indicating what the entire TZD evidence between the original report and the update, indicating what new data were available. You see a paucity of head-to-head trials, and I will describe those briefly. The bulk of the evidence was in placebo-controlled trials, and we did do indirect comparison for A1c, and then add some active control trials that were added on to the AHRQ report that I had mentioned.

Going on to the fifth slide, please. It says Key Question one. So this is effective pioglitazone versus rosiglitazone on A1c, looking at the direct evidence, as they say there were few data here, five head-to-head trials, two of which were new to this update, one of which was poor quality. There was a mixture of monotherapy and combination therapy, the one that formed study, combination therapy, was the new trial. And this direct evidence did not find a difference in A1c outcomes between pioglitazone and rosiglitazone in any of the trials.

Going on to the sixth slide, please. Because of a few head-to-head data, we obviously went on to look at placebo-controlled trials for A1c and you see the results of our meta-analysis there. Looking at good and fair quality studies in the first row, we had nine with sample slides and in part due to the coactive trial. And the difference between the pioglitazone and placebo, with respect to A1c, is in the last column. You see for the various substrata that we looked at, approximately, a 1%, 1.0%, decrease in A1c with pioglitazone versus placebo.

The next slide, slide number seven. Similar analysis for rosiglitazone on A1c. Similar results of little more variability across the stratum, but between .8 and 1.0 decrease in A1c with rosiglitazone compared with placebo.

The next slide shows our indirect meta-analysis, assuming comparability in the placebo groups across the studies, which is a significant assumption comparing then rosi versus pio for A1c, and you see the results there. Under monotherapy, there is, unfortunately, I apologize, there is an error in the slide; it should be -.3. So, what you see in the first row for good and fair quality studies, there is really no significant difference between the two drugs, rosi and pio. And that held true for the different stratum we looked at, whether it's monotherapy or combined therapy. All of the confidence intervals overlap 0.

So in slide number nine, going on to the active control trials. Firstly, very briefly summarizing the...

Susan Norris:

What you see in the first row for good and fair quality studies is really no significant difference between the two drugs, rosi and pio, and that held true for the different stratum we looked at, whether it's monotherapy or combined therapy. All of the confidence intervals overlap 0.

So in slide number nine, going on to the active control trials, firstly, very briefly summarizing the AHRQ report. This was . . . Sherry Bolen(?) was the first author of the AHRQ . . . of the purity paper and annals, and they found looking at TZDs as a class compared to other various drugs listed there, really no difference in A1c, across studies for the various comparisons listed, for example [tape skips] TZDs versus metformin and RCTs. So similar improvements in A1c.

Now looking at pio compared with active control for A1c, we identified 11 new trials for this update beyond what Bolen and colleagues had identified. Approximately half of those were monotherapy and the other half various combination therapies. There were no difference in A1c in nine out of the 11 trials between pio and the active comparator, two trials did find significant differences, one was a small trial where [inaudible] produced more of an improvement in A1c than pioglitazone, and the other was a study of glimepiride having less of an effect than A1c than pioglitazone. So the other two disparate files had disparate results.

And the same in the next slide, slide 11, looking at rosiglitazone versus active control studies for the outcomes of A1c, ten trials identified for the update. Here, most of these were . . . the majority were combination therapy. This did include the ADOPT trial for your follow-up that showed that rosi was superior to glyburide and metformin, at least for monotherapy failure rates, which are listed there. They were lower with rosi at 15% compared to 34% for metformin, and that was a significant difference. The two smaller trials of monotherapy did not find a difference between rosi and the active comparator, but they just had one-year follow-up data. It is often different in the follow-up; the mean was close to four years. In looking at combination therapy studies with rosi compared to metformin, studies were not able to demonstrate a difference between rosi and that comparator.

Going on . . . slide 12, going on to Key Question two, the effect of TZDs on health outcomes or cardiovascular disease events. We identified no head-to-head data with rosi versus pio; therefore, we are looking at indirect evidence which are listed there, several placebo with no treatment trials for both rosi- and pioglitazone.

So those results, starting on slide 13 of the proactive trial, which really is the important one here, a placebo-controlled good quality large trial with over 5,000 participants and close to three-year follow-up. Vast majority of patients were taking other glucose-lowering drugs. Their primary endpoint, which was a composite of the various event and health outcomes listed there, including mortality and CVD events did not show a

significant difference at the three-year follow-up between pio and placebo. Their secondary endpoint, which was more heart events, mortality, MI, and stroke did show a benefit for pioglitazone with a hazard ratio of 0.84. There were three other small trials that did show benefit. These were in patients with coronary artery disease, and the second one was acute coronary syndrome. So there were benefits in those two studies with respect to pio and CVD events [inaudible]. A small study in Nash(?) also showed benefit with pioglitazone for liver enzymes and the liver histologic changes.

So going on with rosiglitazone versus active comparators in the next slide, 14, here the key trial was the record trial. The slide should read that's an active-controlled trial, not a placebo-controlled trial. This was a fair quality study, again a large study in 4,500 patients. This, as you know, with an interim analysis that came out in the *New England Journal* last year. Here, the primary outcome was hospitalization for acute MI, heart failure, stroke, and etc. and found a hazard ratio for rosi with a sulfonylurea versus metformin with a sulfonylurea showed no significant difference for the primary outcome, except we did note there was elevated risk of heart failure in the rosiglitazone group with a hazard ratio of 2.24, confidence interval not overlapping 1. The other secondary end points, other than heart failure, were not significantly different between rosi and the comparator.

The other active controlled trial of main interest here is a trial in a person's newly diagnosed with Type 2 Diabetes. Here they found all-cause mortality similar among the three groups, rosi, glyburide, and metformin. There were slightly more CVD events with the rosi group, 4.3% than the other groups, but those were not statistically significant differences for the CVD events across groups. Heart failure events were greater with rosiglitazone than glyburide, however.

The next question to Question 3, slide 15, looking at the prevention or delay of Type 2 Diabetes in patients with either pre-diabetes or the metabolic syndrome, we identified a total of three fair quality studies, without... we weren't able to draw conclusions about the comparative effectiveness of rosi and pio. However, the first study showed pio or rosi compared to no treatment in impaired glucose tolerance did decrease the incidence of diabetes, but it wasn't powered to compare those two drugs. The second trial, rosi compared to placebo in the metabolic syndrome in patients undergoing percutaneous interventions . . . percutaneous coronary interventions. There the incidence of diabetes was somewhat lower with the rosi group than placebo, but didn't reach statistical significance. And then the third most relevant trial here is, of course, the DREAM Trial large multicenter trial with three-year follow-up. The results of that are on the next slide, slide 16. Here, incident diabetes was decreased with rosiglitazone compared with placebo and a hazard ratio of 0.4. Mortality was not different, however, between the treatment groups. Heart failure was markedly increased with the rosiglitazone treatment with a hazard ratio of approximately 7.

So going on with Key Question 4, our adverse events question in slide 17, there were, again, few direct data here, just three head-to-head trials, which did not find differences between pio and rosi for overall adverse events or withdrawals, weight change, or liver function abnormalities. Those were the only outcomes examined, not the more distal health outcomes in those three trials.

So we went on to indirect evidence for adverse events in slide 18. There, you see placebo-controlled trials of pio in the middle column and rosi in the last column. There were no significant difference with respect to withdrawal rates compared with placebo in either rosi- or pioglitazone trials. Both drugs increased rates of edema, peripheral edema, hypoglycemia, there was no increase with these two drugs compared to comparators, or compared to placebo... these were all combination therapy trials however, various other hypoglycemic agents were in use. And then weight gain, both the drugs produced similar degrees of weight gain compared to placebo. The next slide 19, actually, I'll just make a couple of additional comments about adverse events. Risk of fractures, as you know, was raised as an issue in trial where there was an increased risk with rosiglitazone compared to metformin and glyburide. In the proactive placebo-controlled trial for CHF, rates were increased with pioglitazone compared with placebo, and those were statistically significant. There was not an increased rate of fatal heart failure, however, in the proactive trial. And then rosiglitazone, increased rates of congestive failure in the RECORD and ADOPT trials, as I mentioned.

So in slide 19, we looked at some additional observational data for adverse events. Didn't find any additional data compared to what we had identified previously. Peripheral edema rates were similar in the pio and the rosi trials. Most of these trials were fairly short-term, a year or less. One retrospective cohort study with up to 40 months of follow-up showed increased rates of heart failure in both treatment groups, pio and rosi, with no significant difference between groups, slightly higher rate with rosiglitazone. And seven observational studies compared weight gain with no difference between the two drugs.

Going on to slide 20, adverse events and TZD versus other active hypoglycemic agents. These data are obtained from the AHRQ Report and didn't provide comparative data for pio versus rosi, just the class effect of these drugs. Hypoglycemic episodes were more frequent with the second-generation sulfonylureas than with either metformin or TZDs. Edema rates were higher with TZDs than in the other oral agents and a higher risk of heart failure with TZDs than in other oral agents also.

Going onto slide 21, mortality was looked at in two of the observational studies. Again, this is still a continuation of the Bolen work, and the TZDs did not demonstrate any increased mortality rates in observational studies compared to other oral agents. There was a reduced risk of death with TZDs in older patients with heart failure compared to not using an insulin sensitizer. Two coronary heart disease event studies, one showed a similar risk of events with rosi versus oral agents or insulin. The other showed no increased risk with TZDs. Heart failure comparing TZDs with

sulfonylureas on a fairly short-term follow-up, hospitalization rates were similar. Another study showed an increased risk of hospitalization for heart failure for TZDs and insulin, but not for the other oral hypoglycemic agents.

Slide 22, the examination of subgroup, we identified no new data for the update. Here, there is very little data on racial/ethnic minorities. There appear to be from the limited data similar effects and adverse events from these drugs in minority populations, but we didn't have any direct comparative data. Data were insufficient on other important comorbidity subgroups, such as renal insufficiency.

Going on to the last slide, slide 23: In conclusion, pio and rosi appear to have similar effectiveness for reducing A1c. Between those two and between TZDs in general and in other hypoglycemic agents, their effect on A1c is similar. Effect on macrovascular and microvascular outcomes, again, while here, no direct evidence. Pioglitazone did reduce macrovascular complications in patients with existing heart disease compared to placebo. There was not evidence compared to other active agents. There is a risk of increased heart failure with rosi compared to other hypoglycemic agents. With respect to diabetes and its incidence, rosi has been demonstrated to decrease the incidence of diabetes, the DREAM Trial, but there was an increased incidence of heart failure.

Question 4 with respect to adverse events, in head-to-head data adverse events were similar. TZDs do appear to demonstrate more heart failure and edema than other oral agents or insulin, and there does appear to be less risk of hypoglycemic episodes with TZDs than other oral agents.

And for our subgroup data, population data, we really have no comparative evidence. I'll stop there. Thank you.

Vyn Reese: Thank you. I'll open up to questions from the committee. This is Doctor Reese. I have one question, actually a couple. I am most concerned about risk of the TZDs. The questions about macrovascular outcomes, the proactive trial versus the RECORD Trial: The primary endpoints in the proactive trial did not include congestive heart failure, is that right? Where as in the RECORD Trial, it did include congestive heart failure?

Susan Norris: Yes, that's true.

Vyn Reese: So part of the difference in the two may have been that because CHF was excluded in the first, in the proactive?

Susan Norris: Yes.

Vyn Reese: And my other question is about fracture risk. You didn't mention that in your conclusions, but you did in the body of your report, and can you give us an idea about what type of risks we're talking about. Is it just in women, or is it in men, or is it just not long enough to know if there is a difference in the sexes?

Susan Norris: Yeah, let me just grab my notes. Yeah, it was in female patients, more patients who received rosi experienced fractures than women who received metformin or glyburide. The rates with rosi were 9.3% and with glyburide 3.5%, and most of these were acute upper arm, humerus

fractures or hand-wrist fractures. The incidence in male patients were similar, interestingly, among the three drug treatment groups. So that result led TSK to, I guess, issue their safety warning. Those are the only fracture data that we identified. We did not encounter that in any other study examined.

Vyn Reese: My other question is about the black-box warning for rosiglitazone regarding cardiovascular risk or uncertainty about risk, whereas, pioglitazone doesn't have that black-box warning, probably because of the study that we already talked about. Do you have any comments on that. What did the FDA base that on? Just that there was no evidence supporting rosi, reducing risk, and that pioglitazone has pretty good evidence showing that it may decrease macrovascular risk?

Susan Norris: Yeah, I mean I can't comment on why the FDA did what they did, of course. You know, the data that came out looked at rosi, and there just aren't as much data on pio, and then if potentially protective effect in the secondary endpoint of the proactive trial, but both drugs are increasing edema and failure rates. We just don't have enough data to compare the two drugs to really see how different they are with respect to failure.

Vyn Reese: Other questions from the committee? Thank you. Can you stay on the line, Susan, while the stakeholders give their presentations?

Susan Norris: Oh, sure. Happy to. Thank you.

Vyn Reese: And the first stakeholder is Dr. Nathan Ross, a local endocrinologist, and next up is Drew Garcia, a PA from Bremerton.

Jeff Graham: This is Jeff Graham, and you have three minutes to give your remarks and I'll [tape skips] warning.

Nathan Ross: Which I hope I won't need. I had a few comments about the presentation, which I thought was very good. I would have liked to have heard information about what consideration, if any, was given to the recent ADA guideline changes, which have essentially said, do not use rosiglitazone. It's been adapted so that the second- and third-line agents include pioglitazone specifically exclude rosiglitazone. I would like to hear commentary or at least to have that considered. Second, I would like to have heard something about the publication two weeks ago in the archives of internal medicine, which was a 30,000 odd-patient-year study review from Harvard Medical School or the Brigham Women's Hospital, funded in part by GlaxoSmithKline. Looking at the cohort of patients between 2001 and 2005 begun on a thiazolidinedione and nonrandomized, but looking over that period of outcomes with a conclusion being that there was increased mortality of about 13% with rosiglitazone, or heart failure 13%, mortality 15% with rosiglitazone. There was not an increased risk, the best I could tell, with ischemic heart disease. So, in answer to the question brought up earlier, I think probably that black-box warning is not appropriate, but that is an interesting result, which makes me very reluctant to use rosiglitazone. I think that is pretty much all the comments I have, but I think those are important comments, and I would really, if possible, like to hear the comments of the presenter, because I thought it was a very good presentation.

Susan Norris: Well, thank you for those comments. Yeah, we generally don't, that we are aware of, but we don't generally incorporate the advice of other guidelines in our review. We are not making recommendations per se; we are simply presenting the evidence, and I can't comment on what evidence or how they looked at, reviewed the evidence to make their conclusions of "don't prescribe rosi." And, again, I was aware of the publication a couple weeks ago. We have these rather rigid cutoff dates for our searches that make it somewhat difficult to add more recent data, or add selected recent data, without reviewing the whole gamut. That publication will, of course, be presented with the next update, and it is an excellent, it's an important study. Thank you.

Vyn Reese: Okay, thank you. The next stakeholder is Drew Garcia, and on deck is Zhanna Gudzyuk.

Drew Garcia: Good morning. Thank you for allowing me the opportunity to speak with you this morning. My name is Drew Garcia. I am a physician assistant in Bremerton, Washington. My practice focuses mainly on renal and cardiovascular disease prevention. I would like to ask the committee to, in general, look at adding TZDs to the formulary and, specifically, pioglitazone for its beneficial effects. If we look at some of the data that Dr. Ross mentioned, the most recent guidelines published in *Diabetes Care* by Dr. Busey and his colleagues, recently. The algorithm actually begins with lifestyle metformin. Now, if you look at my population of renal patients, metformin is not a useful medication. It is actually contraindicated in that group, and I will not bore you with that information. However, sulfonylurea has also become dangerous, which are tier II within that category. So, that leaves us with very few options for the treatment of patients with diabetes and renal disease.

The Department of Health website recently reports that there is an estimated 1.4 million persons in Washington State with diabetes. Of those, National Kidney Foundation reports 735,000 are affected with kidney disease of some sort. Effectively, one in two people with diabetes will have kidney disease. Sulfonylureas [tape skips] difficult to use, insulin is even more difficult to control due to risk of hypoglycemia. That's pretty much what I would like to address to the group at this point. I would also like to say that I know I only have three minutes and you know the information better than I do, at this point. I will not change your minds, but your decision here today will affect my patients directly and my colleagues, and I appreciate your consideration. Thank you.

Vyn Reese: Thank you. Any questions from the committee?

Male: I do. Comment, Drew. TZDs are on the formulary.

Drew Garcia: Yes sir, but preferred.

Male: Yeah.

Drew Garcia: Agreed. Agreed. It's just difficult for us in practice to actually get patients go be authorized for those medications without prior authorization. So, I misspoke, and I apologize.

Vyn Reese: This is Doctor Reese, and I'll just give you a comment.

Drew Garcia: Yes, sir.

Vyn Reese: Not all sulfonylureas are the same; some are . . .

Drew Garcia: I agree.

Vyn Reese: Some are renally excreted and others are hepatically metabolized, so they are not all the same and they can be used with patients with renal insufficiency. Plus, insulin is still an excellent drug for renal patients, and far along in the diabetic course, when they do have renal failure, almost all of them are on insulin.

Drew Garcia: Yes, sir.

Vyn Reese: The next speaker is Zhanna Gudzyuk and a local nurse practitioner, and next up is Doctor Frank Torres, cardiology.

Zhanna Gudzyuk: Good morning, thank you for having me. I apologize for my voice. While trying to speak for my patients as their patient advocate, I've lost mine. I have a big panel of patients with diabetes, and I want to make it very personal because I see patients on the receiving end. I want to share you a specific patient's case. When I wrote a prescription for Actos, and it took only almost ten months for patient to get that prescription. With prior approval, it makes it really difficult, because there are many obstacles for the patients, and many of them get lost in between. Patients that don't speak English, patients that don't have transportation, patients that rely on somebody else to help them to make those choices and decisions many times are not even heard. That's why I wanted you to let know about the patient that had diabetes in ten months went much worse from A1c of seven to A1c of nine. And I tried to get Actos approved several times, and it would fall through. It never went through until I got other people involved in making phone calls and making emails until things were worked out for the patient. I want to comment as well, because you had a lot of statistics, a lot of numbers, but a lot of those keep patients out of a one, one difficulties. And I would like very much to avoid that prior approval to make one more less obstacle for the patients. And I thank you for your time and consideration.

Vyn Reese: Thank you. Any questions? There is a program called the Endorsing Prescriber, where you can prescribe without going through the prior auth process. And if it's on the PDL, you can prescribe the drug that you request, so I would encourage you to do that.

Zhanna Gudzyuk: Thank you.

Vyn Reese: The next person on the stakeholder list is Dr. Frank Torres, and on deck is Dr. Brad Wallum. Dr. Torres? Is Dr. Torres here? Okay, so next is Dr. Brad Wallum. On deck is Rob Pearson.

Brad Wallum: Thank you. I'm Brad Wallum, endocrinologist from Bellevue, Washington. I have approximately 4,000 – 5,000 patients who I see in consultation in my practice. My reason for being here is just to represent my patients and my colleagues in primary care in your formulary decisions. I currently [tape skips] the TZDs available for our patients, even

though sometimes it does take a little extra effort, at least we have that available. The motion that is on the screen, I also agree with, so just to briefly summarize, as an endocrinologist, we see very-difficult-to-treat patients with diabetes. And there is basically four causes for high blood sugars: one is the pancreas doesn't secrete insulin, another is the liver dumps too much sugar into the blood stream, the third is that glucose utilization for energy expenditure in muscle and fat cells is impaired, and the last is that the GI system doesn't work properly in terms of the incretin secretions. The TZDs work primarily in that third mechanism but also have other evidence for improving diabetes control and other mechanisms.

Without TZDs in the real world in seeing patients in our practice, it is very difficult to control their blood sugars and to help get their A1c's down to the point where we need it to be. So I totally support having TZDs available. In terms of differentiation between the two TZDs, pioglitazone and rosiglitazone, as Susan said in her presentation, there basically is no difference. They are both good drugs. They both have some risk, mainly CHF. They both have been shown to reduce blood sugars about the same, and their overall safety is very similar. So, we use in our practice both pio and rosi interchangeably; we think that they are both great drugs. And I think that if your unbiased review that Susan did is right on target in terms of the fact that they are both very similar. To answer Dr. Reese's two questions that you addressed, one in terms of osteoporotic fractures, both rosi and pio have data that perhaps there is an increased risk of upper extremity fractures.

Jeff Graham: You have 30 seconds to finish.

Brad Wallum: Okay, sure. The good news is that there does not appear to be an increased risk of hip or spine fracture. We need more data to actually sort this out, but at this point, it is not a major concern of us who treat diabetes. And your last question was in terms of the issue in terms of the cardiovascular decision by the FDA in terms of its labeling. I think the answer that Susan gave is right on target. We just didn't have the data with pio at the time. Thank you. I would be happy to answer any questions.

Vyn Reese: Any questions? I have one comment. The fracture at the upper extremity may be early on in osteoporosis and later on you see the hip fractures. So, we don't have a long enough time frame to really know that. And that's a real concern of mine as a geriatrician. We don't know what these drugs do over decades, and many people will be on them for some time. That would be my only editorial comment on that concern. Thanks.

Brad Wallum: You're welcome.

Vyn Reese: Next up is Dr. Rob Pearson, PharmD, and I can't read your affiliation. It's GSK, I think.

Rob Pearson: Absolutely. Thank you. I am Rob Pearson. I'm with the Research and Development Division of GlaxoSmithKline. So, I appreciate the opportunity this morning to just share a few more comments around Avandia. First of all, I would like to make just a quick point of clarification. There has been some discussion around these guidelines. I would like just to point out that this was a consensus document from seven

authors that was published recently. And at this time, it is not the official position of the American Diabetes Association. But I would like to share a little bit more about the role of Avandia and the treatment of our patients with Type 2 Diabetes. Avandia has been proven in numerous studies to both slow the progression of beta cell dysfunction and also to reduce insulin resistance. From the diabetes outcome progression trial or the ADOPT Trial, which we looked at in the slides earlier that compares Avandia directly to metformin and sulfonylurea comparator, Avandia was able to show sustainment of glycemic control for up to five years, and Avandia is the only agent that has that length of data with regards to sustainment of glycemic control at this point in time. So, with several newer medications available and multiple therapeutic options for our patients, it is reassuring to know that Avandia is the most studied oral anti-diabetic medication and a rigorous clinical trial program is proceeding at this point in time. As of now, there is over 9,000,000-patient years of experience with Avandia, over 1.9-million-patient years worth of experience [tape skips] randomized. Your broad spectrum of follow up as well. Up to eight years of follow-up information available from this wealth of clinical trials at the same time, and this includes the entire spectrum of data from the pre-diabetic patients in the DREAM Trial, all the way out to the late-stage diabetic patients in the ACCOR, via diabetes trials, and so forth, as well.

At this point in time, the American Association of Clinical Endocrinologists includes Avandia as an add-on treatment in their diabetes roadmap guide. So, the bottom line is that diabetes is a leading cause of morbidity and mortality in this state, here in the U.S., 640 patients will die from diabetes and diabetic related complications, daily. So, the clinicians who treat diabetes need the full armamentarium of medications available to effectively treat these patients. So, just a couple quick summary points: Avandia, once again, through numerous trials including the Diabetes Outcome Progression Trial has been shown to decrease insulin resistance and also decrease beta cell dysfunction as well. Again, it is the most studied oral anti-diabetic medication to date, with a wealth of efficacy information, and again, the only agent that has been proven to sustain glycemic control for up to five years. So, based on this evidence, and this robust clinical trials program, I would like to request that Avandia remain the preferred agent for the Medicaid patients here in Washington. Thank you very much.

Vyn Reese: Thank you. Any questions from the group? Thank you.

Rob Pearson: Thanks.

Vyn Reese: Are there any other stakeholders that haven't gotten their name on the list for the TZD group? Okay, then, let's open discussion on the committee.

Jeff Graham: Can we let Susan go now?

Vyn Reese: Yes. Susan, you are dismissed. Thank you so much.

Susan Norris: Alright, thanks very much. Bye now.

Man: Just for the record, the endocrinologist mentioned six things that affect glucose control. There is a seventh, and I think very important, is the adherence of diabetic medication. The recent Annals article looking at substance abuse and adherence to diabetes and hypertensive drugs showed there was an issue with substance abuse, but if one looks at 80% compliance as being the marker of success, only 60% of the diabetic population maintained 80% compliance with their diabetes drugs. So, you know, again, back to adherence, we always talk about all the biochemicals, but all the literature is pointing that adherence to these medications for chronic disease is less than adequate. And we provide medication histories for providers when they ask, but typically, we never get asked. So, I just want to put that point there, that it's not all about biochemistry. There is a huge degree of noncompliance in these medications that is seldom looked at as the reasons why people fail in treatment.

Kenneth Wiscomb: Ken Wiscomb. I think my comment would be I think there is no question that this class of drugs probably is effective with people with metabolic syndrome, but I would say to the board that I would go back to February when we talked about the last time, I think right after the black-box warning had come out for congestive heart failure. And we had talked about, a little bit about how our decision is going to sway or represent the standard of care as people see what our preferred drugs are. And we decided to take no action at that time because the FDA had taken no formal action as far as withdrawing either product. And I think now, as I understand, our goal remains to focus on safety and efficacy and outcome, but as I understand it, the preferred drug on our list now is there primarily because of pricing incentives and not, necessarily, because of outcome data. I would just say to the board that it would seem to me now if we look at the data that is available to us, both drugs are efficacious, but it would seem like the other drug now, pio, has a little bit better positive indication, and it does not have the black-box warning. And I am a little bit concerned about having a drug that's preferred, that has a black-box warning over one that doesn't. And I, you know, I would agree with Dr. Wallum that that may very well happen, but as of yet, it has not.

Robert Bray: This is Bob Bray. I agree with Ken's direction on that, and I, as a prescriber [tape skips] is to make and one has macrovascular benefit the other doesn't, the same drug with macrovascular benefit does not have an additional black-box warning, I would like to have that one available. So, one suggestion I would make would be that we consider a change in our motion that doesn't state that they are both safe and asks that pioglitazone be included on the PDL and then, sort of approach it that way.

Vyn Reese: So, in other words, what you're saying, Bob, is basically potentially both of them would be on the PDL.

Robert Bray: No. It would only mandate pioglitazone be on it and then, I'm not suggesting that the evidence is strong enough to completely eliminate one drug, but I think there is a difference in the safety data that we have at this time. And so based on that, I think that we should ask that the drug that

appears to be safer be on the PDL and then whether the other one is on the PDL is an MAA decision.

Carol Cordy: This is Carol Cordy. What would you propose, how would you propose you saying that? Because, what if a black-box warning comes out for pioglitazone?

Robert Bray: What I would propose, I'll just read it off, I guess. "After considering the evidence of safety efficacy in special populations for the treatment of Type 2 Diabetes, I move that pioglitazone and rosiglitazone are efficacious options as second-line therapy." Then the next sentence would be, "Pioglitazone must be included on the PDL."

Carol Cordy: Just with no reason.

Robert Bray: Correct. Just a statement, and I would strike the last sentence. Well, actually, you could leave that, that's fine if you leave it, Ken, on. That's what I would move.

Vyn Reese: Are you making that as the formal motion, Bob?

Robert Bray: Yes.

Jason Iltz: This is Jason, I'll second.

Vyn Reese: Any discussion before . . .

Janet Kelly: This is Janet Kelly. I guess I'm a little confused by why we're saying that these cannot be subject to therapeutic interchange. We pretty much hear that they are equivalent and perhaps the pioglitazone has a safety advantage; so if we are already saying that pioglitazone needs to be on it, why aren't we letting therapeutic interchange? I don't get it. Maybe I'm missing something.

Vyn Reese: Why not, Bob?

Robert Bray: Well, what we don't know, I guess, is whether we're going to have one or two drugs on the PDL. If there are two drugs on the . . . if both of these drugs are on the PDL and someone has been on rosiglitazone and doesn't wish to change, and that drug is on the PDL, then for that . . . I guess if they are both there, why would you therapeutically interchange them.

Donna Sullivan: This is donna Sullivan. If there are both on the Preferred Drug List, they would not be interchanged. If pioglitazone is the only one on the list, then when rosiglitazone is prescribed and substitution is allowed, then pioglitazone would be interchanged for it, but not the other way around.

Barak Gaster: This is Barak Gaster, so I would suggest that we leave that it can be subject to therapeutic interchange.

Male: Yeah.

Barak Gaster: But I agree with having pioglitazone must be included.

Vyn Reese: Do you have any objections to that, Bob?

Robert Bray: I would not object to the friendly amendments.

Vyn Reese: Okay. So, any other discussion on this motion before we vote on it? From, from the committee, from the committee.

Male: Can we have it read one more time?

Vyn Reese: Why don't we go ahead and read it, it's got so many cross-outs and x's and stuff, it's hard to really, you can just delete all the things that have been crossed out.

Male: After considering the evidence of safety, efficacy, and special populations for the treatment of Type 2 Diabetes, I move that pioglitazone and rosiglitazone are efficacious options as second-line therapy. Pioglitazone must be included on the Washington PDL. Thiazolidinediones can be subject to therapeutic interchange in the Washington Preferred Drug List.

Carol Cordy: This is Carol Cordy. When we talk about the Washington PDL, that's the whole list. Are we saying that it needs to be a preferred, aren't you saying it needs to be preferred on the PDL?

Male: Yes.

Carol Cordy: Which I think is different from what this says.

Male: Yes, that's correct.

Male: Well, it's the same . . .

Carol Cordy: It's not the same thing.

Duane Thurman: This is Duane Thurman. That's pretty much our standard language, meaning that it's preferred in that particular class, so I think it's . .

Vyn Reese: It should be "must be a preferred drug" that's what, it's not "must be preferred," it should be "must be a preferred drug" on the Washington PDL.

Male: Right.

Male: Yeah.

Duane Thurman: That would clarify it.

Male: Yeah, exactly.

Male: Good.

Janet Kelly: This is Janet Kelly. This is probably picky, but I can't stand it. Type 2 Diabetes, we no longer use the Roman numerals, so, Carol, I beat you on that one.

Carol Cordy: Good. Thank you.

Vyn Reese: Any other amendments, friendly or otherwise to the motion? This motion has been made and seconded. I'll call the question: All those in favor say "I."

Group: I.

Vyn Reese: Those opposed, same sign. This motion is passed. So now we're going to move right in to the combination drugs, I believe. If we have somebody on the line.

Male: Any minute, should be on the line.

Vyn Reese: Okay. Is there, is Mary on the line?

Kim Peterson: No, this is Kim Peterson, are you on the line yet? We should hear her come in. It will go “kaplunk” or something like that.

Man: Hey, welcome, Kim.

Vyn Reese: Thanks, Kim. This is Doctor Reese; I’m the chair of the Washington State P&T. We have you first slide up, and you’re reviewing Fixed-dose Combination Products for Diabetes, Type 2.

Kim Peterson: Yeah, so this is a presentation on original final report, which we completed back in October of 2007. Go ahead and go on to the next slide. The first couple slides outline the scope of the review. The included populations were adults with Type 2 Diabetes and seven included fixed-dose combination products are listed here. We were primarily interested in the comparisons of the fixed-dose combination products with co-administration of their individual components or with monotherapy with each of their individual components.

Next slide: And here we have the included outcomes for effectiveness and efficacy outcomes, we included all cause, cardiovascular and cerebrovascular mortality, cardiovascular and cerebrovascular events and hospitalizations, and development of nephropathy, neuropathy, or retinopathy. And we were also interested in whether a switch from co-administration to a fixed-dose combination product would improve adherence for persistence outcome, and, of course, also interested in HbA1c lowering. And as for harms, we look at the usual outcomes of overall adverse events, specific adverse events and withdrawals due to adverse events.

Next slide: Here is the information on our search strategy. We searched the usual electronic bibliographic databases through May of 2007, and we also reviewed a dossier submitted from the makers of Actoplus Met and Avandamet. We also reviewed reference lists that included studies as well as public comments for additional study information.

Next slide: Here’s the results of our searches. Overall, we found 488 citations, and among those, we ultimately included 25 studies. Ten of those were randomized control trials, 14 were observational studies, and one was a meta-analysis.

Next slide: Now, on to the results. This slide provides a few details on the nature of the evidence. All of the included randomized controlled trials only addressed comparisons between a combination product and monotherapy with each of its individual components and only provided outcome data on HbA1c lowering and harms. And the majority of the randomized-controlled trials were focused on Glucovance. Otherwise, we found no evidence for Actoplus Met, Duetact, or Janumet. And then, at the bottom, there, we’ve listed the other overall limitations, so the only evidence we could find on adherence comes from just a few observational studies, except one of the main limitations. We also found no studies that reported on any of those long-term health outcomes. And, also there was very limited evidence on the effects of combination products in subgroups.

Next slide: So, starting with the evidence on Glucovance, this slide goes over the characteristics of the patients in the trials. They were . . . there were six in total, and five of them were fair in quality. And they all had pretty similar design and patient characteristics, ranging in duration from 16 to 24 weeks, enrolling slightly more men than women with the mean age of 54 years, mean body mass index of 30.5 kg/m<sup>2</sup> and a mean HbA1C of 8.37%. Dosage ranges of glyburide and metformin in the [tape skips] combination product, as you can see, were quite a bit lower than in the monotherapy groups.

Next slide: So, here's the main findings regarding how Glucovance compared to the component monotherapies on HbA1c outcomes. Glucovance brought patients' HbA1c levels down by anywhere from 0.9% to 2.3%, and those reductions were significantly greater than what was seen in patients taking glyburide or metformin monotherapies. And also a few of the trials reported on the rates of patients who got their HbA1c's down to 7% or below during the study. There were three trials that reported that outcome, and all three of them, there were significantly more patients on Glucovance who met goal than patients on monotherapy. And we've looked at the NNTs there for you, and what they tell you is that in the case of first-line therapy—there were two trials of first-line therapy—there was one additional patient that met goal for every four to six patients that were treated with Glucovance instead of metformin. And for every eight to nine patients given Glucovance instead of glyburide. And then in the case of the one trial, a second-line therapy, only three to four patients had to be treated with Glucovance instead of metformin or glyburide in order for one additional patient to meet goal. So, those NNTs are pretty low. And then what the note at the bottom of the slide means is that there were some subgroup analyses—results from subgroup analyses reported and showed that the advantages of Glucovance over monotherapy on the HbA1c-lowering outcomes were consistent, regardless of variations in age, gender, race, HbA1c or BMI.

Let's go on to the next slide: Looking at the evidence on the question of whether Glucovance improved medication adherence compared with co-administration of glyburide and metformin. We found two fair quality population-based cohort studies that looked at these outcomes using six-month refill data. And what they found was that Glucovance was associated with some improvements in adherence, but only in previously treated patients who were switched from monotherapy to either Glucovance or adding a second drug, so people who were used to taking one pill and then going to either one pill, one combination product, or then two pills. So, in patients who were initially put on either Glucovance or co-administration of glyburide and metformin, so that was their first experience with taking medication, either Glucovance or co-administration, there wasn't any advantage in terms of adherence rates for people who were initially put on Glucovance.

And then as for data in subgroups, one of these studies also conducted an analysis of co-variance. To look at whether the advantage of Glucovance over co-administration in adherence changed, based on any patient

characteristics, and what they found was that as age increased over 55, improvements in adherence seen with Glucovance over co-administration started to drop off, but that no other patient characteristics affected Glucovance's potential for improving adherence in people who were going from monotherapy to Glucovance or co-administration.

Next slide: Okay, so now on to the evidence from Metaglip, and there we included two fair-quality trials of Metaglip as compared to either glipizide or metformin monotherapies, either as first- or second-line therapies. The trial of first-line therapy was actually still unpublished at the time that we completed this review. So, the details we have about it are from an FDA medical and statistical reviews that we found online on the FDA website. Compared to patients in the trial of second-line therapy, more patients in the trial of first-line therapy were women with shorter durations of diabetes; otherwise, in both trials, the patients were mostly white, with a mean BMI of 29.9 kg/m<sup>2</sup> and a mean HbA1c of 9%. And, again, those levels of glipizide and metformin in the fixed-dose combination product groups were quite a bit lower than in the monotherapy groups.

Next slide: So, here are the main findings regarding how Metaglip compared to glipizide and metformin monotherapies on the HbA1c outcomes. In both the first-line and second-line therapy trials, Metaglip brought patients' HbA1c levels down by anywhere from 1.3% to 2.15%, which were greater reductions than what we're seeing for patients taking glipizide or metformin monotherapies. And, again, those differences were significant with the level of P lower than 0.001. And in the first-line therapy trial, no subgroup based on age, gender, or race were any more or less likely to be helped by Metaglip than monotherapy. There are no differences in effects in any subgroups based on age, gender, or race. And then, only the second-line therapy trial reported on the rates of patients who got their HbA1c down to 7% or below during study. And there, 36.3% of patients met goal in the Metaglip group compared with only 8.9% in the glipizide monotherapy and 9.9% in the metformin monotherapy groups. And so, the NNT for the comparison between Metaglip and glipizide and metformin was four, meaning that only four patients would have to be treated with Metaglip instead of glipizide or metformin to get one additional patient to reach goal.

Next slide: So, for Metaglip, we didn't find any evidence regarding how it impacts adherence rates compared with the co-administration of glipizide and metformin, so we don't have any answers to that question at this point.

Next slide: So, now on to the evidence for Avandamet, we only found one randomized controlled trial that compared Avandamet to metformin and rosiglitazone monotherapies, and it was fair quality. Thirty-six weeks in duration—I'm sorry—thirty-two weeks in duration and included 468 patients, like the other trials, there were slightly more men than women, and in this case, there were only 57% white, having a mean age of 51 years and a mean BMI of 32.8 kg/m<sup>2</sup>, mean HbA1c of 8.8%, and having diabetes for a mean duration of 2.6 years. The rosiglitazone dose was 7.2 mg in the combination product group and 7.7 mg in the monotherapy

group, so just a little lower here. And then, metformin dose was 1799 mg in the combination product group and 1847 mg in the monotherapy group.

Next slide: So, here's the HbA1c outcomes for Avandamet compared with rosiglitazone and metformin monotherapy. Avandamet brought patients' HbA1c levels down by 2.3%, which was a significantly greater reduction than the 1.6% seen for rosiglitazone and the 1.8% reduction seen for metformin, and the P value is there on the slide. And then, also, this trial did report the outcome of the percent of patients who had HbA1c met goal of 7% or below by end point. In this trial, 77% of patients on Avandamet met goal, whereas only 51.8% of patients on rosiglitazone alone did so, and only 57.3% of patients on metformin alone did. And then NNT for Avandamet compared with either rosiglitazone or metformin monotherapy was 5. And there were no subgroup analyses done or reported in this trial.

Next slide: Here's the adherence outcomes of Avandamet and co-administration of rosiglitazone and metformin, so we did find one population-based cohort study that used, again, six-month refill data to compare the medication possession ratios for Avandamet and co-administration of rosiglitazone and metformin. Medication possession ratios were to find as the calculation of the medication supply actually received divided by the medication supply that should have been received. So, what the study did was to look at the medication possession ratios in patients who were originally on a monotherapy treatment regimen and see how the ratios changed after they were switched to either Avandamet or co-administration of rosiglitazone and metformin. And they also looked at changes in medication possession ratios for people who were initially on co-administration and switched to Avandamet compared to those who stayed on co-administration. And what they found was a significantly lower decline in medication possession ratio when monotherapy patients were switched to Avandamet compared with those who were switched to dual therapy co-administration of rosiglitazone and metformin. So, switching to Avandamet, their medication possession ratio only dropped by 1.5% compared with a drop of 12.4% in the co-administration group. And then they also found that patients switched from co-administration of rosiglitazone and metformin to Avandamet experienced a 3.5 increase in medication possession ratio compared with a slight drop of 1.3% in the group who stayed on co-administration. And that difference was statistically significant as well, although it's not clear how clinically significant those very small drops, or changes, in medication possession ratio actually are.

So, let's go on to the next slide: The evidence for Avandaryl compared with glimepiride and rosiglitazone monotherapy, again, only found one randomized control trial for that comparison, which we rated fair quality. It was 28 weeks in duration and enrolled 901 adults, slightly more men than women, mean age was 54 years, they were mostly white, having a BMI of 32 kg/m<sup>2</sup>, mean HbA1c of 9.1%, and had diabetes for a mean of 3.0 years before entering the trial. And the mean final doses of glimepiride were 2.9 and 3.2 mg in the combination product groups. There were two

groups, two regimens on combination therapy, but then 3.5 in the glimepiride monotherapy group. Whereas the mean final doses of rosiglitazone were 4.0 and 6.8 in the two combination product groups and then 7.5 in the monotherapy.

Next slide: Here are the HbA1c outcomes for Avandaryl compared with glimepiride and rosiglitazone monotherapy. Again, Avandaryl brought patients' HbA1c levels down by 2.41% in regimen A, the lower-dose group, and 2.5% in regimen B, the higher-dose group, which were significantly greater reductions than the 1.72% reduction seen for glimepiride and the 1.75% reduction seen for rosiglitazone. And this trial also reported the percent of patients who reached HbA1c of 7% or below by the study end, and here, 74.5% of patients who were in regimen A in the lower dose of Avandaryl and 72.4 on the higher dose met the HbA1c goal of 7.7% or below by end point, whereas only 49.1 of patients on glimepiride alone did and only 46.2% on rosiglitazone monotherapy did with NNTs and compared with glimepiride or rosiglitazone monotherapies of three to four, so only needed to treat three or four patients with Avandaryl instead of rosiglitazone or glimepiride to get one additional patient to meet goal. And then in this study, again, there were no subgroup analyses reported, so can't draw any conclusions about whether the effect of Avandaryl differs in patient different patient subgroups. And I also forgot to note here that for Avandaryl, we didn't find any evidence on how it affects adherence rates compared to co-administration.

So, now let's go on to the next slide: Which now we're getting in to... the next few slides are evidence of adverse events across all the combination products. So, we only have data for having adverse events of the fixed-dose combination products compared to monotherapies of their individual component drugs. So, in those observational studies, they didn't report on adverse events compared with co-administration. And the big thing of concern here was [inaudible] how much the risk of hypoglycemia increased when using specifically, a sulfonylurea containing combination product compared with using the sulfonylurea alone. And so in this table, we've listed the hypoglycemia rates for Glucovance, Metaglip, and Avandaryl compared with monotherapy of their sulfonylurea components.

So, on the first line of the table, we have our results from a relative risk analysis where we quote data from the three trials that used similar dosage levels of Glucovance and found that it did have a 3% greater risk of hypoglycemia than with glyburide alone, but that difference was not statistically significant, as you can see with that confidence interval and the relative risk crossing zero.

Then in the second line of the table, that shows the relative risk of hypoglycemia for Glucovance compared with glyburide monotherapy from the trial that used higher dosages of the drugs. And it shows that the risk of hypoglycemia was close to four times higher for Glucovance compared with glyburide alone, and that there the difference was statistically significant. So, I guess that follows logic that your risk of hypoglycemia increases with your increased dose of Glucovance. And in the next few lines in the table shows that the hypoglycemia data from the

trials of Metaglip. For Metaglip, again, higher rates of hypoglycemia were found in comparison to glipizide regardless of dose, and the differences were statistically significant.

And then the final line shows the hypoglycemia data from the one trial of Avandaryl, and in this case, the rates were pretty similar for Avandaryl and glimepiride. Although you couldn't achieve a greater degree a significantly greater degree of HbA1c-lowering with Avandaryl compared with glimepiride, that didn't come at the expense of increased risk of hypoglycemia in that one trial.

Next slide: As for Avandamet, since it doesn't contain a sulfonylurea, no increased risk of hypoglycemia was found for it compared to its component monotherapies was expected and none were found. The differences found between Avandamet and monotherapies related to GI adverse events. So, there was more nausea, vomiting, and diarrhea with Avandamet compared with rosiglitazone monotherapy, but that was not unexpected since GI adverse events are pretty common for the metformin component of Avandamet relative to rosiglitazone.

Next slide: This is the last slide, and it just gives you a quick rundown of the main findings. First, regarding findings from comparisons of the combination products to their component monotherapies, the main benefit of the combination products is that you can get better glucose control at lower doses of the component drugs than are required when the component drugs are used as monotherapies. But, as we just went over in some cases that superior glucose control with the combination products came with an increased risk of hypoglycemia. So, that the only case that we didn't see... well, for the lower... where we pooled the three trials of Glucovance at the lower dosages, the difference was not statistically significant and the difference was not statistically significant for Avandaryl either. And then as for how the combination products affect adherence compared with co-administration of the dual components, we only found evidence from a couple observational studies, but they did show that there was significant improvement, statistically significant improvements in adherence for both Glucovance and Avandamet. But we didn't find any evidence on how any of the other combination products affect adherence. And then, finally, just a reminder that we didn't find any eligible evidence for Actoplus Met, Duetact, or Janumet. So, that's the last slide, so now I can hand it back to you for questions.

Vyn Reese: This is Dr. Reese, are there any questions of Kim from the committee? Kim, can you stay on the line while the stakeholders talk?

Kim Peterson: Sure.

Robert Bray: I have some questions.

Vyn Reese: Oh, you have a question?

Robert Bray: Yeah.

Vyn Reese: Wait, one question from committee at least.

Robert Bray: This is Bob Bray. On slide 15, where they were looking at the medication possession ratio.

Kim Peterson: Yes.

Robert Bray: And you had a less of decline in the combination drug. The question I had is did that study identify how many drugs the patients were on on admission into the study?

Kim Peterson: So the sample size of the study?

Robert Bray: No, the other drugs that the patients were on in addition to the study drugs.

Kim Peterson: Oh, I see. Yes, generally, patients taking these types of medications are taking other medications as well. No, that was not clearly... that was not looked at in this study.

Robert Bray: It wasn't looked at, but they didn't exclude patients that were on additional drugs, then?

Kim Peterson: No.

Robert Bray: The other question I had related to slide 18 with the hypoglycemic rates. What was considered hypoglycemia? Was it a symptomatic report by the patient? Was it actual blood glucose readings? Was it clinical requirement for care, like, you know, going to getting assistance or getting... going to the emergency room? What was the criteria for that?

Kim Peterson: Yeah, that's a good question, and it differed from trial to trial. So, in some cases, it was just investigator-reported and not... there was no actual cutoff used. I'm looking at the report now for Glucovance. The evidence on Glucovance, I think there's a table you scroll down where we list out what the definition was for each of the trials...

Woman: So in some cases, it was just investigator reported and not... there was no actual cutoff used. I'm looking at the report now for Glucovance, the evidence on Glucovance. I think there's a table... let me scroll down where we list out what the definition was for each of the trials. So table seven in the report. So that the three trials that we pulled together, for one of them it wasn't defined, and then for the other two it was equal to or below 2.8 millimoles per liter. In the high dose trial, the cutoff was at or below 3.3 millimoles per liter. So that's what... those were the rates, those were the definitions for the Glucovance trials.

Man: For those of us who remember milligrams per deciliter, can you translate those for us?

Woman: Oh, boy, is that not the standard way of defining... that's how they were defined in the trials and I sure don't know the conversion.

Man: Do we have the conversion from the committee?

Woman: I think that 126 mg per deciliter is equivalent to six millimoles, but I can't do the math.

Man: That's pretty low. Okay, thank you.

Vyn Reese: Any other questions? Okay, let's move on to stakeholder comments. And there are two stakeholders that have signed up. And I don't know if there are more. The first is Dr. Brad Wallum. Go ahead and start talking.

Brad Wallum: Thanks again. I just wanted to clarify an issue in terms of the learned gentleman to the left of Dr. Reese, whose name I didn't catch mentioned that one of the concerns of the decisions of this committee is how it could affect the standard of care in the practice based on what's recommended. I just wanted to clarify two issues as it related to the discussion of safety of TZDs. Several members of this committee have concluded, I think incorrectly, that there's data to suggest that Pioglitazone is safer than Rosiglitazone. Case in point,

Kim Peterson: I'm sorry to interrupt, this is Kim, but I'm hearing Christmas music.

Woman: Yea, so am I.

Kim Peterson: I'm having a hard time hearing the speaker because I'm hearing Christmas music.

Jeff Graham: Kim, this is Jeff. Someone's put theirs on hold and we don't know who it is.

Man: It's the one who will come back.

Kim Peterson: You can continue, but if there's a question I can't really hear it.

Vyn Reese: You have to speak very loudly.

Man: You have to talk very loudly to get over the Christmas music.

Brad Wallum: I can do that. Thank you. I think inclusion that both Pioglitazone and rosiglitazone are considered equally safe in contrast to one agent being safer than the other. Case in point, when the FDA did their review of the data, they made the conclusion that there is no oral agent on the market in the United States that has been proven to reduce the risk of cardiovascular disease and I think also someone here has made the incorrect conclusion that Pioglitazone has been demonstrated to reduce macrovascular disease. In fact, in their primary end point of the trial, which is what we use in clinical investigation, there is no statistical reduction of the primary end point, which was non-fatal MI, stroke, total mortality acute coronary syndrome, coronary artery peripheral revascularization amputations. So just to clarify, both of these TZDs are equally safe based on interpretation of the currently available research that's on the market and I think that if we had the decision of both of those drugs being available, that would make the most sense from an endocrine perspective in terms of providers that are trying to help people get their blood sugars under control. And I think, unfortunately, there's a decision that's been made that one is the

preferred agent. I think the more correct interpretation based on scientific data is they are equally safe.

The last comment I would make is in terms of the FDA black box warning. The black box warning for rosiglitazone did not say that there is increased risk of ischemic events for rosiglitazone. What it said was there was data from meta-analysis suggesting a possible increased risk. There is data from outcome studies showing no difference, and the conclusion was that there was no conclusive evidence of an increased risk of cardiovascular ischemic events. Since that time, two huge studies, the ACCORD study and the VAT(?) study both showed no difference in ischemic events with rosiglitazone. So I just wanted to clarify those issues. I think you need to make your own decisions on how you want to proceed, I just wanted to be sure there wasn't misinterpretation of the scientific evidence in terms of the safety of those two agents.

In terms of combination therapy, I also think that even though Actos Plus has no data showing improved in compliance, I think that and the combination of Avandia and Metformin, such as an Avandamet are both good drugs, even though you don't have comparative data. Thank you.

Vyn Reese: Thank you. I want to make a comment. It doesn't mean that both of those drugs will not be on the PDL. It means one of them has to be, and that was... I think that a conclusion was drawn from the black box warning that was made and from data making it look like Pioglitazone might be, might decrease macrovascular events and there wasn't any data yet on the other drug. So it's like it's very scant, scanty data. And I agree with you personally. I don't think the data's very good and until it's better, people need to have both drugs available. That would be my take on it.

Man: If I could just add too. I don't think anybody was trying to make a comment about that we represent the standard of care. I think that we, the comment was that some people infer or perceive that we do. And it's inconsistent then with that regard if we have a drug as a preferred drug that has a black box warning versus one that doesn't, when the only difference as far as the committee is concerned is pricing. If that makes sense. In other words, it's not consistent to me that we have a drug approved that has a black box warning only because it's the least expensive, when as compared to a drug that does not have a black box warning when the efficacy is essentially the same.

Vyn Reese: So anyway, the next... but thank you for talking to us and I appreciate your comments. The next speaker is Rob Pearson, Pharm D from GSK.

Rob Pearson: Thanks again. Just a quick comment. I really appreciate the committee's careful and thorough review of the fixed dose combination product class of medications. And it appears that the only two TZD fixed dose combination products they had trials robust enough to be included into this analysis, of course were Avandamet and Avandaryl. So I would like to

request that the committee consider making those two agents the preferred fixed dose combination product TZD agents. Thank you very much.

Vyn Reese: Okay, thank you. Any questions? I'll open up for discussion. And Kim, you're excused. Thank you very much.

Kim Peterson: Okay, have a good day, bye bye.

Barak Gaster: This is Barak Gaster. I have a question. So are we thinking that this fixed dose combination pill will be its own separate class of drugs on our formulary?

Jeff Graham: This is Jeff Graham. This committee has never put a fixed dose combination product on our preferred drug list, and we have heard other ones before. I mean, that's a decision you can make or not make.

Barak Gaster: I mean, it just strikes me as complicated. I mean there's lots of fixed dose combination antihypertensive drugs that sort of cross among the different classes that we have, which are not... which have never been considered and so I'm a little confused and daunted as to how this is going to fit into the overall classification scheme of the drugs that we have on our list.

Jeff Graham: This is Jeff Graham again. I think this was a review that was requested by the participating organization and our Drug Effectiveness Review Project and we've brought this forward because it has been presented and we have the information, but the decision is up to the P&T committee whether this is a class that we would add. There are some classes that we have never added to our Preferred Drug List.

Vyn Reese: We don't even, Barak, we don't even have to make a motion to put this on... this class, this isn't even a class, as you said. We can just say nothing and not put it on the PDL. And personally, I do not like combination drugs, especially for diabetes, because the side effects of these drugs are different, and if usually you're going to max people out on Metformin then I add a sulfonylurea or another drug, and oftentimes if they lose weight, then you'll have to take away one of those drugs. Usually the sulfonylurea if they lose weight for any reason or if they become ill. And then you have the combination pills. They have all these together. There are lots of times that the side effects are different with each drug in the combination and sometimes you'll want to increase the drug that's not causing as much in the way of side effects and decrease the other one or keep it very low, and then you have to add maybe another second pill of the like Metformin added on to your combination Metformin sulfonylurea drug and it gets to be, I think it's difficult and confusing for patients. I think if you had maybe a combination drug at the maximum dose of both a sulfonylurea and Metformin or a TZD, that might be something that would work, but that's people who are already maxed out and just putting them on that drug at the end, but then they aren't in a steady state either, because those patients may graduate on to insulin, you may want to take

away the sulfonylurea if they're on one when they go on insulin. So it just takes away, I think, your flexibility and your ability to really sort of [tape skips] make the regimen to the patient. Those are my biases against combination drugs, especially for this indication. It makes it easier for patients who you've already titrated and they're on a fixed dose, but as I said before, nothing stays the same in diabetes. Things are always changing and you have no flexibility with combination drugs for diabetes. That really... it strikes me as very foolish to use these drugs unless... except for very limited circumstances and I think that we don't need to add them to the PDL. That's my biased opinion.

Kenneth Wiscomb: This is Ken Wiscomb. I would agree entirely. I mean, I think the... although there was a statistically significant percentage of people that showed some increased improvement with as compared to co-administration, it wasn't clinically significant. So we're not... there's not even real evidence that that increased adherence is going to help matters. And one has to think that it's more expensive, when you combine a generic with a non-generic and make that a choice as compared to...

Duane Thurman: This is Duane. I just want to, sorry go ahead.

Kenneth Wiscomb: Go ahead.

Duane Thurman: I just want to clarify how we get to this point. One of the things we rely on the DERP project and the participants to select which drug classes we're going to review. In the past there have been times when you have decided not to put something on a PDL or not appropriate. The reason that we do that I think is that the information is always good. It gives us more information about how the agencies purchase, even if it's not on the Preferred Drug List. But I think most importantly, we want it clear that the agencies are not gaming the system by individually choosing which drug classes to put forward. So occasionally we will bring one forward that you don't think is appropriate and you have the discretion to do that. The other thing I wanted to go back to address on the previous motion was that in terms of safety I think we have to be very careful that what your motion did was it had no statement about safety. It simply found that they were efficacious and there was not an implication that it was unsafe as opposed to the other drugs. So I think that that's a... it's no statement at all, it's not a negative...

Vyn Reese: And that's because we didn't have... we don't have the data now, really. I mean we are uncertain. And that's purposely so. And I think that was wise.

Duane Thurman: Correct. And then the final thing is when... in this final drug class when they say that there's no eligible studies for the other drugs, I'm assuming what that means is that there... it wasn't within the timeframe of the study, like if a drug comes out too late and we can't get it in to the period of the

study, it's just not before you for consideration. It's not a matter of us saying we're not going to deal with these drugs because we didn't find any evidence. It didn't happen during this time period and the process that we follow with all of the other states.

Robert Bray:

I guess Bob Bray, my two cents worth is I think what would be real good information is if we could always look at the combination drug versus the two components being given individually. And I think what this evidence shows us is when we think we want to use an oral hypoglycemic drug, we should use two and therefore use lower doses. But it doesn't help us to know whether we should put combination drugs on a formulary. The only study they had that showed co-administration with both components, didn't look at efficacy, it only looked at the medication position ratio, and it didn't show improvement, it showed less deterioration. And I guess from a practical standpoint, since we don't know what other drugs they're on, most of these people are going to be on five drugs, not one or two and so the difference would be between four and five rather between one and two, and I think when you're talking about adherence influences, that's probably a big difference. So I don't think that information helps me to understand adherence issues with this combination drug. So those would be my reasons to support what's already been said, which is I don't see that there's a benefit by having these fixed combinations on the PDL.

Barak Gaster:

I agree completely with what's been said. I think that diabetes oral hypoglycemics for diabetes are really different from one another, need to be individually titrated that there may be some small role for fixed combination products, but that it's complicated and dangerous, and although it may improve adherence a little bit, I think it has also the potential to confuse not just patients, but also providers as to what exactly they're prescribing. And that I think that some of the data that's been presented may not be real world data in terms of picking up that kind of confusion and medication errors that can occur. And I try to think of other situations where fixed dose combination may have more of a role and I guess HIV anti-viral comes to mind, which is a situation though where there's less individual dose titration of each component of the combination, which I think it's good to have one pill instead of taking four pills in some situations, but I don't think that this is one of them and so I would move that we do not make this a new class of drugs on the PDL.

Man:

I'll second the motion.

Carol Cordy:

This is Carol Cordy. I just have a question. I was just checking. It's interesting that Epocrates, which is the drug list that's available on the internet and for palm devices. It lists many of these as covered as preferred drugs. Are they wrong?

Donna Sullivan:

This is Donna Sullivan. If you're speaking about Uniform Medical Plan it's because typically what we do is if we have a product family where currently Avandia is the TZD that's preferred, because it's a product

family we would make the Avandaryl the Avandamet preferred as well. So for Uniform Medical Plan we do cover, you know, pretty much all drugs, it's just considered a non-Washington PDL class so no tip or therapeutic interchange occurs. But we do cover them.

Carol Cordy: I was looking for non-Medicaid...

Duane Thurman: This is Duane, let me complicate it further. When we're talking about the Washington Preferred Drug List what we're talking about is the one used by Labor and Industries, Medicaid, and the Uniform Medical Plan. And once you say it's not on that preferred drug list, it drops out of the program. So there's no endorsing provider provisions, there's no dispense as written to override the prior authorization. It's treated as though it were never... that we didn't exist here in this program. And so basically they are available, they're just treated separately by the agencies how they would treat all of the other drug classes that are not on the Washington State Preferred Drug List. So it will vary depending on whether Medicaid has a prior authorization or an EPA on it and it'll vary because the public employees health plans, the Uniform Medical Plan has a tiered structure and it's very different between the agencies, so you will, it will be treated differently by the agencies. It's just not a part of this process where all three agencies have to follow it, and it's preferred, and then you have the dynamic of being able to sign up with an endorser so that you don't have to do the paperwork to get through dispense as... you can use dispense as written to get through the prior authorization process, that sort of thing.

Carol Cordy: So as it stands now, because this is the first review, if I prescribe one of these combination drugs, it'll be covered? Is that what you're saying? And we can change that?

Jeff Graham: Let Siri respond.

Siri Childs: ... Medicaid.

Jeff Graham: Let Siri respond for Medicaid right now.

Duane Thurman: Speak up, Siri, please.

Siri Childs: The combination drugs are currently covered because they are not part of the PDL program as Duane just described.

Duane Thurman: So the point of this Preferred Drug List is if you put it on the Preferred Drug List we look at... then our next step is to look at the cost experience spread among the three agencies that participate. That takes in to account the supplemental rebate bids that come from manufacturers for Medicaid and then we use the evidence based decision that you've made to make our purchasing decision between the three agencies. So, once you step out of that, the agencies are going to do what they're going to do. In Donna's case, it usually defaults to our formulary for PBN nationally. So it may or

may not continue to be preferred at the agencies. It'll just go through their normal processes.

Jeff Graham: And maybe Siri could say what covered means. What's the definition of covered Siri?

Siri Childs: Covered in Medicaid means that there's no restrictions. If you write for Avandaryl or Actos Plus, it just goes right through the computer without stopping.

Vyn Reese: I have another question. What if we just say we reviewed this and we decided not to place them on the PDL [tape skips].

Duane Thurman: It would probably cleaner to just do a motion that you move not to include this on the PDL, simply.

Vyn Reese: Before, I think we reviewed products where we just reviewed them and just didn't do anything and so they didn't become part of the PDL.

Jeff Graham: I think you've made motions previously.

Vyn Reese: Okay, if you want to go ahead and do that we can. We have the motion before us, let's go ahead and discuss this a little more.

Woman: I just wanted to clarify. So if we do as Vyn says, then nothing will change.

Duane Thurman: It may change in the future, right. And I guess the final point I'll make is that you won't always find that the drugs are covered. It's going to depend on how the agency treats that particular class if it's not on the PDL. But at this point it sounds like it is covered and no changes result of today.

Jason Iltz: This is Jason. So I'm confused now. So the current motion on the table is to not put these combination drugs on the Washington Preferred Drug List. So just to reiterate, can we hear then from Siri and Donna, would that change how they're being currently handled presently? Because I think what I've heard was that we really don't feel that these should be covered, at least first line maybe in certain instances, and so if they're all covered now and this recommendation doesn't change that, is that was this committee is trying to achieve?

Duane Thurman: I think that it's outside the committee's discretion in terms of a coverage decision. I think that all of your discretion is within the context of what goes on the PDL and what should be called out as preferred. Other than that it defaults back to the agency's authority for coverage decisions and how they individually would make a drug preferred or available.

Man: We're powerful, but not that powerful.

Siri Childs: Duane, let me just add one little thing. This is Siri. When we in the PA program, when we make a decision to put a drug on PA for safety reasons, it impacts our resources. We have to be very careful about not overloading the workload for our folks on the PA line, because we do have an obligation to deliver good customer service. So we have to always prioritize based on what is really critical as far as safety.

Carol Cordy: This is Carol Cordy again. If somebody could explain this really quickly, if we were to put this on the Preferred Drug List, but let's say we chose not to have any of them preferred, they would all be just there on the right column, how would that impact...

Donna Sullivan: For Uniform Medical Plan if you were to do that then we would make them all non-preferred, but if an endorsing provider wrote dispense as written they would get it, and there would be no interchange.

Carol Cordy: Okay, and would that be...

Donna Sullivan: They would be tier three, so they would be covered at the highest cost share tier for Uniform Medical Plan or the other public employees health plan that we have, but they would still be covered and currently we do have these all on step therapy, or most of them on step therapy, at least the Avandaryl and those, and so that would remain in place.

Carol Cordy: So are they tier three now?

Donna Sullivan: Well, currently we... I can't speak to all of them, Actos Plus Met is tier three, I want to say Januvia or Janumet is tier three. The Duetact, I think those are all tier three. But Avandia and Avandaryl are tier two in line with the current PDL decision. Now based on your TZD decision today, it's likely that there will be changes made to the TZD combinations on our Preferred Drug List to just coincide with the product group or the, you know, they call them market buckets in the pharmaceutical industry. So to coincide with market buckets, we would probably put the associated combinations at the same tier level as the TZDs or the other individual products.

Jeff Thompson: This is Jeff Thompson for Medicaid. So as you heard from Siri, they are covered, there are no restrictions. I would remind you that if there is any drug that has a federal rebate they have to be on our... we don't have a formulary we just... everything's available. We are authorized to do prior authorization and under our administrative code we look at whether there is a safety issue, whether they are high cost drugs with low cost alternatives [tape skips] abuse of these drugs. And if they score high on those measures of quality, safety, and abuse misuse, then we would put something on PA, but they are not on PA at this time. So they are covered without restrictions. And were you to not put them on the Preferred Drug List, it would be the same as what it is currently.

Woman: But more work to... if they were all PA.

Duane Thurman: Yes, I mean there's a cost associated with that and then also my constant reminder that we don't want you to use your decisions as guidelines. Again, it's the discretion of the individual provider here that is going to make the call as to whether they think that's necessary. So I think that with Medicaid they have to cover all of the drugs. If they find a safety issue in the future they may put a prior authorization on it. But at this point I don't think there's any change.

Vyn Reese: So I'm still confused about whether we need a motion or not. If there are already basically... if we keep them off the PDL is that going to increase the number of people calling in for...

Duane Thurman: No, it would allow us to effectively communicate that you said we specifically do not think that this is good to be on the PDL. That it wasn't a decision that we made individually or as agencies. It's just purely formal to say you looked at it and you said our decision is we don't want it on the Preferred Drug List.

Vyn Reese: If we have a motion it seems like it's sort of a cumbersome worded motion. So you might want to take a stab at... Carol do you want to take a stab at sort of rewording that? Instead of not make something.

Carol Cordy: I would say I move that, let's see. The combination drugs not be included on the Washington PDL.

Man: As a class.

Vyn Reese: The motion has been a made and a second. Is there any further discussion? I'll call for the motion. All those in favor say, "I."

Group: I.

Vyn Reese: Those opposed same sign. The motion is passed. And now are we adjourned at this point?

Jeff Graham: Yes, the DUR meeting has been cancelled.

Vyn Reese: So it'll be placed on the agenda for the February meeting, is that correct?

Duane Thurman: Correct

Jeff Graham: Yes, that's February 18<sup>th</sup>.

Duane Thurman: This is Duane, and I just want to thank the committee again for another year of hard work and participation and especially showing up today and have a good holiday and see you next year.

Vyn Reese: We're adjourned, thank you.