



Washington State Health Care Authority  
**Prescription Drug Program**

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UNOFFICIAL TRANSCRIPT\*  
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

August 15, 2007  
SeaTac Marriott Hotel  
9:00am – 4:00pm

**Committee in Attendance:**

Angelo Ballasiotes, Pharm D  
Robert Bray, MD  
Carol Cordy, MD (Vice Chair)  
Alvin Goo, Pharm D  
Jason Iltz, Pharm D  
Janet Kelly, Pharm D  
Daniel Lessler, MD (Chair)  
T. Vyn Reese, M.D.  
Patti Varley, ARNP  
Kenneth Wiscomb, PA-C

Daniel Lessler: I think just as a – seems like as a general rule it's probably a good idea to go through and have everybody introduce themselves so, so folks in the audience know who we are here. So, why don't we start down there, Doug if you could begin.

Doug Tuman: Doug Tuman, Labor and Industries.

Jaymie Mai: Jaymie Mai, Labor and Industries.

Siri Childs: Siri Childs, HRSA.

Steve Hammond: Steve Hammond, HRSA.

Jeff Thompson: Jeff Thompson, DSHS.

Jeff Graham: Jeff Graham, Healthcare Authority.

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\* 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).

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

Janet Kelly: Janet Kelly, P&T committee member.

Ken Wiscomb: Ken Wiscomb, P&T committee member.

Angelo Ballasiotes: Angelo Ballasiotes, P&T committee member.

Carol Cordy: Carol Cordy, P&T committee member.

Dan Lessler: Dan Lessler, chair of P&T committee.

Vyn Reese: Vyn Reese, P&T committee member.

Alvin Goo: Alvin Goo, P&T committee member.

Jason Iltz: Jason Iltz, P&T committee member.

Bob Bray: Bob Bray, P&T committee member.

Nancy Fisher: Nancy Fisher, Healthcare Authority.

Ray Hanley: Ray Hanley, Healthcare Authority.

Duane Thurman: Duane Thurman, Healthcare Authority.

Donna Sullivan: Donna Sullivan, Healthcare Authority.

Elizabeth James: Elizabeth James, Uniform Medical Plan.

Regina Chacón: Regina Chacón, Healthcare Authority.

Dan Lessler: Thank you. So for the first, well actually let me ask Jeff if you've got any, any announcements before we.

Jeff: Well I have – excuse me – I have one announcement. Particularly for the P&T committee members and staff, when you speak please give your name before. Recently we read the transcripts on some decisions and we had no idea if sometimes who was speaking. We kind of guessed. So if you would please do that and actually the staff, if I noted it's more of this problem than the P&T committee members too. So that's the main announcement I have.

Dan Lessler: Thank you. The first order of business today is we needed to briefly revisit our – the motion that we adopted at our last meeting regarding the newer sedative hypnotics. And actually, if you could – could we make that

motion so it's a – so everybody could see actually the text of the motion from last time? I don't know who's got the – just scroll down there. Yea, that's great. So, what we did with this motion last time is we recognized that there within this class of newer sedative hypnotics there are really two subclasses based on mechanism of action. Those that are benzodiazepine like in terms of the receptors that are being acted on and so forth, and those that are melatonin like.

And when we created the motion, we drafted the motion, we crafted it such that we recognized these two subclasses and based on the reviews that we heard, felt that both the subclasses were safe and effective, although there was not any compelling data within either subclass – of well actually with the melatonin like meds there was just the one medicine, Ramelteon. But within the sedative hypnotics that no one agent was better than others.

And because of concerns of the different mechanisms of action and some of the other clinical details what we specified is as people can see in the middle of this motion, just from the bottom up just going one, two, three, four, five, so the sixth line up where it says the benzodiazepine receptor agonists can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of insomnia, Ramelteon cannot be substituted for other drugs in this class and at least one benzodiazepine receptor agonist must be preferred.

So what would help the agencies here is just a bit of clarification with respect to Ramelteon substitution in as much as we want to be clear that really this goes both ways. That is, that if somebody, as written here if somebody writes for Ramelteon, then that could not be substituted for one of the agents that works in the benzo like class of sedative hypnotics.

But vice versa we want to be clear that this would also go the other way, so if somebody wrote for one of the benzo like subclass sedative hypnotics it would not be possible to substitute Ramelteon and in so doing, from a practical standpoint what this means is – obviously we don't know where the agencies will end up in terms of what is put on the preferred drug list, but in the event – or which drug is preferred on the preferred drug list I should say.

But in the event that Ramelteon is not so chosen, then what this would mean is that if somebody – but if an endorsing prescriber wrote for Ramelteon, they would have to write dispense as written and being that the medicine is on the PDL, it would be dispensed. But if somebody was not an endorsing provider then the agencies would each deal with that as they – using the processes they currently use when somebody writes for a

medicine that is not preferred and the person writing it is not an endorsing provider.

So that's the reason for the clarification and so at this point what would be helpful I think would be just a separate motion that specifically said that the benzodiazepine class of newer sedative hypnotics cannot be substituted with any other agent that's not part of that subclass I guess that's not a benzodiazepine like sedative hypnotic.

So with that – let me ask here first whether from the agency standpoint as we just discussed whether that provides the clarity that is needed.

Duane Thurman: Okay, this is Duane Thurman. To clarify what you're saying is that essentially the clarification is that Ramelteon cannot be substituted for the others and the others cannot be substituted for Ramelteon.

Dan Lessler: That's correct.

Duane Thurman: Then the issue as to the application of dispense as written. If the scenario arises where this is a non-preferred drug that's on the preferred drug list, I hear you saying that dispense as written would apply for endorsing practitioners, but that for non-endorsers then how the drug is dispensed would defer back to the individual agencies benefit structure on how they would handle it.

Dan Lessler: That's correct. So is there any from the agencies.

Jeff Thompson: Well I think – this is Jeff Thompson. From the application, I mean there's – they are very differential medicines and the type of client that you would use the for, these two subclasses as you identified. And so we would be fine with that, it just – it does sort of mix and match a class with two different agency – two separate ways of making – having mechanisms and at least as we understand it in talking with the sleep specialist that will come talk to you today, two different types of individuals would find benefit from these subclasses. So it does [inaudible] but we could make it work.

Dan Lessler: Siri.

Siri Childs: I'm – this is Siri Childs from HRSA. I'm trying to think how a non-preferred drug, if it should happen to be non-preferred. Could those be on the preferred drug list and in our regular prior authorization program. The issue is the DAW. It's either in or it's out. I don't know how to do it both ways.

Dan Lessler: Well can you – what do you mean by it's either in or it's out? Can you clarify that?

Siri Childs: It's either in the drug class on the PDL or we handle it according to our regular prior authorization program.

Duane Thurman: Let's make – this is Duane again, let's make sure we understand what the committee is saying. The committee at this point is saying that dispense as written will apply because it is part of the preferred drug list, and that to the extent a non-endorser tries to get the drug then your [inaudible] will apply according to what your agency processes are. I just want to clarify that's what the committee is telling us right now, so.

Jeff Thompson: This is Jeff Thompson, yes we can make that work.

Jaymie Mai: This is Jaymie Mai. In the event that Ramelteon is non-preferred, the issue here is how do we develop criteria for the non-endorsing practitioner. Usually it's try and [inaudible] something. And so that's where we were having issue was trying to figure out how we would implement this if that's the only drug in the subclass.

Patti Varley: This is Patti Varley. And that's my confusion, if it's the only one then it's the only one. So doesn't it automatically get on the PDL if it's the only one?

Duane Thurman: This is Duane again. In this motion you've said that we have to have one of the non-Ramelteon drugs on the list. You did not say we had to have Ramelteon on the list. And so if our – in our cost analysis that will, is what determines what ends up on the list if you don't give us that direction. One of the things you could do is tell us that we must have Ramelteon on the list because there is no other drug in that subclass. But that's not what this motion does.

Dan Lessler: So if a non-endorsing prescriber wrote for Ramelteon, could you not require that, for example, that one from the other subclass of sedative hypnotics be tried prior to authorizing it under those circumstances? What would you...

Jeff Thompson: This is Jeff Thompson again. The reason why we're sort of [inaudible] on this. When we've talked with Dr. Pascualy who will be talking with you this afternoon. Is his opinion as a certified sleep specialist is that these type of drugs – the non-benzodiazepine receptor agonist work better on people that are naïve to sleep medicines. At least that was – and so tried and failed in his world is less of an issue versus somebody that's naïve and has special circumstance. The bottom line is Dan is if you take off the subclasses, make them all part of the preferred drug list, DAW endorsing

[inaudible] we can make it work. But when you put subclasses in there we were confused as to whether you were actually signaling us to make this drug preferred. Because it's the only drug in that subclass. That was the confusion that we had.

Duane Thurman: Dan, this is Duane again. One added thing. In terms of trying to put on a tried and failed, we find that hard to do because if it's not substitutable then a therapeutic interchange sounds – you know that's essentially what we would be doing if we tried and failed a non-Ramelteon class drug. So we're sort of...

Patti Varley: Right, because it can't be sub – the motion. This is Patti Varley again. When I read the motion as it stood it said Ramelteon could not be therapeutically interchanged. So that's where my misunderstanding was. If it was written, that was written because it couldn't get filled for – with anything else. So I'm confused.

Duane Thurman: One thing we've – let's back up. The first thing we've clarified is that Ramelteon can't be substituted for or against, either way. And so the question is, we now have a situation where we have one drug in a subclass that doesn't have a substitute and does not have an option for tried and failed. And we're looking for direction on how we should proceed. If you continue with what Dr. Lessler's first statement was then we're reading it as dispense as written will apply to prescriptions for Ramelteon for endorsing practitioners and that for non-endorsers whatever the standard agency treatment of those drugs is currently they will be subject to that.

Vyn Reese: This is Dr. Reese. I think that's what the committee intended. So, can we go back to the original motion? It was my motion originally. And so what you want us to say is Ramelteon cannot be substituted for other drugs in this class and benzodiazepine receptor agonists cannot be substituted for by Ramelteon. Is that basically what – you're basically going to say it both ways. And that's fine, I mean we can just add that little addendum to that sentence.

Duane Thurman: And we will defer to the committee. I've given Dan a rough badly handwritten template that I thought summarized that issue and if that's the way you want to come out we just would like to clarify it can't be substituted either way and that dispense as written will apply for endorsing practitioners.

Patti Varley: This is Patti Varley again though. What happens if a non-endorsing prescriber signs for Ramelteon? What's going to happen?

Duane Thurman: This is Duane, I can't speak for HRSA but I assume there would be some sort of limits or prior authorization required.

Man: Sorry Patti, is it with the current recommendation as it stands? The way we've interpreted your recommendation is that this drug would have – would be a preferred agent because we can't do – there is no alternatives. So it's preferred. And so DAW doesn't even come into play because it's preferred.

Patti Varley: That's why – Patti Varley again – that's why I was confused because I was confused by that point.

Duane Thurman: Siri did you want to comment on that please?

Siri Childs: Part of the – this is Siri Childs. Part of the difficulty is that we have an afternoon program to present to you and we want to tell you why we believe this drug is different from the other drugs in the sedative hypnotic class. And to be perfectly honest, I think that after you hear our presentation that you would see that it might be wise to remove it from the drug class and let us handle that the way we are proposing to handle it this afternoon.

Duane Thurman: Okay, I'm going to have to interrupt. This is Duane. I don't want to bring in the DUR issues into the decision as to the preferred drug list so. I mean I think you know what our question is and I think you should clarify this before we get into the whole discussion about – that we'll be having this afternoon.

Bob Bray: This is Bob Bray. I – and I appreciate that because I think – and see if there's any dissent among the committee. We specifically did not say that we felt that Ramelteon should be on the PDL. We did not state that in our information, in our conclusion after looking at the evidence. And so I'm happy with the clarification that's been made about the substitution both ways and I personally would not want to see a motion added that it should be on the PDL. So if, in order to make that clear we take that out of the subclass, since it is different and I'm – I think we all agree on that. Then I would be in favor of that rather than trying to make Ramelteon by default on the PDL.

Jeff Thompson: Just a clarification, this is Jeff Thompson. When you say on the – it is on the preferred drug list. What you're really saying if I might ask is its preferred status. In your motion what we were confused with is Ramelteon automatically preferred drug list – preferred drug on the list. That's how we interpreted your motion. Because [inaudible] the fact you made it a subclass.

Dan Lessler: Well – and I guess what I'm saying Jeff is I don't think that was our intent.

Jeff Thompson: That's what needs to be clarified.

Dan Lessler: Yea. I agree, that was not our intent. I mean what we're asked to do is comment on safety, effectiveness, and comparative safety and effectiveness and I think there was a recognition that this is – has a different mechanism of action so it, I think we all agree independent of the presentation that it's a different subclass of sedative hypnotic and there was no intent to sort of say this must be preferred. It was only to say we've looked at the evidence and this is a safe and effective medicine. Jeff?

Jeff Graham: This is Jeff Graham. I don't know it's not like I heard Bob say this is my interpretation of what he said. We should remove this from this class so that it doesn't cause so much confusion.

Dan Lessler: I was going to ask Bob if that's what.

Bob Bray: Correct.

Patti Varley: This is Patti Varley. If you look up there it says they're two subclasses. I mean we've already – that's what we said in the thing. So we've – I guess we've said they're different.

Duane Thurman: Excuse, this is Duane, let me – I'm sorry to make this so confusing. The real issue here is that if it is part of the class then this whole legal stuff starts to apply. Whether it's a subclass or not. If it's not part of the class, and I believe you did this with one of the anti-emetic drugs. If you say it's not part – see we have this situation where it can be on the preferred drug list but non-preferred. And that's where we have a problem if that's how it ends up. So the cleanest thing for us would be for you to say it acts differently, it's not a part of this class, and we treat that as we would any other drug that's not a part of the preferred drug list. And I'm sorry that's so complicated but that's really what we're getting to.

Vyn Reese: This is Dr. Reese. It is a sedative hypnotic, but it's in a different class than the benzodiazepine receptors. So and that's basically what we said. I don't know how else to say that. It's a sedative hypnotic, I mean it is. That's its – but it's not the same as the others and we said that in the previous motion.

Alvin Goo: This is Alvin Goo. Would it be one possible option is to – since we agreed that there's really no difference and that the effectiveness of these are sort of small that if we just remove the class and call it the newer sedative hypnotics and suggest – and then state that at least one benzo receptor agonist must be on the PDL.

Duane Thurman: See I guess my only analogy is that in the anti-emetic class there was a drug where you said this is safe and effective but this is not a part of the PDL. And that would be recognizing that – that’s the problem with calling it the newer sedative hypnotics. I mean that’s a very broad categorization. You can read it as saying this is one or isn’t but it’s a legal problem that our statute brings up.

Dan Lessler: So Vyn’s point here. This is a sedative hypnotic so should we – do we go back and say what we want to, what we’re going to consider and comment on are the benzodiazepine receptor agonists, sedative hypnotics and then just. What about if I just delete Ramelteon altogether? Is that what you’re saying? Not even consider it?

Duane Thurman: I’m thinking. Go ahead Jeff.

Jeff: Basically let’s just start with the interpretation from the agencies is what we interpret this recommendation is Ramelteon is part of the class and automatically has preferred status. We cannot look at it and its efficacy and make it non-preferred based on cost. That is how we interpret it. We need you to redo that language because that’s how we basically feel you gave us instructions. There are three options that I see on the table.

You either just say it stands and Ramelteon must be preferred. Or, you want we can either remove it from this class and then all agencies will work together to try and come up with a way of making it work. Or, you can say that it can have either preferred or non preferred status as your original sort of look at this again. It just – it plays with all the rest of DAW and it, those are the three options.

Dan Lessler: So I think the cleanest way – I mean looking at all the complexities here. I think the cleanest way might be if looking at the motion is to revise the motion where it says after considering the safety and efficacy and special populations for the treatment of insomnia, I move that the benzodiazepine receptor agonists and then parentheses, and that’s it. And just make that the motion in this case. Does that make sense to?

Carol Cordy: Can I ask a question? Of Duane actually, this is Carol Cordy. You said in your last statement that then Ramelteon would not be on the PDL. Did you mean that?

Duane Thurman: Yes, it would not be part of the preferred drug list.

Carol Cordy: Okay, not the preferred drugs on the preferred drug, just not part of the list at all.

Duane Thurman: Right.

Man: And that would be my interpretation of what Dan just said.

Dan Lessler: Right. So actually I think in the spirit of moving us along, I actually think I'm going to.

Vyn Reese: This is Dr. Reese. I think they just removed at least one benzodiazepine receptor agonist must be preferred. I think we need to leave that on, because that's what we decided. And I think I can redo the motion just that way just leave Ramelteon off since it's a different class and it's quite confusing. Do you want me to just go ahead and recraft – remake the motion and we'll second it and just get done with it.

Dan Lessler: That would be great.

Jason Iltz: This is Jason. Before you do that let me just ask the question though because I think for clarity's sake maybe we should handle it like we did for the anti-emetics and at least speak to it from the standpoint of saying Ramelteon, due to its differing mechanism action should not be considered part of the benzodiazepine receptor agonist class. Because then it leaves it open for while – it was part of the review but there was no speak to it. And so I think it's appropriate to at least say that for clarity's sake.

Dan Lessler: That's a good point.

Patti Varley: This is Patti Varley, I agree with you totally because the way that he review was was for sedative hypnotics which it is one of, and it was reviewed. So I feel more comfortable with that.

Duane Thurman: That would meet our needs.

Dan Lessler: Okay, so see if they're.

Man: Can you – you just added that to the end and then you took it off again.

Dan Lessler: So why don't you go ahead then.

Vyn Reese: After considering the evidence of safety, efficacy, and special populations for the treatment of insomnia, I move that the benzodiazepine receptor agonists (Eszopiclone, Zaleplon, Zolpidem, and long acting Zolpidem) are safe and efficacious. Ramelteon, due to its differing mechanism of action, should not be part of the benzodiazepine receptor agonist class. The benzodiazepine receptor agonists can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of insomnia. At least one benzodiazepine receptor agonist must be preferred.

Dan Lessler: Okay, is there a second?

Patti Varley: I'll second.

Dan Lessler: All those in favor say "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, thanks.

Duane Thurman: Thank you for your patience on that issue.

Jeff Graham: Dan, this is Jeff Graham, I think Marian is on the line there.

Dan Lessler: Yea, Marian?

Jeff Graham: Did she hang up?

[Background discussion about caller]

Dan Lessler: Hi Marian?

Marian McDonagh: Yes, hello.

Dan Lessler: Hi, it's Dan Lessler. Thanks for joining us. Your first, the title slide of your PowerPoint presentation is before us and we're ready to go so you can just take it away.

Marian McDonagh: Alright, thank you. So this morning I will tell you about our review of the disease modifying drugs for MS. And we just completed that in July. If you move to the second slide those are our key questions which include effectiveness and safety for patients with MS as well as patients with clinically isolated syndrome. And of course looking at any evidence for differentiation by subgroups.

Looking to the next slide, we did also break down the data by the categorization the type or state of MS with relapsing, remitting, secondary progressive, primary progressive, and progressive relapsing. And for progressive relapsing there is no evidence for any of the drugs so it will be the first three that we'll be discussing evidence for. And then of course evidence for adult patients with CIS.

On the next slide is the list of drugs that were included in this review. So all three interferons,  $\beta$  1a as well as  $\beta$  1b and then Glatiramer,

Mitoxantrone, and Natalizumab. On the next slide the effectiveness outcomes

Marian McDonagh: Are disability which is measured as progression. So either the percent of patients who have progressed in a period of time or looking at changes on a disability scale such as the EDSS. And then the other major outcome that is typically measured is relapse. So those are the two top outcomes we had identified to begin with. We were also interested in looking at quality of life, functional outcomes, and persistence – the ability of the patient to continue taking the prescribed medication over time. We did not find a lot of evidence on those three types of outcomes. For clinically isolated syndrome we have the same outcomes except that really the primary outcome is the proportion of patients who progressed to a diagnosis of MS.

On the following slide we looked at the outcomes that we were looking for for safety and some of those are listed because they are known to be a problem with particular drugs. Hepatotoxicity with the interferons for example, PML with [inaudible] etc. And then we also decided that it was important to look at the impacts of neutralizing antibodies on the efficacy of the interferon  $\beta$  product.

On the next slide we have our inclusion criteria for study design, and the only thing I want to point out here is that for effectiveness we added observational studies that were – included at least 100 patients and were at least a year in duration. The trials here are primarily all two years in duration so we felt that requiring that any observational study be at least a year long to be able to add some new information was probably very reasonable.

Now on the next slide our literature search was finalized in September of 2006. We did receive dossiers from most companies, the only drug for which we did not receive an information dossier was for Glatiramer. And then of course we were – got additional studies suggested to us from peer review and public comment in April.

On the next slide we just itemized what we found, 55 trials. A lot of those are placebo controlled trials, very few head to head trials. A few systematic reviews and then quite a large range of different types and quality of observational studies as well were found.

On the next slide I want to summarize the general effectiveness of the interferons. And most of the data in this report actually does refer to the patients with RRMS. So I'm going to spend some more time on that than on the others. So here we have just the ranges of effectiveness so for progression at two years, [inaudible] to analyze relapse rate over a two

year period. And you can see that there is a benefit of these products over placebo. It's not typically very large, but there is a benefit. And the ranges in head to head trials are a little bit lower, a little bit different than the placebo controlled trials. So probably the patients enrolled were slightly different at the outset.

Now moving on to examine the comparative evidence. Looking at Betaseron on the next slide compared to Avonex in patients with RRMS. Starting with relapse outcomes, we found there is only two trials comparing these products and we found based on these two, and again they're not large trials, 278 patients total between the two of them that Betaseron had a benefit over Avonex for the proportion of patients who were relapse free at two years with a resulting relative risk of 1.51 and an NNT of 6. However, then we did find a cohort study and it also found no significant differences here. It had a different finding that we did in that there was no difference between the drugs for relapse outcomes. We decided that we should do an adjusted indirect meta-analysis using the placebo controlled trials using the method of Bucher(?) et al. And here is again only three trials so it is limited evidence, and this analysis found no difference between the products. We also did an exploratory Bayesian meta-analysis using the placebo controlled trials as the prior condition and then the head to head trials as the main analysis. And here the finding is very similar to our own standard meta-analysis with a relative risk of 1.48 favoring Betaseron.

On the next slide, moving on to the comparison of Betaseron and Avonex in progression outcomes, here looking at the proportion of patients who had progressed at two years, their relative risk was 0.44. Again favoring Betaseron with an NNT of 6. Now here the cohort study that we just talked about which was about 4,000 patients. They found the actual opposite of what we had just found in that they found Avonex to be superior based on the proportion of patients who were progression free. So a slightly different – a different outcome. We are measuring the same outcome. With 83% versus 76% and an NNT of 14. Again our adjusted indirect meta-analysis found no differences between the drugs and our Bayesian analysis found a result very similar to our classical analysis in that the relative risk was .48 in the Bayesian and .44 in the classical. And we found no differences in the adverse event profiles between the drugs based on the head to head trials.

Looking at Rebif versus Avonex, starting with relapse outcomes. Again only two trials, slightly larger, 767 patients included overall. Here we found a benefit of Rebif over Avonex with a proportion of relapse free being 48% versus 56% in the evidence trial, and 20% versus 57% in the much smaller Etemadifar trial. And we did not pool these because the – there is a lot of statistical heterogeneity. And while both trials individually

found a statistically significant difference based on these proportions, pooling them, because of the variability the finding actually results in a non-significant difference, which is nonsensical. The cohort data we found a study, again that same study with 4,754 patients. Differences were not found between the products. Adjusted indirect meta-analysis did not find a difference and Bayesian meta-analysis found a difference that was similar to our original difference again favoring Rebif over Avonex for the relapse outcomes.

For progression on the next slide, the progression outcomes, trial data did not find any differences. Here we have one study that was two years long and one that was only 16 months long. Primarily it is considered that you need to have a trial of at least two years to identify progression, so the trial that was 16 months may not have found difference because it was too short. It was not designed to identify progression, but based on the 16 month data and the two year data from the other trial there were no differences. The cohort data – Avonex was superior to Rebif in the proportion of patients who were progression free and the NNT resulting from that is seven. And both our adjust indirect and Bayesian meta-analysis found no differences. So all of our analyses found no differences between the products for progression and again that may be based on including that 16 month data whereas the cohort study found a significant difference favoring Avonex.

On the following slide, looking at Betaseron compared to Rebif, we did not pool the two studies involved because they had significant - what we consider clinically significant differences in their patient populations and they also had differences in their dosing for Rebif so we didn't pool them. Based on these two trials the individual results the evidence is not able to identify any differences between Betaseron or Rebif in patients with RRMS.

Now considering the interferon neutralizing antibodies, there are differences between the products in terms of the timing of the appearance of antibodies and also the rate, the number of – the proportion of patients who become antibody positive. So Betaseron can be – the antibodies can occur as early as three months, whereas Rebif and Avonex occur later, usually after nine months of treatment. And the Betaseron also has the highest proportion of patients 30 to 40%. For Rebif the range is quite broad 12 to 46, and Avonex does clearly have the lowest rate of antibody conversion. However, 48 to 50% of patients who are antibody positive will become antibody negative over time and usually this occurs within the first two years of treatment. After two years it's very – there's only a few patients who become antibody positive that late into treatment.

On the next slide, looking at the correlation of clinical outcomes to the antibody status. Rebif and Betaseron there is some evidence that indicates that consistent positive neutralizing antibody status with high titer. So both of those conditions can reduce the benefit that was seen in relapse rate. So reducing the improvement in relapse rate by  $\frac{1}{2}$  to  $\frac{2}{3}$  after two years of treatment. There's not enough evidence for making this correlation with Avonex at this time. And differences were not seen for any of the products in the shorter follow up period, so less than two years in clinical results. And there is actually not – inadequate evidence at this point in time to make any comments on the impact of neutralizing antibodies on disease progression.

Looking at Glatiramer in RRMS, there are no head to head trials. There are placebo controlled trials, three. Again, not terribly large 541 patients overall and I think that the slide that I have given you has an error. It should say that for relapse outcomes Glatiramer was superior to placebo for the difference in mean relapse rate but not for the proportion relapse free. As you can see the p value is .086. For progression outcomes, based on changes in the disability symptoms scale [inaudible] the EDSS at two years. Again Glatiramer was superior to placebo.

On the next slide, there are two – the previous slide shows you the results of our own meta-analysis. There are two other meta-analyses that have been published. And they found differing results to each other. The Cochrane meta-analysis did not find a benefit with Glatiramer. They were looking at disease progression at two years and found a non-significant difference. The risk of relapse within one year of randomization, again no difference. A different meta-analysis that was based on using individual patient data meta-analysis did however find differences looking at slightly different ways of measuring those outcomes. The mean difference in the annualized relapse rate was .31. On the previous slide the difference that we found in mean relapse rate was .64. On trial relapses in this meta-analysis were a relative risk of .64, and that was statistically significant. And they also found a difference in the time to first relapse favoring Glatiramer. Some variability in the findings there depending on how you slice it.

Now looking at the next slide, looking at the evidence for Natalizumab in RRMS. Again only placebo controlled trials, two of them. One was Natalizumab versus placebo and one was Natalizumab plus interferon versus placebo. And both of those trials did find Natalizumab to be superior to the placebo group for both relapse and progression outcomes.

On the next slide, looking at Mitoxantrone, there we found only one small placebo controlled trial and this trial did find Mitoxantrone to be superior based on both disease progression rates and relapse free – the proportion

of patients relapse free. And then I've included some information on the kinds of adverse events that were found with the Mitoxantrone group in this trial. And we'll get back to adverse events more in a comparative way in just a minute.

Now moving on to the patient population with secondary progressive MS, we found five placebo controlled trials of the interferons. And they vary a lot in their findings. Our conclusion is that the evidence on time to progression reported in these four trials for Rebif and Betaseron looking across those appear to favor Betaseron. But again, you can't make direct comparisons across these trials because of differences in either dosing or patient populations. In one of the trials, the trial of Avonex used a different outcome measure instead of using the EDSS they used a newer multiple sclerosis functional composite score which is thought to be better, more precise than EDSS and using this measure they did find a difference that Avonex was superior to placebo in [inaudible].

Several of the outcome measures for Rebif and Betaseron were not statistically significant. It was really time to progression that was the – area where a difference was seen.

So next we have – we're moving on to the patient population with primary progressive MS, and here we found information on Avonex and significant differences in time to sustained progression was not found compared to placebo. And again it's only one small trial. In this trial they did try a higher dose, 60 µg once a week and that does was not more effective and also led to a much higher withdrawal rate due to adverse events. And we found no studies of the other drugs for PPMS.

We did find a few studies that included mixed populations so patients who had either RRMS or SPMS. Typically the patients in these trials who had RRMS were probably more ill and starting to transition to SPMS. So it's probably why the included these two populations together. We found three trials of Natalizumab, four of Mitoxantrone, and one study of Betaseron in these mixed populations. And all of these found the product – the drugs so Natalizumab, Mitoxantrone, and Betaseron to be superior. The study of Betaseron was a quality of life study, and it actually compared Betaseron to historical controls. And while they did find that Betaseron improved quality of life they – in further analysis they did find that that was true only if the EDSS for a baseline was less than three. So the patients who were more ill it didn't make a significant difference, the addition of the drug. For Glatiramer we found one mixed population study that was patients with secondary progressive and primary progressive MS and Glatiramer was found to be superior to placebo in disease progression outcomes for these populations.

On the next slide a quick summary of where we did not find evidence. We found no studies of Glatiramer, Natalizumab, or Mitoxantrone in patients with secondary progressive MS. We found no studies of Rebif, Betaseron, Natalizumab, or Mitoxantrone for primary progressive MS.

So for patients with clinically isolated syndrome, each of the  $\beta$  interferon products has been shown in a single trial to be superior to placebo in preventing conversion at two to three years. So for Avonex it was a three year trial with a relative risk of .56. And the relative risks were quite similar across the three drugs. For Rebif at two years .65, in Betaseron .50 at two years. And we did not find evidence for any of the other drugs in this patient population.

Now looking at adverse events, the next slide shows you the rates of adverse – of the most common adverse events with the interferons. On the next slide after this one I'll show you the relative rankings but I thought it was important to point out – just show you the evidence for what the incidence is because it's quite high for most of these adverse events of injection site reactions as high as 60%. These are pooled rates across all trials. And so for Betaseron 60.5% is the pooled rate whereas for Avonex injection site reactions the pooled rate is 10%. Flu-like syndrome again, as many as half the patients will experience flu-like symptoms.

So I'll move on to the next slide then and show you the relative rankings. It comes directly from that previous table. Where injection site reactions are most common with Betaseron and least common with Avonex. Flu-like syndrome however is highest with Avonex and very similar between Betaseron and Rebif etc. And if you move on down the all cause and – all cause withdrawal and withdrawals due to adverse events are most common with Betaseron and least common with Avonex.

Now on the next slide, looking at some of the more serious long term adverse events. For thyroid autoimmunity there were no direct comparisons but based on placebo controlled trials two of the products, Avonex and Betaseron do have – we found no significant difference. The relative risks are .86 and .63 but they are not statistically significant.

Moving on to the next slide, looking at liver toxicity. So we had said earlier on that one of the adverse events that we were asked to look for specifically was liver toxicity with the interferon. There has been one case of liver failure reported with Avonex. There was a case [inaudible] that was reported with Rebif but that was considered to be questionable as to whether it was related to Rebif because of the patient also taking another hepatotoxic drug. All of the interferons have a similar risk of ALT elevations and ALT elevations are the most commonly seen. There is a correlation between higher dose and more frequent administration, and are

also patient age of greater than or equal to 40 with elevations in ALT. They generally occur early and resolve while on treatment and very few patients discontinue – have to discontinue treatment due to ALT elevations.

On the next slide will – looking at the evidence for the differences in depression or the relationship of depression to the  $\beta$  interferons. We found a meta-analysis of six placebo controlled trials and 17 unpublished non-comparative studies of the interferon  $\beta$  1a, so Rebif and Avonex. We – looking at the relationship between these drugs and depression, the incidence of depression. So with Avonex the rate was 18% and with Rebif it ranged from 5 to 12%. Both of those were significant compared to placebo at six months but at two years it was not statistically significant compared to placebo. Now our own adjusting direct meta-analysis of four placebo controlled trials looked at Betaseron versus Rebif and here we found no difference. Betaseron versus Avonex no statistically significant difference and Rebif versus Avonex we were also unable to find a difference between the products based on that adjusted indirect meta-analysis.

Now looking at Glatiramer on the next slide, adverse events. This is based on only three trials, but we do again find injection site reactions to be common – a common problem. And the relative risks [inaudible] significantly higher than in the placebo group. Post injection reactions are seen with Glatiramer and that includes flushing, sweating, palpitations, and anxiety. And those do occur more commonly in Glatiramer quite a lot. Relative risk of 3.4. However, they do resolve over time with continued treatment in most patients. And withdrawals due to adverse events again were higher with the Glatiramer group although in this case the p was .08, so not statistically significant.

On the next slide, looking at trying to look across  $\beta$  interferons versus Glatiramer for adverse events. You can see that for flu-like syndrome it's not reported for Glatiramer in the trials and very low rate in non-RCTs. Injection site reactions, however, we found in the trials the rate – a pooled rate of 51%, so very similar between Rebif and Betaseron and Glatiramer for that injection site reaction. Fever not reported with Glatiramer and withdrawal due to adverse events was low, lower with Glatiramer than with some of the other two, the Rebif and Betaseron in particular and similar to Avonex. At least in the trials. And the non-trial data does tend to be a lot more variable. Those are often – we call them non-trials because they are often open label either follow up studies or just open label observational studies that are not – don't have a comparison arm.

On the next slide looking at again, interferons versus Glatiramer for depression, there's a small study only 163 studied, it's an observational

study. That found a rate of depression 34% with the interferons and that would be any interferon in this case versus 25% with Glatiramer, and while the rate is higher with the interferons, the study is so small it really didn't – there was a – it did not find a statistically significant difference. A larger study would need to be done to [inaudible] that if that difference in rate is significant.

Now looking at cancer, the incidence of cancer we found one cohort study. Just again not terribly large, 1,300 patients. This study found some interesting findings. The incidence of cancer in women with MS was lower than in healthy women. So comparisons to the healthy women in that cohort population. The  $\beta$  interferons were associated with lower, but non-significant risk of breast cancer, but a increase in the risk of other types of cancer. While Glatiramer was associated with increased but not statistically significant increase in risk of cancers in women. So again, very interesting findings but not significant in most – for most of those outcomes and would need to be examined more closely in a larger study.

Moving on to the Natalizumab adverse events. Adverse events in the trials did not find significant differences between placebo and Natalizumab or in – I do say controlled there because one of the trials had interferon in both groups. Looking at the incidence of progressive multifocal leukoencephalopathy three cases occurred in trials. So two patients who were being treated for MS in the SENTINEL trial and one who was being treated in a [inaudible] Crohn's disease trial with Natalizumab. Since then an observational study of over 3,000 patients also examines incidence of PML and did not find any additional cases. So based on the combined evidence it is estimated that the incidence is one per 1,000 treated patients and that the use of the immunomodulators or immunosuppressants may be a factor in PML development. Again with the interferon being used in the SENTINEL trial where those two cases were found for the patients with MS.

For Mitoxantrone adverse events and long term safety we looked at the incidence of acute leukemia and the incidence was 0.15%, two cases at a dose of  $70\text{mg}/\text{m}^2$  then in an additional study only 242 patients however, did not report any additional cases. So while we have an incidence rate it is really not based on a lot of evidence. 1,300 patients again. Cardiotoxicity, looking at fatal CHF. It was – the incidence rate is 0.15 as well. And a confidence interval of .02 to .52, so not statistically significant. And it could not be definitively linked to Mitoxantrone with the comment of the authors in this case because many of the patients it was unclear if there were other reasons for developing fatal congestive heart failure. And then for asymptomatic left ventricular ejection fraction less than 50% 2.18% was the rate and [inaudible] for accumulative dose less than  $100\text{ mg}/\text{m}^2$  versus greater than  $100\text{ mg}/\text{m}^2$ , the incidence was

1.8% versus 5%. So again, there is a difference in the rate, but it was not statistically significant and a larger study might need to be done to examine whether there is a significant difference there.

Finally, looking at evidence in subgroups, we did not find very much and but I did want to tell you about the little bit of evidence that we did find. For African American patients there was a subgroup analysis of the evidence trial, which was a comparison of Avonex and Rebif in patients with RRMS. This subgroup was very small, only 36 patients. They found based on this that there were more exacerbations in the African American patients than in the white patients. But they were unable to make any further comparisons between the two drug products because the numbers of patients were so small in the two groups.

Next we found a couple of studies looking at the impact of interferons on pregnancy in patients with MS and we found one was a study of non-live birth in women with MS and those who had been exposed to interferon compared to the health cohort – so not compared to a cohort of untreated patients with MS, the observation was 6.94, and that was statistically significant. No interferon exposure compared to the healthy cohort however also showed an increased [inaudible] ratio 2.91, however this was not statistically significant. Then we also found an individual patient data meta-analysis looking at exposure to interferons during trials. And this included 69 pregnancies, pregnancy loss was increased in those who were exposed in-utero so during pregnancy rather than immediately before conception to the  $\beta$  interferon 1a product. Either of the two products, 29% versus 0% with placebo or prior exposure. So neither of these are very large and we don't feel confident that you can make conclusions based on the evidence either in African American patients or on pregnancies based on the subgroups [inaudible] information. But we do think it's important to point out for looking at future research for updates of this report.

And that concludes the summary of the report and I'd be happy to take any questions.

Dan Lessler: Good, Marian thank you. And actually we'll open it up here to the P&T committee members for questions for Marian. So Marian it does not look like there are any questions at this point. We're going to take stakeholder input and I was wondering if you could stay on the line for another 20 minutes or so?

Marian McDonagh: Sure, that'd be fine.

Dan Lessler: That'd be okay? Okay. So folks who wanted to provide comment should have signed up on one of the sheets here and again ask that people limit

their comments to three minutes and I will be pretty strict about that. As well...

Tori Magee:

... program. Tysabri was re-approved in the United States in 2006 under a risk map called the touch prescribing program, which monitors safety and restricts distribution of and access to Tysabri. Under the touch prescribing program, only prescribers, infusion centers, and pharmacies associated with infusion centers that are registered and approved with the touch program are able to prescribe, distribute, or infuse this product. Under the guidelines of this program, prescriber eligibility or type is not limited to neurology or strictly to physicians. Eligible prescribers under this FDA approved risk map program include other providers such as physician assistants, ARNPs, and DPs. Tysabri can be prescribed by PAs and ARNPs under Medicare and having a policy in agreement is necessary for dual eligibles.

Now, absent the complete removal of the prior authorization process, we respectfully request that the committee consider changing the current language in the guidelines or criteria for the use of Tysabri to include prescribers who treat MS other than just neurologists. As you are aware, there are affiliated prescribers, such as nurse practitioners and physician assistants that specialize in the treatment of multiple sclerosis within the state of Washington. The language in the DSHS Tysabri [inaudible] form states that Tysabri must be prescribed by a neurologist. We would like you to reconsider the wording of this language in your form to read "must be prescribed by a neurologist or ARNP or physician assistant specializing in neurology and with the prescriptive authority in the state of practice." Adoption of such language would be in accordance with the FDA mandated risk map program and approved labeling for the prescribing of Tysabri in the United States, and would not limit access to this therapeutic advance to Medicaid patients. Thank you.

Dan Lessler:

Thank you, any questions? Thank you. Next is Dr. Sharon Cahoon-Metzger.

Sharon Cahoon-Metzger:

Hi, I'm Sharon Cahoon-Metzger, PhD, I'm a medical science liaison with Biogen Idec. And so I'm medical support for both Avonex and Tysabri. First, the position of Biogen Idec is that we feel that all of the MS therapies, the disease modifying agents and Tysabri ought to be available, free, and accessible for physicians to make appropriate judgment calls for appropriate patients. MS appears to be a heterogeneous disease and there isn't a uniform response to any of the agents. As you can see, there's a lot of conflicting data. So it is our companies position that – I mean it would be based on a clinical judgment call in terms of accessibility. But given that, we want to make sure that you have relevant information about

Avonex, which is the interferon market leader. And the phase three – the pivotal phase three study for Avonex was the only phase three study that used progression in disability as the primary end point, and it's pretty well accepted that prevention or slowing down of disability progression ought to be our primary objective in treating MS.

That class one evidence demonstrated a 37% reduction relative to placebo in terms of disability progression that was sustained over six months, not just three months. Moreover, Avonex is the only interferon – is the only MS therapy that has an indication for disability – decrease in disability, decrease in relapse rate, and an indication for CIS. It's the only one that has all three of those. The role of neutralizing antibodies is not clear, but it's pretty well understood that the clinical impact of neutralizing antibodies is not going to occur within the first two to three years of the patient being on the drug. The incidence of neutralizing antibodies with Avonex is the lowest of all of the interferon agents and we know again, like was just reviewed for you, that discontinuations due to adverse events and overall discontinuations are lowest with Avonex and there are two large studies that were able to demonstrate that the adherence to the drug – misdoses there's a significantly fewer misdoses on Avonex.

Very quickly with Tysabri as you know it was reintroduced to the market a year ago. We now have 14,000 patients on Tysabri globally. It has a 67% reduction of relapse rate, 42% reduction of sustained disability progression, and we have had no confirmed cases of PML or other serious opportunistic infections to date. We continue to do at least quarterly deep dives – sort of safety evaluations that were using the touch program for getting that information both from the U.S. and globally and continue to report at scientific meetings and to physicians directly that safety information. Thank you.

Dan Lessler:

Thank you. Any questions? No, thank you. Next is Dr. Lily Jung.

Lily Jung:

Good morning, I'm Lily Jung and I'm a MS neurologist and chief of neurology at Swedish Medical Center in Seattle. I also sit on the physician advisory committee for central and peripheral nervous system diseases for the Food and Drug Administration and I'm the advocacy editor for the American Academy of Neurology website. I work very closely with the national Multiple Sclerosis Society and the MS Association of King County. I'm here to advocate for full and equal access of the six FDA approved therapies for multiple sclerosis. Studies have shown that therapies with one of the four first line therapies is warranted in patients as soon as a diagnosis of MS is made or in clinically isolated syndrome.

These drugs have been shown to be effective in one, reducing the number of attacks in MS, two, the number of MRI lesions in MS, and three,

reducing disability. Although the efficacy of these drugs are similar, patient tolerability and clinical response is extremely variable because of the disease. Those patients with more aggressive disease are treated with either Mitoxantrone or Tysabri and the only treatment currently FDA approved for progressive disease is Mitoxantrone. Natalizumab has been shown to be clearly efficacious in patients with more aggressive disease. Early treatment has been shown to reduce the irreversible damage in the central nervous system, even when patients have been completely asymptomatic.

I would like to share with this committee the American Academy of Neurology's evidence based guideline on disease modifying therapies in MS that was published in 2001. This showed that interferon  $\beta$  has been shown to be effective in patients with remitting, relapsing MS or clinically isolated syndrome. Glatiramer has been shown to be effective in remitting, relapsing MS, and Mitoxantrone has been shown to be probably effective in remitting, relapsing MS. It is anticipated that with the current evidence available on Natalizumab it will also get a type A recommendation from the academy when it completes its guideline revisions in 2009. I would also like to point out that the American Academy of Neurology physician paper on neutralizing antibodies that was published this spring showed that there was no clear evidence of significance of neutralizing antibodies on clinical course either positively or negatively so we just don't know.

I would like to thank you for the opportunity to advocate on behalf of our MS patients. I believe that the guidelines from the academy and the consensus statement from the national MS society are very strong evidence based guidelines for keeping – arguments for keeping all six of the currently FDA approved drugs accessible to all of our patients with MS. Ultimately it will be more cost effective to have access to these drugs than to incur the medical costs of hospitalizing these patients for a tax and for taking care of these patients when they become disabled. We'll be able to keep our patients healthier and they will be able to remain in the workforce for a longer period of time which ultimately benefit our society more than the alternative. Thank you.

Dan Lessler: Thank you. Are there any questions or comments for Dr. Jung? No, thank you. Next is Ruth Cashell.

Ruth Cashell: Good morning, I'm Ruth Cashell and I'm here with the National MS Society. The mission of the National MS Society is to end the devastating effects of MS. MS is the most common disabling disease of young people in the United States with 10,000 new cases each year. Over 9,500 people in Washington state are diagnosed with MS. Although there is no cure, there is clear evidence that the comprehensive treatment of patients, including the early use of immuno-modulating agents – sorry about that,

I'm not used to medical terms – offer the best chance for control of the disease and prevention of longer term disability. The disease management consensus statement, published by the medical advisory board of the National MS Society clearly states that all of these FDA approved agents, Avonex, Betaseron, Copaxone, Rebif, Novantrone, and Tysabri, should be included in formularies and covered by third party payers so that physicians and patients can determine the most appropriate agent on an individual basis. And failure to do so is unethical and discriminatory.

The National MS Society takes a strong position that both physicians and patient should have equal access to all of the currently available agents for MS. We view the selection and availability of only one or two of the agents for coverage or financial penalty to a patient for not being treated initially with the highest tiered medication approved by his or her health plan as the first barrier to equal access for patient and physicians. Therefore, the executive committee of the medical advisory board of the National MS Society has adopted the following recommendations. The society recognizes that the factors that enter into a decision to treat are complex and best analyzed by the individual patient's neurologist.

The medical advisory board does not feel that there a is clear evidence that any one drug is appropriate for every patient with multiple sclerosis. All of these FDA approved agents should be included in formularies and covered by third party payers so that physicians and patients can determine the most appropriate agent on an individual basis.

Movement from one disease modifying medication to another should occur only for medically appropriate reasons. Although we are all concerned about the costs of healthcare, saving should not be the expense of best care practices. Without open and equal access to all of the MS therapies, our patients will not have access to the best quality of care. When people with MS are not able to access treatment, they become more disabled and eventually may be unable to work leading to a further drain on Medicaid and increasing the cost of overall healthcare. Thank you for your attention and cooperation in this – in addressing the needs of people with MS.

Dan Lessler:

Thank you. Any questions or comments? Okay, next is Dr. Ines Ibrahim.

Ines Ibrahim:

Good morning, I am Ines Ibrahim, M.D., I'm the medical scientific liaison for the southwest region at Bayer Healthcare pharmaceuticals. And today I would like to share with you that Betaseron or interferon  $\beta$  1b is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in home advocacy have been demonstrated include patients who have experienced a first clinical [inaudible] and have MRI features consistent

with multiple sclerosis. The new indication is based on the results from the benefit trial which stands for Betaseron [inaudible] emerging multiple sclerosis for initial treatment. The study of patients with a first clinical [inaudible] event and MRI features suggestive of MS. Betaseron is the only high dose, high frequency interferon  $\beta$  FDA approved for use in the early stages of MS.

In benefit, Betaseron significantly delayed progression from the first single clinical [inaudible] event to the time when there was evidence of clinically definite multiple sclerosis. [inaudible] regression [inaudible] of 50% reduction in risk of regression to [inaudible] MS. The three year integrated analysis of data from the benefit trial which is an [inaudible] open label extension which published last week in the Lancet, confirmed a sustained affect of early Betaseron treatment in reducing the risk of regression to [inaudible] MS. 51% of patients in the delayed treatment group with [inaudible] MS versus 37% of patients in the immediate group. Furthermore, immediate treatment with Betaseron resulted in a 40% reduction in the risk of sustained disability progression measured by EDSS as compared to delayed treatment. Betaseron is the only drug [inaudible] to delay disability when used at the earliest stage of MS.

First [inaudible] event of MS also referred to as clinically isolated syndrome, or CIS. To date, Betaseron has the longest evaluation period of clinical efficacy of any interferon  $\beta$  in multiple sclerosis. A current [inaudible] with using interferon  $\beta$  treatment for multiple sclerosis is the emergence of neutralizing antibodies, or NABs which are theorized to interfere with or affect the clinical efficacy of interferon  $\beta$ . However, recent data presented in benefit demonstrate that NAB presence is transient. In benefit, positive neutralizing antibodies were detected at least once in 30% of patients, yet 23% of these patients later became NAB negative. In summary, benefit demonstrate that NAB associated with the use of Betaseron often transient and had no significant impact on clinical efficacy. Thank you very much for your time.

Dan Lessler: Thank you. Any questions? No, thanks. And finally, Ms. Laurie-Jane Babb.

Laurie-Jane Babb: My name is Laurie Babb and I'm a medical science liaison for EMD Serono. I'm here today to speak on behalf of the inclusion of Rebif on the Washington state formulary. In 2002 the American Academy of Neurology published the article Disease Modifying Therapies in MS. The article was a review of the published data for all disease modifying drugs with an emphasis on each of the drugs, pivotal trials, and class one evidence. One of the opening remarks of the review states the most important therapeutic aim of any disease modifying treatment in MS is to prevent or postpone long term disability. The article defined the three key

efficacy parameters as being reduction in relapse, delaying progression of disability, and reduction in the number of active lesions as seen on an MRI. When looking at these endpoints, each one of the drugs pivotal trials, only Rebif had statistically significant affect on all three efficacy parameters.

While Rebif was approved outside the U.S. in 1998, it was not allowed to enter the U.S. marketplace because Avonex held the orphan drug status which protected it from competition. Thus to gain entrance into the U.S. marketplace, Serono had to prove clinical superiority to overturn the drug act of Avonex and to obtain its FDA approval. In order to show clinical superiority, Serono undertook the evidence trial. This is the only published class one head to head trial of disease modifying drugs. Based on the results of the evidence trial, Rebif was allowed to overturn the orphan drug protection act and Rebif entered the marketplace in '02. It was the first time in over the 20 year history of the orphan drug act that the act was actually overturned based on clinical superiority.

The primary endpoints of that evidence trial where Rebif was statistically significant were the proportion of relapse, patients relapse free at 48 weeks, and reduction in the active lesions also at 48 weeks. Also in the evidence trial, the side effects, severe adverse events, and drug discontinuations were all comparable between Rebif and Avonex.

Next I'd like to highlight the information regarding Rebif and Betaseron as shown in the DERP report. In an effort to compare the efficacy of Rebif and Betaseron. The DERP report reviewed two small studies, neither of which found significant difference in efficacy. However the DERP report states both on page 16, table two, and page 21, table five, Rebif had superior tolerability as measured by fewer injection site reactions, flu-like syndrome, and less depression. In closing I would like to mention currently 27 states have reviewed this class for PDL inclusion. All 27 have included Rebif. We hope that Rebif will also be made available to patients in Washington state. Thank you for your time.

Dan Lessler: Thank you. Are there any questions? No. And Marian are you still there? I was just going to ask if there are any – give the committee here one last chance to ask you for any – ask any questions. No, okay Marian thanks a lot.

Marian McDonagh: Okay, thanks a lot.

Dan Lessler: Yup, bye. So we can jump in here with our deliberations. And again I think just would ask for any observations or comments on the presentations or this class of – this class of drugs.

Vyn Reese: This is Dr. Reese. It's a very heterogeneous group of drugs and it's I think MS is such a devastating disease it's like reviewing oncology drugs I think. You have to be very cautious that you include drugs that have an indication even for a subset of patients and make it not really difficult to get them prescribed. It looked to me – my take on the interferons is it looks like Avonex has the fewest withdrawals but maybe the least effective. Rebif and Betaseron are more effective but may have more adverse effects, but in subsets of patients you could choose one over the others. And Mitoxantrone and Tysabri and Copaxone have their own sort of groups of – maybe more serious side effects and possibly they treat a different group of patients. So it's very difficult to sort these out and to figure out which ones to put on and which ones to leave off. And my take on it would – is if it's not a group that's easy to pick a favorite and that it's – we probably should have all of them. I don't see a reason to reject any at this point and I think it'll be too complex trying to figure out how to substitute one for the others since they're so different and diverse. That's really my take on the group.

Dan Lessler: Reactions to Vyn's comments? Bob.

Bob Bray: This is Bob Bray. I agree.

Dan Lessler: Other comments or questions?

Man: One other comment, we were asked by a stakeholder to review the terms of prior authorization and I don't think that's within our purview. Is that how other people would take that?

Dan Lessler: I agree with that. That might be something we could take up separately with the DUR at some point, but I think we're just commenting on safety, efficacy, appropriateness for the PDL. So I'm curious just now how these drugs are – how you all handle these medicines.

Siri Childs: All of the drug – this is Siri Childs. All of the drugs are covered without any restrictions except Tysabri. And it requires prior authorization just as the speaker said. And I don't believe that HRSA would be opposed to taking her suggestions and modifying that criteria if indeed there's – the evidence shows that that's the case.

Dan Lessler: Again that's – appreciate the comment but that's not something we're going to consider here specifically. And then what about uniform medical?

Woman: I was just checking on those. They're in our specialty drug program, so right now they're restricted to a 30 day supply and they're covered at tier one. And there's no restrictions on them at this time.

Dan Lessler: I mean the – both are sort of current policies are sort of consistent with I think the comments that have been made here by committee members. Any other thoughts, comments? Then I guess I would – I'd ask if Vyn or Bob if you'd be willing to put forth a motion.

Bob Bray: Sure. This is Bob Bray. So following our template. After considering the evidence of safety, efficacy and special populations for the treatment of MS, I move that, insert drug names, are safe and efficacious. No single drug is associated with fewer adverse effects in special populations and that these drugs cannot be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of MS. Does that – does leaving it at that cover the issue of having them all available or do we need to specifically state that?

Dan Lessler: I think we should specifically state that. So the last sentence should be all of the above medications should be on the preferred drug list. Should be preferred on the preferred drug list.

Woman: When you say that the drugs cannot be subject to therapeutic interchange, did you call them the drugs to treat multiple sclerosis or? I'm sorry, I missed that.

Dan Lessler: I think if you just put these disease modifying drugs cannot be subject to therapeutic interchange that that's fine, I think it's pretty clear.

Woman: Thank you.

Dan Lessler: And then down in that last sentence, all of the medications should be preferred on the – you corrected it, thank you, that's fine.

Vyn Reese: I second that.

Dan Lessler: So the motion is before us, it's been seconded. Any other comment? Alright, all those in favor, I.

Group: I.

Dan Lessler: Opposed same sign. Alright, I think...

Man: The motion wasn't made by Dr. Lessler.

Dan Lessler: It, yea, it was by Dr. Bray.

Woman: Sorry.

Dan Lessler: That's okay. So I think we're running on time and we're going to adjourn until 10:45, thanks.

Dan Lessler: Summaries of anything new that we're going to go through now and we are going to begin here with drugs that treat Alzheimer's disease and Dan Jonas from. Dan you're in North Carolina? Is on the phone to take us through this. So Dan, what we've got the title slide of your PowerPoint up in front of us and you can just take it from there and let us know when you want us to go to the next slide.

Dan Jonas: Okay, great, thank you.

Jeff Graham: Dan, this is Jeff Graham. I wanted to – this is not your PowerPoint, this is just material I put together from your scanned report so we could tell you what's on our slide but I don't think you have it. Unless somebody shared it with you from OHSU, did they?

Dan Jonas: Yes, I think I have the slides.

Jeff Graham: Oh well great, good, thanks.

Dan Jonas: I hope they're the right ones.

Dan Lessler: We'll let you know.

Dan Jonas: Okay, so. My name is Dan Jonas, I'm at the University of North Carolina evidence based practice center, and we have in the past done the drug class review on Alzheimer's drugs in 2005 and we did the first update in this class last year and so this was the next scan to help determine if there was going to be another update of these medications and that was done in June of 2007.

Slide number two has the list of that last update which was February, 2006 and included literature searches up through December of 2005. The intervention that we're looking at in this drug class includes Donepezil, Galantamine, Rivastigmine, Tacrine, and Memantine.

On to slide number three. Are my slides matching up?

Dan Lessler: Yes.

Dan Jonas: Okay, great. On to slide number three there's a summary of the literature search that we did for this scan. And we searched several MEDLINE databases from – it actually says March 2005 on this slide, but we searched from December 2005, which is when the last scan was for the previous report, up until May of 2007. We used the same search terms as

we had used for the previous reports and limited it to humans, English language, randomized controlled trials or controlled trials. We also searched the FDA website and Health Canada.

On to slide number four, we found 313 citations that met our search criteria and out of those there were 49 potentially relevant studies. Those 313 were just reviewed by one person, they haven't been dually reviewed which is the protocol for the scans. There were no new drugs that have been released in this class since the last update and there are no new safety alerts at this time. And I think that's the last – yea that's the last slide on here so I guess I should say that the drug effectiveness review project did vote to update this drug class based on this scan. And so now we're starting the update...

Dan Jonas: - which I believe is supposed to be completed some time between March and May. So with that I guess I'll open up to you guys for any questions or clarifications.

Dan Lessler: Thanks, are there any questions from Dan? So Jeff if you could – could you just – so it sounds like there is going to be a full update on this class coming in the late spring.

Jeff: That's correct, and I think there was one new indication after this was completed. I think there was an indication for the dementia associated with Parkinson's disease added for – I can't remember which one but. So but that was not included in this review.

Dan Lessler: Okay, actually there are some people who want to provide some stakeholder input at this point. So I'm going to stop and take stakeholder input. Dan are you on the line?

Dan Jonas: Yes I am.

Dan Lessler: Great, if you could stay on the line just for another ten minutes or so? That'd be great.

Dan Jonas: Sure.

Dan Lessler: That'd be great because sometimes questions arise in the context of stakeholder input.

Dan Jonas: Okay.

Dan Lessler: First is Mr. Jake Knee.

Jake Knee:

Hi, I'm Jake Knee with Forest Laboratories and a regional account manager at Northwest. And I want to thank the committee obviously again for giving me time today. One of the main reasons I obviously wanted to address the committee today was in representation of Memantine or our brand new name is Namenda. Quite often at P&Ts that I've visited around the country, Namenda is getting lumped in with the other treatments for Alzheimer's and I wanted just to make it very clear to the committee that the United States Pharmacopoeia has in fact given its own designation, its own class of medication that it is a different mechanism of action. It works on glutamate as opposed to the use of cholinesterase inhibitors.

So it does have its own classification and we would just respectfully request to the committee that they consider that when reviewing the process or reviewing the medications to know that it is the first medication indicated for severe Alzheimer's, it does work on a different mechanism of action. For total side effect profile Namenda has the least amount of side effects of any of the medications.

Our utilization data we've looked at for the state Medicaid program shows that the overall utilization of these medications is very low at the Medicaid level because of the simple factor looking at a class of medication where almost 100% of the patients treated fall into part D. Not everybody, but most patients fall into part D. So when they get to that stage, part D takes over the cost of medications and the filling of those prescriptions. So the financial burden on the state – yea I don't really like making a financial argument for medications that involve such an emotional disease state, but the financial burden for the state is very low considering the implications of not treating these patients.

These are big cost drivers, these patients. Our nursing home study show that in a control group of the placebo group many cases well over \$800 a month in additional costs were [inaudible] of patients not treated with Namenda. So additional medications, usually they're watershed events that cause people to be institutionalized to begin with, behavioral outbursts. The clinical evidence is very apparent that behavioral outbursts are delayed and current behavioral outbursts are – the severity is lessened.

As you guys all know I'm sure, institutions in the state of Washington roughly run from 2,500 to \$5,000 a month. So if you can delay the institutionalization of these Alzheimer's patients just one month, it pays for their medication for the rest of their lives. So certainly we don't make an argument that these medications will extend life – there is no evidence anywhere in the world for any medication that would show that, but our argument is one – we plead to help the caregiver burden be less and to just give more life to the years these patients have left, and just remember that

Namenda is in fact in a class of its own, so. Thank you for your time, appreciate it.

Dan Lessler: Thank you. Any questions or? No. Next is Dr. Susan Heineman.

Susan Heineman: Hi good morning, my name is Sue Heineman. I'm a pharmacist. I am employed by Pfizer as a clinical education manager and I just want to thank you for the opportunity to present today in support of Aricept, Donepezil. It is the only drug that has both mild, moderate, and severe indication. And in fact I believe it was – the last time this committee reviewed this class of drugs last October is about that time when Aricept [inaudible] that severe indication and so that's all the difference that occurs in the DERP report from before, and that wasn't mentioned in – within the scans was the fact that this does have the severe indication.

And I do respectfully request that this is maintained as a preferred agent because it is a preferred drug. When looking at your own – when you look at your own data, the CMS data that's publicly available for Washington Medicaid, 84% of the time, the prescriber uses this agent versus Rivastigmine or Galantamine. Within those age – within Donepezil or Aricept. 65% of the time they reach that maximum therapeutic dose. The other agents aren't receiving those maximum therapeutic doses, the doses that their indications were supported on in the clinical trials.

And you know within – when patients are in the real world and are taking their medications, medication adherence does decrease dramatically. So this is an agent that – where patients are able to get on to their maximum dose, it has shown proven efficacy, proven tolerability, benefits to the caregivers. And again this is the only agent that does have the mild, moderate, and severe indication. So again, I just respectfully request that this maintains a preferred status without limitations.

Dan Lessler: Any questions? Thank you. Next is Dr. Jim Leverenz.

Jim Leverenz: Good morning. My name is Dr. Jim Leverenz. I'm an associate professor at the University of Washington in neurology and psychiatry with a clinical and research focus on neurodegenerative diseases such as Alzheimer's and Parkinson's. And my purpose here today really is just to advocate for choice in the class of drugs of the aceto-cholinesterase inhibitors.

Both my experience and research in the literature suggests that there are differences between the medications that are available in terms of tolerability, in terms of effectiveness, and particularly in certain subtypes of dementia. All three medications, Donepezil, Rivastigmine, and Galantamine are indicated for mild to moderate Alzheimer's, as the

individual from Pfizer just mentioned. Donepezil is now indicated for severe Alzheimer's as well as now Rivastigmine has been approved for treating dementia associated with Parkinson's disease as you mentioned earlier. Rivastigmine also has the only data available showing effectiveness in a double blind study in dementia with Lewy bodies, another prominent form of dementia.

As you probably all know, the medications are given slightly differently, at least in their oral formulations. Donepezil and Galantamine are once a day, Rivastigmine is twice a day which has sometimes advantages and disadvantages as well. I think it's also worth noting and I haven't heard it mentioned yet that there is a new formulation of Rivastigmine coming out that's a patch formulation, a non-oral formulation that will be once a day. It's quite well tolerated, shows equal clinical effectiveness, and I think really is a nice alternative to oral medication in this class, particularly in patients such as Parkinson's disease dementia patients where swallowing is often a difficult problem, they're often taking multiple medications, it might be a real advantage to having the patch available. So I think in summary please consider allowing clinicians such as myself to have choice in this class of medication, the aceto cholinesterase inhibitors. Thank you.

Dan Lessler: Thank you. Any questions? No, thank you. Next is Dr. Tracy Durgin.

Tracy Durgin: Hi, I'm regional scientific director with Novartis and I just had a couple of quick comments based on the discussions earlier. And Dr. Leverenz already addressed it, but.

Dan Lessler: Could you just move a little closer to the microphone so we could hear you better?

Tracy Durgin: Sure, is that better? Just that the patch will be available to patients next month in September. And hopefully it will make its way into the review that's coming up. And although it is a new dosage form it will be treated as a line extension. It will be used – it's FDA approved for mild to moderate Parkinson's disease dementia, as well as Alzheimer's disease dementia. And that's really all I wanted to say, everybody else did a good job at addressing it.

Dan Lessler: Thank you. Any questions or comments? No, okay. Any other questions from the committee for Dan Jonas at North Carolina? No, so Dan thanks, we can let you go, we appreciate your being with us.

Dan Jonas: You're welcome. I'm also supposed to do the one in a little bit on inhaled corticosteroids. Should I just call back in like 15 minutes?

Dan Lessler: Well, you can stay on, sorry. Why don't you just stay on here. So looking at the brief scan and also would ask people to look at the previous motion on this class of medications, I'm wondering if anybody has any comments or observations at this point.

Vyn Reese: This is Dr. Reese. And maybe the previous motion. I mean Rivastigmine the patch form and the treatment of Parkinson's related dementia is intriguing. We just haven't had the data yet – we haven't looked at that and it's not going to be able to do that until the formal review so it may be something we want to look at in the future, but at this point I don't see any reason to change the motion that was made last fall. So I would just move that we just confirm that motion until further – until we've had a chance to review more evidence.

Dan Lessler: Bob.

Bob Bray: Bob Bray, I would second that.

Jeff Graham: Excuse me, this is Jeff Graham. Usually we ask you to accept this scan as an update.

Dan Lessler: Right, so right first and then we can do the motion. So is there a motion to accept the scan as an update?

Vyn Reese: So moved.

Dan Lessler: And a second?

Jason Iltz: Second.

Dan Lessler: Alright, looks like Jason over here seconded. And then all in favor I.

Group: I.

Dan Lessler: Opposed same sign. Okay, so we've accepted the update. And next then I would say that their wish is to – a motion on the table that the previous, that we accept the previous motion and continue with that in terms of our recommendation. And Bob Bray has seconded that. Is there any other comment?

Man: Dan, could we ask that that be read into the minutes so we have a?

Dan Lessler: Sure, Vyn would you read that.

Vyn Reese: After considering the evidence of safety, efficacy, and special populations for the treatment of Alzheimer's disease, I move that Donezepil,

Galantamine, Rivastigmine, and Memantine are safe and effective. Donepezil and Memantine must be included as preferred drugs on the Washington State Preferred Drug List. The evidence indicates that Tacrine is less safe because of Hepatotoxicity than the other drugs in this class and should not be included as a preferred drug on the Washington Preferred Drug List. No drug in this class can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of Alzheimer's disease.

Dan Lessler: And so the motion's been seconded. All those in favor, I.

Group: I.

Dan Lessler: Opposed same sign. Okay, and we'll look forward to the update in 10 months or so. Sounds good. Okay, Dan we're ready to move on to the inhaled corticosteroids then in terms of – just in terms of the scan.

Susan Carson: Excuse me, this is Susan Carson and I was on the agenda for PPIs, can you just tell me when I should call back.

Dan Lessler: Let's see, actually Dan was supposed to be the last, but Susan are both of you, Kim and Susan are you in the same place? Or is Kim on the line yet?

Susan Carson: No, I was going to let her know when I was done.

Man: Well we'll move to Dan's since he's on the line. Can you call back in 15 minutes?

Susan Carson: 15 minutes, okay. Thanks.

Man: Thanks a lot Susan.

Dan Lessler: Thank you. Alright, go ahead Dan.

Dan Jonas: Okay, do you have the slides for the drug class for you for inhaled corticosteroids?

Dan Lessler: We do.

Dan Jonas: Okay. So this is also a scan to determine if an update is desired. The preliminary scan report is from April, 2007. The date of our last update was April, 2005 and included literature searches up through March of 2005. On to slide number 17, the interventions included Beclomethasone, Budesonide, Flunisolide, Fluticasone, Mometasone, and Triamcinolone as the inhaled corticosteroids.

On to slide 18 summarizes our literature search which the – was essentially the same as the one I described for Alzheimer’s as far as the databases that we looked at. The dates for this one were from January, 2004 through December 21<sup>st</sup> of 2006. And again we limited it to humans, English language, and randomized controlled trials or controlled trials.

On to slide number 19 we found 244 citations that fit the search criteria. Out of those, 21 were potentially relevant trials. There are no new drugs at this time but there is one, Ciclesonide which is in the process of applying for FDA approval for an asthma indication. And there are no new safety alerts at this time. As far as – I guess the other thing I should say is that for the drug effectiveness review project, they were planning to actually do an overall medications for the treatment of asthma review instead of updating this particular drug class.

I guess with that I’ll open it up to you guys.

Dan Lessler: Okay, are there any questions for Dan from committee members? Alright, so we’ll turn to stakeholder input. Again if people could limit their comments to three minutes and also identify if you’re here being sponsored by any organization. First is Dr. Bao Hoang.

Bao Hoang: Good morning, my name is Bao Hoang. I’m with Abbott laboratories and I’m the regional clinical executive. To begin I want to just thank you for the opportunity to highlight several key points about Azmacort or Triamcinolone. Azmacort is indicated as preventative therapy in the long term treatment of asthma and it’s also indicated for asthma patients who require systemic, orally administered corticosteroids to reduce or to eliminate the need of systemic corticosteroids. Azmacort at doses of 400 µg to 1,200 µg daily provides safe and effective relief in adults and children with added convenience of a built in spacer.

In one particular study of 53 patients receiving Azmacort 300 µg twice daily, the mean percent change in forced expiratory volume in one second, noted as an FEV<sub>1</sub> was 15% as early as the first week, compared with 0% for placebo. At six weeks, the mean FEV<sub>1</sub> was sustained over time at 17% compared to 2% with placebo. In a second study to evaluate the improvement of asthma symptoms, 60 patients receiving Azmacort 300 µg twice daily achieved a 17.5 change in FEV<sub>1</sub> compared to 2.8% of 61 patients receiving placebo. Of the 60 patients who were receiving Azmacort, there was also a decrease in Albuterol use of 3.4 puffs per day compared to 0.6 puffs per day in the placebo group. The adverse events as far as Azmacort [inaudible] incidence of greater than 3% summarized from three studies, varied slightly by dose and a dose of Azmacort of 300 µg twice a day among 170 patients. Sinusitis was reported at 4%, pharyngitis at 25%, headache 21%, and flu syndrome was reported 5%.

Other adverse events included facial edema, diarrhea, bursitis, dry mouth, rash, and chest congestion.

In conclusion, I just want to say that Azmacort is considered a preferred agent in controlling asthma, it's also an inhaled corticosteroid that may reduce or eliminate the need for systemic corticosteroids and it also provides safe and effective relief in adults as well as children with the added convenience of a built in spacer. Thank you.

Dan Lessler: Thank you any questions or comments? Alright, next is Dr. Randy Legg.

Randy Legg: Good morning, can you guys hear me okay? It's easier for me to bend down than raise the mic, so I'll do that. My name is Randy Legg, I'm a Pharm D with AstraZeneca from Spokane. And I just want to talk to you about two of our inhaled corticosteroid products. The first one is Pulmicort Respules. It's the only inhaled nebulized corticosteroid available on the market. It's indicated for asthma age 12 months to eight years of age and it does carry a category B safety rating, pregnancy rating. And is available in a .25 and a .5 mg strength with once a day and twice a day dosing.

The other part I want to mention is we have reformatted and re-formatted, excuse me Pulmicort Turbuhaler in the form of Pulmicort Flexhaler. It's now available in a 180 µg strength as it was a 90 µg strength. 120 puffs for the 180 and 60 of the 90 µg. It's still a category B and it's still treating for asthma age six and above. Any other questions for me about those products?

Dan Lessler: I don't think so.

Randy Legg: I have a question. Duane, did you want me to speak to the Washington asthma initiative letter or are you going to take care of that?

Dan Lessler: That's been distributed. We have a copy of it.

Randy Legg: Okay, thanks. I was supposed to deliver that, thanks.

Dan Lessler: Okay. Next is Merideth Zarling.

Merideth Zarling: Good morning and thank you for the opportunity to present information on Flovent HFA and diskus. My name is Merideth Zarling and I'm a pharmacist as well as regional medical scientist for GlaxoSmithKline. I'd like to present to you information in support of the retention of Flovent on the PDL. First I'd like to update the information in the OHSU drug effectiveness review report on inhaled corticosteroids. There's no longer a Flovent MDI containing CFC formulation on the market, nor is there Rotadisk. Flovent is available as an HFA formulation in three strengths,

and a diskus device in a 50 µg strength with two higher strengths that will be available in the future. Also, all formulations of Flovent are indicated in patients down to the age of four.

In a Cochrane collaboration review from 2005, it was concluded that most patients with mild to moderate asthma experience similar results with lower doses compared to higher doses of Fluticasone propionate. The use of a lower dose may optimize the risk benefit ratio and may provide cost savings. One approach to assess this is a retrospective analysis of health plan data. Study by David Stumple and colleagues compared the monthly costs of Fluticasone at the low strength to other corticosteroids. A total of 1,956 patients were included in the study. Results determined that annual asthma care charges both pharmacy and medical over the 12 month observation period were significantly higher in patients treated with Beclomethasone dipropionate, Triamcinolone acetonide, Budesonide, and Flunisolide compared to Fluticasone.

In addition, patients treated with Beclomethasone, Triamcinolone, and Flunisolide were associated with significantly higher total healthcare asthma and non-asthma charges compared to patients on Fluticasone. Compared with Beclomethasone or Triamcinolone at therapeutically equivalent doses, that is Flovent at ½ the Beclomethasone or Triamcinolone dose in adult asthma, patients in randomized double blind studies, Fluticasone demonstrated similar to significantly less suppressive effects on HPA access.

In summary, there's some comparative clinical evidence favoring Fluticasone as evidenced in the EPC drug class review on inhaled corticosteroids. There's three available strengths of Flovent available in an MDI and a 50 µg strength available as a diskus device. This provides an effective way to deliver the needed dose with a reasonable amount of puffs. Finally, there's a database analysis which suggests that the asthma care and total healthcare costs may be lower for patients filling Flovent low strength prescriptions compared to patients filling prescriptions for other inhaled corticosteroids. Based on this information, the Medicaid population would be best served if Flovent were available on the preferred drug list for the state of Washington without restriction. Thank you very much. Are there any questions?

Dan Lessler: Any questions? No. Thank you. Next is Russ Fotheringham. Sorry if I.

Russ Fotheringham:

That's one of the better attempts, I'm impressed. My name is Russ Fotheringham, I'm regional account manager with Schering-Plough pharmaceuticals. Schering usually has our medical science liaison present to the committee, but he has had a death in the family so I will be filling in

for him today. There are three points regarding Asmanex that I'd like to briefly share with the committee. The first regarding Asmanex is efficacy. Asmanex is demonstrated in placebo and in comparative trials improved FEV<sub>1</sub>, improvement in asthma symptomatology, decreased need for rescue medication in patients previously treated with bronchodilators alone or inhaled corticosteroid therapy and reduction in nighttime awakenings with effectiveness with once daily administration.

The second regarding safety and tolerability for Asmanex. Asmanex has total oral bioavailability of less than 1%. At recommended doses Asmanex has shown no significant effects on HPA axis activity with total effects similar to placebo. Overall, side effects in clinical trials were mild to moderate and no patients required the discontinuation of therapy as a result of drug related adverse events.

Third, regarding Asmanex is device and dosing. Related to the device, since Asmanex Twisthaler contains no propellant. Patients do not need to coordinate actuation and inhalation. Also the Asmanex Twisthaler has a dose counter which counts down each time a dose is taken. Consequently, the patient or caregiver will always know how many doses remain in the inhaler. Related to dosing, Asmanex is the only FDA approved inhaled corticosteroid indicated for once daily administration at initiation and for maintenance therapy of asthma in patients previously treated with bronchodilators alone or inhaled corticosteroid therapy.

So in conclusion due to Asmanex's q.d. dosing convenient device, and excellent safety and efficacy, I'd ask the committee to continue having Asmanex on the preferred drug list for Medicaid patients. Thank you.

Dan Lessler: Thank you. Are there any questions? No. Thanks. Finally, Dr. Juan Guerra.

Juan Guerra: Hi, my name is Juan Guerra, I'm a primary care doctor in Seattle, I work at Swedish. I'm here because I treat asthma commonly at my practice. I'm interested in asthma, and I want to – as a primary care doctor and for other primary care doctors make sure that we have the tools to treat asthma effectively. I want medicines that are in the inhaled steroid category that are powerful, that are safe, and that are easy to use. I use almost primarily Fluticasone Budesonide and the new one, Mometasone. And specifically talking about Mometasone today, I want to make sure that we have the ability to treat patients who are not likely to take a medicine twice a day with a safe choice, with a reassuring, safe medicine that has a low bioavailability like Mometasone for long periods of time, once a day, assuring that they will take it, assuring that they're not going to come back to my office again with an asthma attack, going to the ER with an asthma attack. And with these safe, higher potency medicines I can actually use

these medicines now for acute exacerbations by quadrupling or octupling the dose and still know that I have safety on my side. And I wanted to make sure that as a primary care doctor we keep these options on the table for our patients who generally cannot afford their medicines. Thank you. Any questions?

Dan Lessler: Any questions? No. Thanks. Alright, any questions for Dan Jonas on the phone? No. Alright, so Dan now I think we can – we'll let you go here.

Dan Jonas: Okay.

Dan Lessler: Thanks a lot.

Dan Jonas: Thank you.

Dan Lessler: So if first if we could have a motion just to accept the scan.

Bob Bray: This is Bob Bray.

Alvin Goo: So I move that we accept. This is Alvin. I move we accept the scan.

Dan Lessler: And Bob can we accept your comment as a second?

Bob Bray: I'll second it.

Dan Lessler: Great, all those in favor.

Group: I.

Dan Lessler: Opposed same sign. Alright, and if folks on the committee could turn to the previous motion that was passed and that was effective January of this year. And take a look at that and I'm wondering if there are any additional comments or any changes that people. Is this – Bob did you make this? Is this your motion? I can't remember.

Bob Bray: No, it was him.

Vyn Reese: It was mine in August of '06. I would really – I don't see any new data that's been presented to the committee to change our previous recommendations. On the scan there was nothing really new that we saw. I don't know when the next official update is going to be in this group – I don't know whether they've decided to update it again.

Dan Lessler: I think.

Vyn Reese: In the near future.

Jeff Graham: I think – this is Jeff Graham. I think information actually the DERP was going to do a drug class review for those drugs – controller drugs that are used to treat asthma, which this class would be in that. Leukotrienes would be in that and also some of the – I think some of the longer acting  $\beta$  agonists will be in that too. That'll be out probably about this time next summer.

Dan Lessler: Okay, alright.

Vyn Reese: Until that update I stand by my prior motion.

Dan Lessler: Bob did you have a comment?

Bob Bray: Agree.

Dan Lessler: Agree, okay. So any other comments or discussion? Vyn do you want to – could we look at the previous motion and you can just read that and.

Vyn Reese: After reviewing the updated information on inhaled corticosteroids, I move that Beclomethasone, Budesonide, Flunisolide, Fluticasone, Triamcinolone, and Mometasone are safe and efficacious for the treatment of asthma. Fluticasone and Budesonide (DPI and nebulizer) must be on the preferred drug list. For the treatment of asthma on the Washington Preferred Drug List inhaled corticosteroids can be subject to therapeutic interchange using resources such as the National Asthma Education and Prevention Program, expert panel report, or the International Primary Care Airways Group, as long as the above concerns are addressed.

Dan Lessler: Okay, is there a second?

Dan Lessler: You're going to speak to the proton pump inhibitors just in terms of the scan.

Susan Carson: That's right.

Dan Lessler: Okay, that would be great. Do you have the slides that I guess Jeff Graham had put together?

Susan Carson: I do.

Dan Lessler: So we've got the cover slide, the title slide in front of us and you can take it from there.

Susan Carson: Okay, thank you. Alright, so this is the update scan for PPIs. This would be update number five. It's one of our oldest reports. And this was done in

June, 2007. The last update report, update number four was finalized in July, 2006 with searches through November of 2005.

The next slide just shows the included drugs. There are five PPIs including the two forms of Omeprazole. Zegerid is the sodium bicarbonate form which is a new drug.

Next slide. Dan probably went over this on his scans, but just to update you we searched – for the update scans we searched for randomized controlled trials or controlled clinical trials in the English language only. And for this scan we did the searches through the middle of June, 2007. For safety information we also searched the FDA Med Watch website and the Health Canada safety database, the website for new indications, new drugs, and any safety alerts.

Next slide shows the results of our scan. So we came up with 118 citations. And after abstract review we came up with 20 new trials that were potentially relevant from reviewing the abstracts. So I'll just go over what these were in a little detail. We found eight new head to head trials. As you recall, the PPI report already has a lot of head to head data, especially for GERD – for short term treatment of GERD. So we found some new studies. There are two studies of Esomeprazole versus Omeprazole for short term treatment of GERD and just something about the doses here. One of them looked at Esomeprazole 20 mg versus Omeprazole 20 mg and the other looked at a higher dose of Esomeprazole, 40 mg compared with 20 mg. And then another head to head trial looked at Esomeprazole 40 mg compared with Pantoprazole 40 mg for GERD. And then we had a couple of new head to head trials looking at the maintenance treatment of GERD. I think those were six months, longer term than the eight week short term trials. And these were both looking at Esomeprazole 20 mg compared to Pantoprazole 20 mg. There's also a study of Esomeprazole versus Lansoprazole for maintenance treatment. And then for other indications there's one trial of Rabeprazole versus Omeprazole for peptic ulcer and one new trial of Lansoprazole versus Omeprazole for H pylori eradication.

And then the other group of new trials that we came up with are in children or adolescents. This is a new indication that was added I believe in our last update. None of these trials are placebo or head to head trials. There are five trials of Lansoprazole, Pantoprazole, or Esomeprazole for short term treatment of GERD, but these are either dose ranging studies where there was no placebo, they just looked at different doses of the same PPI, and then or else they were before after studies where they gave the children the drug and then looked at the follow up with no controlled group. So these probably wouldn't meet inclusion for efficacy, but they do provide – they potentially provide information about adverse events in

children and this information is lacking currently. But again these are all short term.

And then the last group of studies are the new placebo or active control trials. So there's two placebo controlled trials for maintenance treatment of GERD. One in Lansoprazole and one in Pantoprazole. And then we've got two long term studies, seven year with a seven year followup. And they looked at PPI versus surgical treatment for GERD. One of these was in Omeprazole and in the other one it wasn't clear from the abstract which PPI they looked at or if it was – if they looked at several different PPIs. And then lastly there were two trials of Esomeprazole versus placebo for the prevention of NSAID induced ulcer. So those are the new trials of efficacy.

And then I'll move on to new drugs or indication which is on the next slide. The new drug that was approved by the FDA in February, 2006 is Zegerid, the sodium bicarbonate form of Omeprazole. We do mention that in our report – our last report but we just say that no studies of Zegerid met our inclusion criteria because we don't have studies with health outcomes, with you know symptom relief or healing of GERD. The only studies we've identified in the past are in looking at stomach acid things like – outcomes like that which weren't included outcomes for our project. So that was approved in February, 2006 for short term treatment of active duodenal ulcer, treatment of heartburn, and other symptoms associated with GERD. Short term treatment of erosive esophagitis and maintenance healing of erosive esophagitis. And then the 40 mg capsules of Zegerid were approved for short term treatment of active benign gastric ulcer. And the suspension of Zegerid had already been approved in June, 2004.

Another new FDA action was the Rabeprazole 10 mg dose was discontinued. But the 20 mg dose is still available. And then lastly in April, 2007, Esomeprazole was FDA approved for the treatment of pathological hypersecretory conditions including Ellison's syndrome. These conditions aren't addressed in our report, that was – they weren't included populations. But we wanted to mention that update scan.

And then we found no new FDA or Health Canada safety alerts for any of the PPIs. There are some new drug interaction warnings added to the Omeprazole and Esomeprazole product labels for – I cannot pronounce that. And the Lansoprazole product label for Warfarin. These are indications that the other PPIs had already had.

And then we also wanted to mention nested case controls study that was published in 2006 which reported an increased risk of hip fracture in patients who were taking high dose PPIs for one year or longer. And the study found that the risk of hip fracture increased with a longer duration of

use. That was published I believe in JAMA in 2006 and your update scan report has a copy of the abstract. And that's new information.

Dan Lessler: Great, thank you. Are there other questions from the committee for Susan?

Angelo Ballasiotes: This is Angelo Ballasiotes and I'm wondering if you are aware of a Med Watch from the FDA on two small studies that are fairly long with regards to Prilosec and Nexium causing heart disease.

Susan Carson: Yea, that's actually new information that came out just I think in the last week or so. And you know it did get publicity and it's – you know we haven't looked at that in detail and it isn't in our report because it came out after this was completed. But yea, that is something that the committee would definitely want to be aware of.

Angelo Ballasiotes: Thank you.

Dan Lessler: Other questions or? I just – I had one question I was just curious because of the case control study you mentioned about high dose PPIs and hip fracture and people hypothesized that maybe that has to do with calcium absorption and such. I'm wondering if anybody has looked at potential bone metabolism problems in kids on PPIs. Is that something that?

Susan Carson: Yea, that's not something that I'm aware of. We didn't find any evidence as far as I know about that. And we did find that the evidence about safety, especially long term safety in children was really lacking in the report. And the scan shows that there really isn't any additional information, at least from trials.

Dan Lessler: Thanks. Any other questions? Susan can you stay on the phone just for about another three or four minutes?

Susan Carson: Sure.

Dan Lessler: Okay. We're going to take stakeholder comment and first is Judy Mar-Burbidge

Judy Mar-Burbidge: I'm Judy Mar-Burbidge and I'm a clinician as well as a clinical marketing manager for TAP pharmaceutical and I'm here to address the issue with Prevacid. As you well know that the PPI class provides symptomatic relief of GERD, and that's pretty true across the board on the PPI class. They all show some degree of acid suppression and I can share with you some information like in the Ernst and Robinson study it shows that Prevacid actually has a healing or maintenance of erosive esophagitis up to 95%. But that's not the issue that I want to share with you today. Because that's

– that isn't the population that needs our special needs and our special attention.

And I want to address the population that – the pediatric population. They tend to have very complicated case when they have symptomatic GERD they tend to – they lack the ability to be able to share verbal skills like sharing their symptoms to their caregivers. And so oftentimes their symptoms tend to be overlooked, they tend to – they present with refusal to eat, they start losing weight, they start having failure to thrive, they have chronic crying. These are issues that are addressed in the pediatric population. And oftentimes if these are overlooked and not addressed, they progress on to further damage and causing more hospitalizations and further costs on the health dollars. And so this is where Prevacid can actually provide a means for addressing the needs of this special population. Prevacid has FDA indication for one to 11 years of age and in the [inaudible] study it actually shows that they have 100% efficacy after 12 weeks of using Prevacid for erosive esophagitis. And the beauty of Prevacid is that it also has multiple administration options. It has capsules that you can open and that you can sprinkle on foods or acidic juices. You can put it into an NG tube, and it also has the Prevacid solutabs which you can dissolve under the tongue with or without water. And that's a big plus because if you look at the [inaudible] studies in managed care, the number one obstacle for good healthcare is patient non-compliance. And if you can get a patient to actually take the medication that is willing to take the medication, then you're going to get better healthcare and you're going to eliminate some of the cost of further problems. Also the beauty of Prevacid is that it's already on your preferred drug list and it is going to be the first of the next generic that is coming out. So you do have the aspect of being able to convert your clients. So, I appreciate sharing that information with you.

Dan Lessler: Are there any questions? No, thank you. And next is Dr. Diana Orentas Lein.

Diana Orentas Lein: Good morning, my name is Diana Orentas Lein and I'm am the scientific affairs liaison for Santarus and I want to thank all of you for the opportunity to present information today about Zegerid which is an immediate release formulation of Omeprazole that is a combination product of both micronized Omeprazole and sodium bicarbonate. It's now available in both a capsule as well as a powder for oral suspension form. Zegerid is different from the other oral PPI formulations including the soluble tablets and the dissolvable formulations in that all of those contain enteric coated beads. And that's to protect the [inaudible] drug from degradation by gastric acid. What Zegerid does is utilize an antacid buffer to neutralize the gastric acidity. This protects the [inaudible] drug and allowed the micronized Omeprazole to be absorbed rapidly and

effectively. This is different from the other compounded formulations of Omeprazole and sodium bicarbonate in that the pharmacy compounded formulations typically begin with an enteric coated bead. And in three separate pharmacokinetic studies, it's been demonstrated that there is no pharmacokinetic advantage to using the enteric coated bead together with the sodium bicarbonate. Whereas Zegerid has peak plasma levels by 30 minutes. This translates into superior pH control.

There are head to head studies looking at gastric acidity which is a non-subjective measure. It's an objective measure of performance and in the pharmacodynamic trials that were registered with the FDA, Zegerid demonstrated a gastric pH over four for 18.6 hours. And that is longer than any of the other delayed release PPIs in terms of the number of hours the gastric pH is over four on their label. In head to head studies, Zegerid has demonstrated superior efficacy in nighttime heartburn patients in terms of raising the gastric pH over four. Compared to Pantoprazole when administered prior to dinner and when compared to Esomeprazole and Lansoprazole when administered prior to bedtime. These studies demonstrated effective pH control without the requirement for a meal.

The American College of Gastroenterology has recommended that all delayed release PPIs be taken 30 minutes prior to meal, because the meal is required to stimulate the parietal cell. Zegerid does not require a meal for effective pH control. In fact in our hospital study there was an effective pH control in NPO patients, they were NPO for the first three days, and in these patients that were critically ill, the gastric pH was raised over six in 95% of the patients on all 14 days of the trial. This trial led to the indication for the reduction of risk of upper GI bleeding in the critically ill patient. It is the only PPI listed with this indication and in fact that indication is missing in this particular review so I'd like to point that out to the committee.

In previous years there has been some discussion on the need for a soluble formulation. We would like to recommend the powder for oral suspension form of Zegerid to meet special needs in patients that have difficulty swallowing, patients with an NG tube, and patients with dysphagia. The powder for oral suspension is different from the capsule in that it's specifically formulated for NG tube use. In our critical care study, we did not have any issues with clogging of the NG tube that you may have with some of the other products. And so for that reason we don't recommend breaking apart the capsule and administering that through the tube.

Dan Lessler: Thank you.

Diana Orentas Lein: Any questions? I would be happy to answer.

Dan Lessler: Any questions?

Man: I had one question. I was noticing that there's a caution for patients over 50. Are you familiar with that?

Diana Orentas Lein: I am not aware of that caution. You do need to take into consideration the sodium load from the sodium bicarbonate so that if you have a patient with – on a sodium restricted diet this may not be the appropriate drug for that patient. But for the other patient populations this would be something that you could consider.

Dan Lessler: Jeff when is this – is there a plan for a full update on the PPIs then or?

Jeff: Not at this time.

Dan Lessler: Other comments? Sue are you there?

Susan Carson: Yes.

Dan Lessler: I was just wondering. Can you comment on some of the comparative data that was just presented?

Susan Carson: Yea, well the issue with Zegerid is those studies that were mentioned – they don't, they look at pH and that was not an outcome that we included. So because we look at health outcomes, outcomes that patients can feel such as symptoms or we also included esophagitis healing. But just simply looking at pH wasn't an outcome that we looked at. So while there are head to head studies of pH, that – we don't know whether that translates into better health outcomes for the patients so we – the participating organizations decided not to include studies of just pH in our report.

Diana Orentas Lein: May I address the committee for a moment?

Dan Lessler: Sure.

Diana Orentas Lein: There have been two published studies, very recent published studies that were not performed by the company, by Santarus but rather small studies performed by investigators. One was performed by Jane and Costell, another one by EcoHerrano at Northwestern University and they looked at refractory GERD patients, patients who were failing b.i.d. PPI therapy. In both of those patients they demonstrated that the majority of those patients had been failing other PPI therapies were actually demonstrating symptom control on once a day or twice a day Zegerid.

Dan Lessler: Okay, thanks.

Diana Orentas Lein: Thank you.

Dan Lessler: Okay, any other questions or comments? Alright, Sue we can let you go. Thank you very much.

Susan Carson: Okay, thank you. Now is Kim up next?

Dan Lessler: Kim is up next but probably in two or three minutes. First if we could have a motion to accept the scan.

Jason Iltz: This is Jason. So move to accept the scan as an adequate update review.

Dan Lessler: And is there a second?

Patti Varley: I'll second it.

Dan Lessler: Okay, so next if people could turn your attention to the previous motion which if we could project up here as well. And I think that went – that might have been as well.

Vyn Reese: There really hasn't been any – on the review there was really nothing new that was presented to the committee. There'll be a more systematic review later, I assume. And so I'll just go ahead and I don't see any reason to change my motion that was made in December 20, 2006. After considering the evidence of safety, efficacy, and special populations, I move that Rabeprazole, Omeprazole, Omeprazole plus sodium bicarbonate, Lansoprazole, Pantoprazole, and Esomeprazole are safe, efficacious, and have no difference in adverse events in special populations. They can be subject to therapeutic interchange in the Washington Preferred Drug List. A pediatric formulation needs to be included in the Washington Preferred Drug List.

Dan Lessler: Can we just scan back down to – okay. Is there a second?

Jason Iltz: Jason, I second.

Dan Lessler: Carol you had a comment?

Carol Cordy: As with the previous one do we want to say pediatric formulation needs to be included as a preferred drug on the Washington Preferred Drug List?

Dan Lessler: Right as we're getting more and more clarity in our motions here why don't we do that. If we can accept that as a friendly amendment. It's just that you've got it – the last sentence is just needs to. Right, down the last sentence of the motion. So the motion's on the table, it's been seconded,

friendly amendment accepted. Why don't we go ahead and vote. All those in favor.

Group: I.

Dan Lessler: Opposed same sign. Okay.

Patti Varley: This is Patti Varley. I don't know technically do you need to go back up and vote on the scan because we had a first and second but we didn't.

Dan Lessler: I thought we did. So why don't we. So the motion was made to accept the scan by Jason, I think it was seconded by Ken. All those in favor say I.

Group: I.

Dan Lessler: Okay, opposed same sign. Thanks Patti. Alright then we're on to medications for overactive bladder. And Kim are you on the line?

Kim Peterson: Yes I am.

Dan Lessler: Great. Okay, well I think we're going to again have in front of us the slides that – the title slide. Do you have those slides that I believe?

Kim Peterson: I do.

Dan Lessler: Okay, so if you – should feel free to go ahead.

Kim Peterson: Okay, great. So I'm Kim Peterson with the Oregon EPC and I'm going to be giving a report on the DERP systematic review of the drugs used to treat overactive bladder. And the DERP review on OAB drugs was last updated in December, 2005. And if you go to the next slide, slide 12 you will see there a list of the drugs that DERP has reviewed so far. So in considering whether or not the DERP review on OAB drugs was in need of a full update, in March of this year of - the Oregon EPC conducted an abbreviated literature scan to get a sense of the volume and nature of any relevant trials that had been published since our last search.

And so if you go on to slide 13, again you'll see the method of the abbreviated literature scan there. Basically the process involved a Medline search for any new trials. And then we also searched the FDA and Health Canada websites to see whether there were any new drugs, new indications, or new safety alerts that had come up since our last review.

So now if you go on to the next slide, results, slide 14 and 15. So those two slide show what we found in our scan. So there were no new drugs or new indications approved for OAB that we are aware of. But we did

identify 20 new potentially relevant trials as well as some new safety information. And so I'll just go over what these were. Among the new trials, the majority involved comparisons of – and included is OAB drug to placebo. And so they really wouldn't offer much additional new information about how one OAB drug compares to any other OAB drug.

So the majority of the placebo controlled trials involved the extended release form of Tolterodine. And one common theme we noticed that came up in these placebo controlled trials was a focus on looking at the efficacy and safety of using nighttime dosing of Tolterodine extended release to treat specifically male patients with overactive bladder and concomitant nocturia. And then there were also a few other trials of Tolterodine extended release that looked at using it in males with other concomitant urinary tract symptoms or in men with overactive bladder and urge urinary incontinence. So those are the highlights of the placebo controlled trials.

And then, as for the head to head trials. There were just three new ones and then there was a post hoc analysis of data from a previously included trial of the extended release forms of Oxybutynin and Tolterodine. So among the new head to head trials two of them involved comparisons to [inaudible] or Trospium and the reason I'm pointing this out is that previously head to head data had been pretty limited for these drugs so there's a few new head to head trials for them.

And then as for the post hoc analysis of data from the OPERA trial which was like I said one of the previously included head to head trials of the extended release forms of Oxybutynin and Tolterodine. It was focusing on the compare – how these drugs compare in subgroups of patients based on whether or not they had had any previous history of any cholinergic drug use.

So let's go on to slide 15. The slide that lists the new labeling changes that we found for these drugs. So for Tolterodine information was added to the label that caution should be used when treating patients with histories of congenital or acquired QT prolongations. And then for Oxybutynin and Trospium dizziness was added to the list of potential adverse events for Oxybutynin and then rash was added as a new potential adverse event for Trospium.

So based on this new information the DERP opted to defer a full update of this review at this point. And so the next action for this review will be that we'll scan – we'll do an updated literature scan again in April of 2008. So I can take your questions.

Dan Lessler: Great, thank you. Any questions from committee members for Kim? No, Kim can you stay on the line for about five more minutes? Or a little bit – a bit longer. And we’re just going to take stakeholder comments here and the first is Dr. Jonathan Lloyd.

Jonathan Lloyd: Good morning. My name is Jon Lloyd. I’m a regional medical research specialist employed by Pfizer. Thank you for the opportunity to address you this morning. I’m going to speak on behalf of the inclusion of Detrol LA on your preferred drug list.

Detrol LA is the number one prescribed overactive bladder medication in the United States. It’s been shown in Medicaid populations that treatment with Detrol reduces healthcare costs. I’m not going to spend a whole lot of time going over all of the data we have – we have a very extensive clinical trial database some which were mentioned by your colleague there.

[end side A]

Jonathan Lloyd: Overall, we’ve looked at Detrol’s efficacy and safety in a wide variety of patient populations. The early registration trial showed a 71% decline in incontinence episodes that’s been repeated through various other studies. We’ve looked at – it has a rapid onset of action that separates from placebos as early as five days. We’ve looked at 12 month extension trials looking at the continued efficacy after 12 months. Most trials in OAB medications are down to 12 weeks and we’ve shown efficacy and safety at that time. More recently we’ve looked at the elderly population which is a concern because of safety concerns. We’ve shown again efficacy and safety in that population. The efficacy is maintained in severe patient populations, people who are having you know 15, 16, 17 episodes a day. More recently we’ve looked at – as your colleague pointed out, looked at the male patient population. Men who have OAB and lower urinary tract symptoms who often times are just sort of treated with an alpha blocker because it’s sort of assumed that you’re a man you have a prostate and that must be the problem. So often times there are bladder concerns there. We’ve looked at that and shown efficacy with Detrol LA in those patients without the – without any differences in placebo in terms of urinary retention which is oftentimes the concern in treating those patients.

Now I think we’re all aware of sort of the constraints of clinical trials. You know the concerns of they’re maybe they’re not real world patient populations so we’re now looking more at patient reported outcomes and in our impact trial we actually had the patients decide what their most bothersome symptom is because that’s what patients come in talking about – what bothers them. And whether frequency – be it nocturnal or daytime, or urgency. Whatever they the patient defined as their most bothersome symptom, Detrol LA improved those symptoms such that overall be it

30% reduction in daytime episodes or 40% reduction in nighttime episodes that resulted in up to a 78% improvement in the patient's own perception of their bladder condition. So the patient felt better when they were on treatment. So that's sort of a summary of the efficacy. In terms of safety there's really no other drug in this category that has shown superiority in terms of safety with regard of Detrol whether it's in our own package insert or whether it's in competitor sponsored trials. Consistently Detrol has the best tolerability and safety profile.

Dan Lessler: Thank you.

Jonathan Lloyd: We're one of only two drugs on the FDA approved list. Thank you.

Dan Lessler: Thanks, any questions?

Man: I have one question for the gentleman who just spoke. Sorry, I forget the name.

Dan Lessler: There's a question.

Man: Could you address for the committee the labeling change in terms of the precaution that was added for QT prolongation in – it looks like special populations. But how is your company handling that? Has there been some monitoring that's happening and what are you seeing as a result of that label change?

Jonathan Lloyd: Yea, we were requested – along with the other manufacturers to do a – you know QT study. So the study we actually did showed that there wasn't a clinically significant difference in - or clinically significant difference in QT prolongation. But they did ask us to put a precaution in there. We've looked back at our clinical trial database and found no signals of QT prolongation, no incidence of [inaudible] anything like that in our clinical trial database. It's not a concern that comes up when we speak with urologists. We've looked at – I think there've been 13 million patients been treated with Detrol now so it's not something that comes up and we are – we have been looking through our databases. The adverse event, prescription event monitoring studies that have been done in Europe haven't shown anything either. So we were asked to put it in there as a precaution but we haven't seen any signal of that.

Man: So there's no recommendation for ECG monitoring or anything like that that you folks are recommending?

Jonathan Lloyd: No.

Dan Lessler: Thank you. Next is Leigh Platte.

Leigh Platte:

Good morning. I'm Leigh Platte, I'm a scientific liaison with Astellas pharma. I'm here to talk about Solifenacin Vesicare. In our registration trials of over 1,800 people, we achieved a 51% rate of continence with a rate of dry mouth at about 11%. We have good evidence of persistence and a class of drug where there's – [inaudible] of prescription refill rates. 81% of patients were still on study drug at the end of one calendar year. We did do one head to head star trial versus Tolterodine. It was Tolterodine 4 mg long acting versus Solifenacin 5 and 10 mg. Both compounds performed very well. They had a 49% rate of continence and we did a 59% rate of continence.

Now the new data we have is from a trial called Venus where we looked at urgency as the primary endpoint. The international continence society showed that urgency was the driving symptom of the complex of overactive bladder. And in our patient focus groups the most bothersome symptom to them was urgency. It was that fear or having an accident in public and being embarrassed. So in this trial there was a statistically significant improvement in urgency versus placebo in decreasing the episodes of urgency and the episodes of urgent incontinence.

All the sudden I forgot my train of thought, I'm sorry. Overall there we've seen a tendency to improve urgency in every single trial that we have done. It seems to be of patient benefit. There's also an additional benefit in warning time. We measured warning time by giving patients stop watches and asking them to start the stop watch when they had that strong compelling desire to urge. And stop it when they actually void it. The difference was 32 seconds. And that may not seem like a long time, but to a patient who's looking for a bathroom 32 seconds can be quite meaningful. So I respectfully request that you would consider maintaining Solifenacin on the state's PDL. Thank you very much, are there any questions?

Dan Lessler:

Thank you. Next is Dr. Wall.

M. Wall:

Good morning. My name is Marty Wall. I'm a physician urologist in practice out of Bellevue, Washington for the last 11 years and I can provide a clinician's view of overactive bladder. Overactive bladder is a condition that overwhelmingly affects women. It's interesting to hear the telephone presenter as well as this other presenter talking about the impact, or new trials studying specifically men. However, as a clinician I can tell you that that is an important segment of the population but as I'm treating these patients it's overwhelmingly women. Medicine being a male dominated profession over the years has tended to view these women with overactive bladder as perhaps psychologically unbalanced, a rather patrician view of overactive bladder. The best take on this that I've heard

over the years has been provided by a woman urologist who said I don't think these women are crazy and urinating 20 times a day, but I think if I urinated 20 times a day I would be crazy.

So as regards the medicines available over the years I'm old enough to have practiced with Ditropan and Levecin as the primary medicines in this class and saw the side effect profile that limited the utilization of these or as mentioned by our last presenter the number of prescription refills that did not occur. As regards Detrol which I've been using for I'm guessing ten years I don't really know the history well enough. And now the longer acting Detrol LA. This has made my practice a little easier. The number of patients that I see are of the Medicaid population tend to come from pretty far and wide. There is very limited access to urologists for these patients when I first started seeing patients from 50 and 60 miles away I scratched my head and wondered why they weren't seeing the group of urologists that I knew pretty well in their immediate vicinity.

So these patients have limited access to physicians and if they can be effectively treated with once a day dosing with low side effect profile that will make their life better and it'll make my life a little easier as well as these patients again are finding their access to physician time severely limited. So my take on Detrol LA is that it has provided a lower side effect profile and it would be the patients that I've treated with it – I can't provide you statistics but as regards patients returning with some of their familiar complaints and they're dissatisfied, the primary physicians referring them are dissatisfied, and if they can be better cared for this medicine I feel will make their life more tolerable and their problems with overactive bladder considerably less.

Dan Lessler: Thank you. Any comments or questions? No, great, thank you. Next is Fred Amberger.

Fred Amberger: Good morning. My name is Fred Amberger. I'm a pharmacist and a regional scientific director with Novartis pharmaceuticals and I'd like to speak with you this morning to ask that you include Enablex on your preferred drug list. I'll offer three reasons why Enablex should be considered.

The first is that we do have long term studies that have been published in a 24 month open label trial that was published. It was found that the efficacy of Enablex was comparable to [inaudible] at 12 months. And in fact it improved from 63% to 84% at 24 months. There was no increase in adverse events with Enablex for 24 months and also discontinuations due to constipation and dry mouth were comparable to the 12 week studies that were done.

You addressed the issue of cardiovascular safety previously and I'd like to reiterate that with Enablex studies have been done to measure the electrophysiological effects. And in fact the QT intervals were completely unchanged comparable to placebo with Enablex. Additionally, changes in heart rate can be seen and this could be a potential concern. In the phase two and phase three trials that were done with Enablex there was no change in heart rate relative to placebo.

The third reason to consider Enablex is relative to CNS adverse events. There have been two published trials that measured the CNS effects of Enablex. Some in [inaudible] patients and some in normal volunteers and because in the elderly population you've got a population that frequently takes a number of other drugs. Oftentimes in cholinergics were things like memory deficit, sleep disorders, confusion, and even hallucinations can be seen. In the two published trials that were performed with Enablex there was no change in the CNS effects relative to placebo. So I'd like to ask you to consider Enablex for the Washington Preferred Drug List. Thank you.

Dan Lessler: Thank you. Any questions, comments? Okay, and finally Dr. Bak.

John Bak: Good morning. My name is Dr. John Bak. I'm a practicing urologist in [inaudible] Washington. I've been practicing in the state of Washington for two years now. Since starting my practice I've been trying to grow my practice and so as a result I'm seeing a lot of new patients and I'm seeing more of the difficult patients. And so I'd like to just share with you my experience. So the typical patients that I see are patients that have already been evaluated by the primary care physicians or patients who are looking for an alternative drug because they've already seen another urologist. And so in my experience the patients that I see are a special subset of populations that are difficult to treat. And so it would be nice for me to have an alternative drug. Currently I believe there is one drug that is approved – that's in the preferred drug list. That's the once a day dosage for overactive bladder. So for me if I can have another tool, another drug to be able to treat my patients effectively. And so that's why the drug that I prefer to use is Darifenacin, Enablex and so with that I've had good results and it's also had – it's very safe, safety profile has been very good. And so that's the reason why I've chosen that drug. So I'm asking the committee to consider putting Darifenacin into the preferred drug list.

Dan Lessler: Thank you. Any questions or comments? And before we let Kim go are there any – committee members have any more questions or comments for Kim at this point? Kim, we can let you go. Thank you so much for staying with us.

Kim Peterson: Sure, have a good day.

Dan Lessler: So first if we could – if there could be a motion to accept the scan.

Bob Bray: Bob Bray, I so move.

Dan Lessler: Okay, second? Okay second. And all those in favor?

Group: I.

Dan Lessler: Opposed same sign. Okay. Next we can turn our attention the most recent motion that we adopted relative to this class of medications. If people could just take a look at that and as people are thinking about that based on the scan I'm wondering if anybody has any comments or sees any need for any modifications or change at this point. Alright. Would somebody be willing to put forward a motion here? Bob.

Bob Bray: This is Bob Bray. I would put forward the same motion again. And I could read that.

Dan Lessler: Great, that would be.

Bob Bray: After considering the evidence of safety, efficacy, and special populations for the treatment of overactive bladder, I move that Darifenacin, Oxybutynin, Solifenacin, Tolterodine, and Trospium are safe and efficacious. No single incontinence medication is associated with fewer adverse events in special populations. These drugs can be subject to therapeutic interchange on the Washington Preferred Drug List. Immediate release formulations cannot be interchanged for long acting formulations and vice versa. One long acting formulation must be included as a preferred drug on the Washington Preferred Drug List.

Dan Lessler: Okay, is there a second?

Vyn Reese: I'll second.

Dan Lessler: Alright, all those in favor, say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so the motion carries and we can adjourn for lunch and we'll reconvene at 1 p.m. as the DUR.

Dan Lessler: Folks can take their seats and we can get going here. So the first item of business is to – would actually be to approve the minutes from the last meeting. That I'm looking at these and recognizing that really they're a verbatim transcript. So I don't think there's a need to approve the minutes

formally then if we're going to have a transcript because it just. Alright, well we could sort of do it as a formality here. We sort of decided not to do that as the P&T committee.

So I'm for anybody who has read all 25 or 30 pages here. Is there a motion to approve?

Man: I move that we approve the verbatim transcript as the minutes.

Dan Lessler: Great.

Man: I second the motion.

Dan Lessler: Okay, all those in favor?

Group: I.

Dan Lessler: Alright, so the minutes, or transcript is accepted. And it looks like this afternoon our discussion, deliberations are going to focus on sedative hypnotics and appropriate use and policies and so forth. And so maybe what I'll do is turn it over to you Jeff in terms of introducing the agenda.

Jeff Thompson: This is Jeff Thompson. From the last meeting what we promised to do is come back with verification on where there are some edits in the system as it relates to safety. We ended the discussion with looking at pediatric safety limits, which is five and 30 and working with the pediatric – some pediatric leaders in the community. They agreed to keep that limit, I believe that you guys seconded that motion, but there was not good transparency in what we want to do and go for with adults which the current limit is ten and 30. And it can be extended with medical necessity. What I think Siri Childs and Steve Hammond have done is done a great job of going back, talking with the community, we have an expert here, Dr. Ralph Pascualy and what we'd like to do is present to you a recommendation how we think we can implement a rational approach to sedative hypnotics in this class related to your motion that you had this morning and I think improve the safety and health of clients who are getting long term sedatives. And so with that I want to introduce Dr. Steve Hammond who will go through the presentation. And then with that you can ask him questions and have Dr. Pascualy come up and talk to the rationale with his expertise as a sleep specialist.

Dan Lessler: Great, thanks. Steve.

Steve Hammond: Okay, thank you Jeff. At HRSA we try to base coverage and authorization decisions as much as possible on robust, unbiased evidence. This presentation is meant to be a general overview of chronic insomnia and its

management with particular attention to drug therapy. The briefing paper included in the board's meeting packet includes a survey of the research literature on long term pharmacologic treatment of chronic insomnia.

Next slide. Prevalence estimates are methodologically difficult, but 10% is a conservative evidence of prevalence of chronic clinically significant insomnia in the adult population. Chronic insomnia behaves like other chronic disorders, that is it tends to persist sometimes waxing and waning. A chronic disease management model may be the most appropriate approach to clinical management of chronic insomnia.

Next slide. Optimum management of chronic insomnia is a matter of active discussion and debate. Until recently FDA approval for almost all hypnotic agents was explicitly for short term use. Recent approvals for Lunesta and Rozerem have not included the restriction that they are to be used for short term treatment. The evidence for long term continuous use of the hypnotic agents is sparse and long term continuous use of hypnotic agents is particularly controversial. The most current NIH consensus conference on chronic insomnia was held in 2005. A systematic review of the literature was commissioned for that conference. I apologize that the reports from the 2005 consensus conference weren't included in the meeting preparation materials. Reports of the conference in the systematic review are readily available on the NIH consensus development program website and I did hand out copies of summary reports to the board members. If anyone did not get a copy let me know, because I had one extra copy of each.

Next slide. Often unresolved medical issues such as pain or symptomatic cardio respiratory disease contribute to insomnia. Psychiatric disorders, particularly depression and anxiety very often contribute to insomnia. There is universal agreement among clinicians that it is necessary to address underlying contributing factors when managing insomnia. When no underlying medical or psychiatric contributing factors can be identified, insomnia is considered to be primary insomnia.

Next slide please. Most sleep specialists recognize that cognitive behavioral techniques are an important component of insomnia management. Cognitive behavioral techniques include sleep hygiene, which is establishing behavior patterns that promote normal sleep, sleep restriction, and stimulus control. Research suggests that cognitive behavioral treatment is roughly as effective as pharmacological treatment and that research can be found in the systematic review that was associated with the 2005 NIH consensus conference. Actually the two approaches, cognitive behavioral and pharmacologic seem to be complementary. Pharmacologic may give quicker results at the initiation of treatment. Cognitive behavioral treatment seems to produce more

durable results, especially if pharmacologic treatment is discontinued. Improvements in sleeping pattern seen with pharmacologic treatment usually are not expected to persist after discontinuation of medication unless cognitive behavioral treatment has been part of the overall management program. Most sleep specialists caution against using an exclusively pharmacologic approach to management of chronic insomnia because there are potential benefits of cognitive behavioral treatment, and there are some safety concerns with use of sedative hypnotic agents. And this is a quote from the 2005 NIH consensus conference report. “Adverse effects of the sedative hypnotic agents are residual daytime sedation, cognitive impairment, motor incoordination, dependence, and rebound insomnia. These problems appear to be worse in the elderly. The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half lives.” Note that the 2005 NIH consensus conference did not address the use of Rozerem or Ramelteon which was not yet on the market although that conference and the systematic review do address the use of melatonin.

Next slide. HRSA’s current policy on the sedative hypnotic agents applies to adults 18 years and older. The restriction to no more than ten doses in 30 days currently applies to both the newer sedative hypnotic agents and Ramelteon, Rozerem. There is support for this type of restriction in the recommendations of the 1983 NIH consensus conference report no drug therapy for insomnia. For pharmacologic management of long term primary insomnia and this is a quote from that report, “Intermittent use such as one night in three is advised.” Under HRSA policy more than ten doses in 30 days requires prior authorization. HRSA does not currently apply this limit to the older insomnia drugs which are mainly the benzodiazepines.

Next slide please. So these are categories of insomnia drugs. The newer sedative hypnotic agents are selective benzodiazepine receptor agonists. Eszopiclone was not restricted to short term use by the FDA, largely on the basis of a well conducted six month study of continuous nightly use that showed sustained efficacy and minimal rebound insomnia or other withdrawal effects on discontinuation in adults aged 21 to 69. No major adverse effects of treatment were observed. Rozerem, or Ramelteon, promotes sleep by a distinct mechanism as a selective melatonin receptor agonist. It also is not restricted to short term use by the FDA. on the strength of two 35 day studies of continuous nightly use, one in adults under 65 and one in adults over 65 years old. In these studies Ramelteon showed sustained efficacy and no rebound insomnia or withdrawal symptoms on discontinuation. No other significant adverse effects were observed. The older sedative hypnotic agents are mainly these familiar benzodiazepines that are listed here. Quazepam, brand named Doral, is

another benzodiazepine that is FDA approved to treat insomnia. It was not used by any Medicaid clients in state fiscal year '07. Likewise, some barbiturates have been used as sedative hypnotics in the past. They are schedule two and three drugs, and none of these were used by Medicaid clients in state fiscal year '07. Chloral hydrate has had very limited use in Medicaid clients.

Next slide please. So this presents data on utilization of these agents under Washington Medicaid for state fiscal year 2007.

Steve Hammond:

Benzodiazepine receptor agonists compared to the older which are all benzodiazepines and then Rozerem at a lower level. Now if I can direct your attention to the next column, the average units per prescription. These average quantities per prescription reflect the ten dose per 30 day limit for the newer agents, although less so for Ramelteon than for the newer sedative hypnotic category. The quantity seen for the benzodiazepines seem to reflect the lack of quantity limits for these agents. Finally, in the third column the average number of prescriptions per client per year. These data suggest that the newer sedative hypnotics and benzodiazepines tend to be used intermittently, perhaps on a p.r.n. basis. The higher average number of prescriptions per client per year for Ramelteon suggests that this agent tends to be used differently from the sedative hypnotic agents, perhaps more often for long term continuous use.

Next slide. This chart shows coverage policy by Medicaid managed care plans. I should mention that the HRSA policy that I described earlier was for our fee for service clients. You will note that there are varying degrees of coverage among the managed care plans and that there are some limits to the quantities which range from 12 to 15 per month.

Next slide. Just by way of comparison with other HCA agencies. LNI does not cover chronic use of scheduled sedative hypnotics and HCA uses a tier plan as you can see.

Next slide. So these are our recommendations to the DUR board for management of these prescription drugs. We recommend for the newer sedative hypnotic agents – that is the selective benzodiazepine receptor agonists that authorization to dispense above the ten dose and 30 day limit should require prior authorization. Examples of circumstances that could allow one time authorization of 30 doses in 30 days would be initiation of treatment for anxiety or depression complicated by insomnia or short term induction therapy for insomnia concomitant with starting a program of sleep hygiene and cognitive behavioral treatment. Certain criteria could allow up to six months of continuous treatment. These would include 1. Adequate documentation of evaluation and management of underlying

medical and psychiatric issues and 2. Documentation of an adequate trial and failure of sleep hygiene and cognitive behavioral measures for at least six weeks. We would require sleep specialty consultation for continuous treatment beyond six months and at least yearly follow up by a sleep specialist as long as continuous drug treatment is continued. We recommend that the DUR board consider the pros and cons of extending similar limits to apply to the older sedative hypnotic agents of the benzodiazepines. Finally, we recommend that Ramelteon should be considered as a different class of hypnotic agent. It does not appear to be a sedative. Its indications and optimal usage are different than for the other sedative hypnotic agents. Thus far sedating side effects have not been observed with Ramelteon.

Next slide. That concludes our presentation and we welcome your questions.

Dan Lessler: Thanks that's a very nice, really nice presentation. So why don't we begin with questions for Steve from committee members?

Vyn Reese: Hi, it's Dr. Reese. What one question is the sedative hypnotics are – the benzodiazepines are used for different indications, and some are simply labeled sleeping medications and others are anxiolytic medications and it's sort of arbitrary sometimes how they're classified. So would you be – would this limitation be on patients who are on anxiolytic doses of benzodiazepines or are you going to somehow figure out how to not – some patients like take Lorazepam for sleep and they also take it for panic attack, anxiety, and other indications. So it's like it can get sort of fuzzy.

Steve Hammond: Well, I think we recognize that there would be some logistical problems in applying such limits to the older benzodiazepines and that's why we suggested that we consider the pros and cons of trying to extend those limits.

Dan Lessler: Could you just back up the slide there to the previous slide. That'd help to have the recommendations for. Thanks.

Jeff Thompson: This is Jeff Thompson. Before we did that we come back and talk with you. Right now we're talking about the preferred drug class. But before we did something like that we'd come and talk with you and obviously engage the community in the discussion.

Man: Can you tell me with regards to special conditions or – that you would consider using these medications on the longer term. Let's say you know longer than ten days.

Steve Hammond: Well, I did refer to some situations again sometimes we're requested to approve larger quantities for people who are acutely being treated for – initiated for treatment for anxiety and depression. And we oftentimes would consider authorizing 30 doses to get that sort of treatment started.

Man: I guess I'm speaking specifically for people that have chronically used substances over a period of time. And also people that have pretty severe mental disorders. Schizophrenia and bipolar. And I really find that in my practice that I have to use alternative drugs to get them to sleep and it becomes I think more expensive down the road in doing that. It'd be nice to have some of these sedative hypnotics available on more than a ten day basis. It's very difficult to get it through for a 30 day limit, I've found. It exacerbates their disease state.

Steve Hammond: Well, I think we do recognize that there will be cases where it may very well be appropriate to have long term continuous use of these agents. But perhaps more often than not it's probably appropriate not to do that long term. And that's why we want to review that sort of use.

Dan Lessler: I guess I just want to step back. I guess – and maybe just think through with everybody the basis for a policy like this. Because what I'm thinking is there are with any drug there are appropriate indications and uses and so forth and we trust people who are licensed to prescribe to make those decisions. And it always seemed to me that the reason for the ten day limitation, other than maybe clinically – possibly that was a rational clinical policy has been that Zolpidem prior to recently has not been available generically so it's been an expensive medicine. And I'm wondering what is the compelling reason to control these substances in this way that makes it different from prescribing benzos which we all I think probably I'm safe in saying all of us do that here and probably have patients that get some number per month and so forth after we've gotten into the patient file and I daresay that most of us – most primary care providers probably don't send those patients to psychiatrists for a second opinion and so forth. Or with any other medicine that can have adverse effects if not used appropriately. So I guess fundamentally I'm asking why do this?

Steve Hammond: Well, let me respond and then I'll invite my colleagues also to chime in. But my understanding is that the main drivers of this have been concerns for quality of care and safety. Wanting to give – do attention to non-pharmacologic management. Cost has been really, has not been nearly that prominent as an issue, a driver.

Dan Lessler: Well I understand that, but I guess my point is – I guess sort of a counter example is there are behaviorally oriented management strategies for other disorders where there also may be a pharmacologic alternative and it's

certainly helpful to have guidelines and make people aware of guidelines and educate providers and do academic detailing and so on and so forth. Fundamentally I'm asking why do this for this class of drugs if you're not going to do it for, and not for benzos, not for antidepressants, not for any – not for overactive bladder medicines. I mean we heard that behavioral therapy and I think people here probably all begin with behavioral therapy often can be effective. So what's different here?

Siri Childs: Well I would have to – this is Siri Childs – and I would have to say that we do this because we believe it's the right thing to do. And we do, whenever we do have some drug issue come before us, depending on our resources we do try to guide appropriate drug therapy. We've been doing this for, well since 2003 so four years. And I think that we've been pretty successful in giving those patients who need the sedatives and hypnotics on a regular basis the use of those drugs. But providing the others just as an aid to help them with good sleep hygiene.

Jeff Thompson: Dan, this is Jeff Thompson. I think what's different about this is – when I've come to you in the past with people on three or four SSRIs from a single provider or children that have huge amounts of methylphenidate. What we've done is we've had some controls on this which we need to come back and ask are these the appropriate controls. Historically before I came I think Siri did a nice job of looking at elderly who were getting ten, 20, 30 or more mg of Ambien at night long term and that was part of the genesis of the ten in 30. What we're faced with now is a change in indication, a change in FDA labeling, and coming to you and asking you what is appropriate. Certainly we could take all controls off, make them preferred, and then do I come back a year or two later and talk about dose and duration at – or do we agree on what is an appropriate set of guidelines that can be implemented through a UMUR. And I think irrespective of sort of doing the right thing I think we've been in discussion with Dr. Pascualy who brings a unique perspective from what he sees clinically. But you're right. Why this class why not another class? Historically there was excessive use in the elderly, ten in 30 got placed. Now we've had controls so we don't have bodies in the street from the safety perspective. We can do this proactively. But what is that, and that's why we have to come and talk with you.

Carol Cordy: Hi, Carol Cordy. The other question I would ask too, and I agree with what Dan's asking is the requirement for consultation. And then yearly follow up it looks like. Is that available to our Medicaid clients. Can they go to a sleep clinic and that can be covered?

Man: So the answer is yes. We have, I believe it's 15 sleep centers that we contract with and pay for sleep studies across the state. They're facilities based. We don't do clinic based sleep studies but we do send and transport

clients for sleep studies and have done so for several years. So the answer is yes there is access to sleep study labs and those specialists who actually man – who are on a staff at the sleep study labs.

Dan Lessler: Jeff I mean just to follow up on that. Steven mentioned that the prevalence, I know it's a hard number to get, is 10% of the population with chronic insomnia. So I don't know what the average Medicaid population is at any one time – it's – what is the number of patients?

Man: Let's say 500,000.

Siri Childs: Well, but users of medications there's about 182,000 at any one time. There's 500,000 eligible in fee for service but at any one time there's about 182,000.

Dan Lessler: So we're going to get sleep studies on 182,000?

Man: No, no, no that's who use medications. Right now.

Dan Lessler: But we just said that if you're on meds over a certain – if you need medicines beyond a certain length of time you need to get a study. And we're hearing that there's a large number of chronic users.

Man: 182,000 is not people taking these medications, it's taking any medications.

Man: Right, there's 18,000 a year that are taking it. And that's why we want to come and talk with you about it. That represents roughly 3% of our population.

Steve Hammond: This is Steve Hammond a couple of comments. While the prevalence may be 10%, a fairly small fraction, maybe 25% of those seek care, medical care for the chronic insomnia. And then among those who do seek medical care we expect it would be a small fraction who would require long term continuous treatment beyond six months. Really quite a small fraction, but I can't give you an exact estimate of that.

Dan Lessler: Could we bring Dr. Pascualy in? I mean as long as we're having – because Dr. Pascualy – I'm wondering if you can, just to comment on patients with chronic insomnia and what proportion of those patients should be or end up on long term medications to, and the extent to which that's appropriate.

Ralph Pascualy: Can you hear me okay?

Dan Lessler: Yea.

Ralph Pascualy:

Okay. Well, I'd like to say a couple of things. First is that when we're talking about research based decisions, one thing that you may not know is that the data that's quoted about efficacy for sedative hypnotics – all the drugs that you've looked at [inaudible] participated and I think every clinical trial of every substance that's come out in the last 20 years – is a fact that's very important to keep in mind when we have the discussion. The studies have all been done on people who have primary insomnia. What that means is that all the data that we discuss has nothing to do with the patients we're talking about. When you do a study defined primary insomnia, we have to put ads in the newspaper and radio to find these people. So as a person who does research on this population it's not an easy group to find. So if I were to talk about the kinds of patients that might be in a community clinic in this particular population, it's almost a certainty that there isn't – there's a fraction of them who possibly have primary insomnia. They basically have a more chronic, multifactorial kind of problem. So the first thing we should say is we don't have knowledge of efficacy outcome long term benefit of any of these drugs, and that includes the older ones.

Now there's some occasional open label trials where drugs have been given to specific populations, rheumatology, pain, so on and so forth. But these are not controlled studies, they're not large, and none of them would meet your standards for where we now have the evidence based medicine so I think what I'd suggest is that we step back from that part of the discussion and take a look at it a slightly different way. The way I think it would make some sense is to think of it more like chronic pain. And I'm old enough to remember when chronic pain was not a specialty and we didn't have chronic pain clinics in the state of Washington. Or at least access to them. So with chronic pain you had the same problem where there was a lot of prescribing but not a lot of evaluation and not a lot of inter-disciplinary care. And it was a small number of people we're talking about. So what I like about this, and I don't feel – I don't understand all of the political economic and legal ramifications of your work. I realize this is a complex situation so I'm not speaking to the solution I'm just speaking generally to the problem. The issue is that what you want to do long term is to create a growing group of practitioners, not necessarily board certified specialists – and I'll come to that in a minute why not necessarily that – who are interested in providing evaluation – this is an office visit not a sleep study, and then a disciplinary style of not relying on chronic sedative hypnotics for these patients who have mental illness, physical disorders.

Right now, the sleep disorders field has a big flaw which is that it was geared towards the evaluation of doing a test primarily for breathing problems, sleepiness, narcolepsy. So when people think of getting a sleep consult, immediately I think [inaudible] goes we're going to do sleep

studies on 18,000 people every year? Well, no that in fact is really – there’s really no reason to do a sleep study on someone who comes in and says I can’t sleep until you actually have done other things to find how you get them to sleep. It doesn’t make sense unless there’s an obvious problem, they’re gasping, they’re choking, they’re falling asleep driving. So the first issue is consultation would be actually a clinical consultation.

Second issue, many nationally - I’m speaking here from my national interest – is that sleep labs are directed often by pulmonary physicians or neurologists and their training and interest is not in the area of chronic illness of this type that involves medical and psychiatric problems. And the training there is not on cognitive behavioral training. So if we were to go get the average sleep doctor in the United States out of the 5,000 of them, very few have had any training in doing this work. So I don’t think the concept is necessarily to have them get a consult who’s not particularly trained or interested. I think the issue is sleep clinics to be accredited have to provide to the accreditation team evidence that they are working with community based specialists who can work with the insomnia portion. So any lab that claims to be an accredited lab has to have PhD consultants, psychiatrists who are part of their referral network. So I think the concept is more to make this available through the clinics where in fact other providers are interested in sleep problems and chronic sleep problems. Not necessarily the doctor at hand. It could be, in our center we have access to that. I’m one of them but there’s others in the state of Washington.

So I think if you have that concept then the third thing is that as you look at the long term care, once somebody has been on sedative hypnotics for some time, the problem is when do you stop them. And typically, although the primary insomnia studies show that the newer agents have very little rebound, the issue is that once you are giving these drugs to people who have other factors, conditioned arousal, fear of losing the sedation does create an ongoing issue for these patients, particularly if they have psychiatric illness. So getting someone off a sleeping pill requires that you actually provide a behavioral support for them, a way for them to learn how to cope without taking the pill. And I think that over a number of years that could become more and more common practice just like managing chronic pain has dramatically changed in our own 20 year careers here.

So I think if you put those together as far as the limitation issues I think your point is well taken, why limit – I mean we don’t limit other drugs why limit these. I don’t have a good answer to that other than that there is an opportunity to I think retrain how people think about this problem and provide clinical resources, not tests to begin to set a different way of practicing in our state. And I think the recommendations that were read, kind of the consensus nationally, I think sleep specialists nationally do feel

that it's very important, and in fact now it's a mandatory approach because there's now licensing of behavioral sleep specialists. It's a brand new thing. And it really speaks to this point. Once you're going to have somebody on chronic medicine, there has to be an evaluation and there also has to be behavioral intervention. So that I think is the general feeling of what I think – the opportunity here.

Dan Lessler: That's helpful. I'm wondering if there are other comments and questions in terms of... You must have people with insomnia in Spokane I'm sure.

Ralph Pascualy: No that just stops at the Cascades.

Bob Bray: Well, I had a conversation. This is Bob Bray. I had a conversation with Jeff earlier where we addressed that same issue Carol about the access. Because I think if we do these kinds of things we have to be able to deliver what it is that we're being asked to do if we can't do it and so Jeff was telling me about the fact that they'll even pay for transportation for patients. I guess the one thing – I'm assuming that there are other ways in which we can look for exceptions. I'm thinking about some of the patients that I have on, say in nursing homes where there's – I can't imagine a situation maybe other than an acute care hospital that has worse sleep hygiene than a nursing home. And of course that's not anything they can really do much about. I guess these limits would affect only newer sedative hypnotic agents, it wouldn't affect older sedative hypnotic agents even though I'm not sure the older ones necessarily are better care.

Man: That I think is a very good point if I could interject there. I think that my view is that the newer drugs have actually shown their efficacy and safety in a lot of trials while the older drugs, certainly some of the older drugs that you have listed there have not. In other words they weren't designed as sedative hypnotics necessarily. They were benzos as someone has said they were for anxiety or other purposes. So I think in a perfect world you might approach it from the disease end that is what's the diagnosis rather than what drugs do we start with. To me it sounds like there's a grandfather problem here where it looks like we grandfather a lot of drugs for sleep and it would be very, very tough since those drugs are also being used simultaneously to treat anxiety in the patient or to provide some sedation if they're bipolar or other factors. So I think that there is a logical difficulty there.

The opportunity though is with the new drugs, since I think physicians today want to use the new drugs, the recommendations if you read the recommendations in detail, they really do point us all to use the newer drugs that we really shouldn't be giving people Valium or Clonazepam unless there's another reason for it. But I think what this does do is since

physicians want to use these newer drugs, the shorter acting, the safety that's been proven.

I think it could also create the opportunity of finding these psychologists, psychiatrists. I'm not prejudiced about the practitioners. Nurse practitioners or psychiatric nurse practitioners that are excellent who would be very interested in evaluating these longer term use people. People who now want to be on it year and year after year. And give those people an opportunity to get more appropriate care. And among them, going back to the sleep study business. Recent work shows that about half of those people do have untreated sleep apnea, do have untreated myoclonic disorders, do have the sleep disorders that are being generated by the very medicines that they're taking to begin with. So withdrawing these folks from multiple drugs often improves their sleep.

Man: And Dan, just to follow up. I wasn't suggesting it would be only sleep centers. I mean there are board certified sleep specialists both with the American board and older board certified. And then the question of whether it's neurologists and psychiatrists or ARNP mental health, where do we draw the line. To say okay, if you want to evaluate six months or more, okay who is "somebody you can get a second opinion."

And then I think the other reason why to consider this in the Medicaid population is different. Our mental health issues are quite higher prevalence than anybody else in the state purchasing. And I think we don't spend enough time talking about substance abuse. I can't tell you how many people that continue to be on benzodiazepines or narcotics that carry a substance abuse history. So I think we need to start looking at an integrated approach and not necessarily - it's the disease with the FDA indication. So I think we have an opportunity to set a standard, but you're engaged in the standard setting here and protect our clients but recognizing we got to also have access.

Man: Well I know that's the real issue is the patients with substance abuse. And in my practice that's what I deal with the majority of my patients and sleep is really a primary issue. But I can't use the benzos on them, because I'm going to put them right back in the hole where they came from. So that's a real dilemma. What do I use? And you'll wind up using some of the more expensive drugs like Seroquel.

Man: On that note, another fact that may be helpful in thinking about that fact. I think in the population that has a substance abuse disorder, the evidence is in favor of the newer sedative hypnotics because the way the sedative hypnotic trials are done we have to find hardcore drug addicts for the addiction section. So the way the sleeping pills are tested is you find people who are substance abusers, and then they're given these drugs in

increasing doses and they're asked to rate them. Are the – do they give you a high? Would you buy them on the street? Would you do the following with these drugs? So I think the newer drugs have been tested on actual substance abusers to come up with these ratings where their liability for abuse is low compared to the older drugs. But I think that's where again a consultation with somebody who's knowledgeable about substance abuse, etc., etc. could say this person needs something because they have substance abuse, bipolar disorder, they have chronic pain as well. They really should be on a newer drug and you should put them on Lunesta for a year and then have a reevaluation of what's been done for these conditions we've identified. Pain, mood, etc., etc.

Man: Well I do find them getting better because as time goes on and the nervous system kind of solidifies, they don't need the medicine. Well it makes me tired now. And they don't figure it out. So we don't cut it back and pretty soon they're gone. Not everybody, but a lot of them.

Vyn Reese: About the one time authorization for 30 doses in 30 days. I think that comes up when you have somebody with clinical depression and you're trying to bridge their insomnia with – until their antidepressant works. How cumbersome is that going to be? I mean it's been pretty cumbersome getting prior authorizations and the fighting through the system to get things okd in the past. It says a one time authorization, is it – are you going to have to go through seven different phone calls before you can actually get the drug authorized? I'd like to be able to use Zolpidem or something for patients in their first – when they have major depression so they can sleep through the first couple or three weeks until they can, until their antidepressants start to work. But right now with this setup I only can give them for ten days, and so they – it's unlikely their antidepressant is going to work in that time to improve their sleep.

Man: Just to comment on that question. I think that that – your comment is really to the point. It may be a useful modification. When you look at the response rate of insomnia with behavioral treatment and then you look at it with sedative hypnotics, usually they're looking at around six weeks, a lot of the studies have picked six weeks. And again with depression you know that the number is six weeks, seems to be the number of drug response if you have luck with the first one or failure. Maybe a little shorter with some of the SSRIs. So it is possible that you could deliberate on allowing the first prescription for these drugs to be 30 days. Because that allows an acute insomnia to settle down, it allows a follow up visit to come and see how things are going and so on and so forth. And by allowing the first one to be 30 days, then it would make sense that they would hurry – the clinician and the patient would hurry to try and work on this condition, because there might be then the need later on to limit it. To cut it back so that in fact is a tapering or there's an application or a review of whether

the behavioral help has happened. So I don't know how well that would fit with the goals here.

Vyn Reese: This is Dr. Reese. I think that's a better idea for – I mean as far as how I use it for – I mainly use it for patients who have depression for short term use. And these other circumstances too, but that's the type of thing I'd like 30 days at least, and maybe another ten days or so just to make it to the six weeks, but once their antidepressant is working, most of these patients don't need it anymore. So I'd like to have some type of – where I didn't have to go through prior auth to get that special 30 day first dose. I think having a 30 day first dose and then having that be a one time deal is a good idea.

Man: If that works for you then when you look at acute insomnia, which is what – these drugs actually, as you know, acute insomnia is what they're best for. That's where all the work has been done, in the primary insomnia. So the thought there is that if you begin with a thought like that, let's say our practitioners need to have that flexibility when they initially approach the patient and they have maybe it's six weeks, maybe that is the right number. But then after that if you don't cut that back there will not be the quality – I don't think quality will happen after that. There'll just be the...

Vyn Reese: This is Dr. Reese, I totally agree. If it's beyond that and they keep on coming back and getting it again and again and there's some other problem that you need to address. And it may be that the antidepressant is the wrong one. But or something else is going on that you haven't taken care of. But I would not want to see somebody who's on these drugs for months and months and months. I think the six months continuous use or whatever with a sleep specialist, a consultation at least for behavioral sleep specialists is totally reasonable. I think that's a good safety concern. But I think that having the initial one be longer would be in my practice would help me as far as being able to write the first prescription for 30 days and then after that it could be the ten 30 limit or whatever you wanted to do. That would be helpful. If I'm looking at trying to tailor this how I practice, that would make it a lot easier.

Dan Lessler: I'm wondering as one of the mental health providers and specialists if you've got any thoughts about this.

Patti Varley: Well, this is Patti Varley and my frustration with this conversation is the consumer end of things as I'm listening. Because I have a problem where even offered the opportunity to go learn good hygiene, sleep hygiene techniques, a lot of my cases want the pill and they don't – I mean I don't know if you. So I think, I'm kind of curious about this conversation from my end because if there was a limit and that limit was there, maybe that would add some extra motivation to someone to look to alternatives. But

my frustration is that if you don't take the Nintendo out of the room and you don't take the TV out of the room and you don't have a bedtime ritual because you work 'til eight o'clock and you're having dinner at nine, I have a hard time justifying clinically the medicating of that sleep problem. So for me, the interesting thing is that I also agree that with depressed or anxious patients, having the ability to have the agents that are treating the core symptoms in place makes more sense than ten days worth and maybe they sleep better for ten days and then they think it's the pill that made them sleep and they don't have any faith that once the antidepressant or the anti-anxiety med kicks in that they can sleep without it. So the 30 day makes more sense to me clinically.

Dan Lessler: I believe we – this might be a good opportunity to take some stakeholder input because I think there are people in the audience who would like to – am I correct, that there are people in the audience who would like to comment? I don't think we have a sign in sheet but that's okay, anybody who would like we can make time for if you would just, when people would just identify themselves and we'll give you three minutes and please let us know if you're sponsored by any organization. So please, sir, go ahead.

Jay Jennings: My name is Jay Jennings, I'm with Sanofi-Aventis pharmaceuticals. We produce Ambien and Ambien CR. I'm not a clinician by any means. I would like to comment a little bit on the process and some of the – some of what we are hearing in the field and that is procedurally it has been difficult, as Dr. Reese said, to know what the criteria for approval on those PAs from the ten to 30 are. And doctors are often frustrated by the process and somewhat uncertain I would say. The six months seems like a different issue, and consultation might very well be absolutely appropriate, but initially I think one of the questions I would have and I don't know if Dr. Hammond has this information, but how many PAs have been approved for the ten to 30 and is there a particular for to get, and treatment criteria that meets those criteria?

Steve Hammond: Can I defer to Siri?

Siri Childs: We do, this is Siri Childs. We do have a [inaudible] form that we send out when someone requests more than ten for 30. As long as they're using ten for 30 it goes through without a stop. And you saw that on those patients receiving newer sedative hypnotics or the benzo agonist type that we had over 10,000 of them and the average number of units per prescription was ten. So the majority of folks are not hitting the [inaudible] at all. And I was asked to keep track of how many units – or how many requests I might have per day and I went a couple of days without any requests at all. And then a day that I got one request for more than 30 in a 30 day period. Or 30, excuse me more than ten.

Vyn Reese: This is Dr. Reese. I think you – prescribers prescribe ten because that’s the limit and they don’t want to go through extra hoops. I mean I can’t tell you exactly that’s what I’m thinking I don’t want to get on the phone and I don’t want [inaudible] one more prior auth form out to do it. And it is – it’s a definite deterrent whereas, and then I’m liable to give them Trazodone or something else that I can give them 30 days worth. I mean that’s what happens, and it’s not a great drug so, that’s the where the bind that clinicians I think are in.

Man: I have [inaudible] a little bit, prescribe the ten mg then have them break it in half and it lasts 20 days anyhow so.

Jay Jennings: If I might just conclude. We’ve heard that it’s safety in the FDA indication before. Now the new products don’t have the same indication. And the older products, which in many cases as you’ve already referred to are not the best treatment, are unlimited, so I think that what we hear from the field is that clinicians question the policy and very much... We hear a bunch of frustration as not being able to get to the PA criteria and furthermore they say that ten days isn’t a really good determination of chronic use, still primary insomnia. Thank you.

Dan Lessler: Thank you. Are there other folks that? Please.

Jennifer Stole: Hi, I’m Jennifer Stole. I’m the government affairs director for Sepracor pharmaceuticals. We manufacture Lunesta. And I just wanted to echo Jay’s comments about the confusion about the prior auth process in the field and getting the extended quantity limits because it doesn’t seem to have been consistent. The other thing I wanted to throw out and Dr. Reese had commented about this too, and so did Dr. Ballasiotes. Many states are also looking at over utilization of the atypical anti-psychotics. In this class particularly, low dose anti-psychotics as, or combination anti-psychotic therapy which is a very, very expensive way to treat sleep. Many states like California are really looking at it in their DUR boards so I would also encourage this DUR board to consider this in the future as an opportunity to evaluate some of the areas to improve quality in the future.

Dan Lessler: Thanks, and I think your comments, what it brings up is just unintended consequences. I mean it’s the old pushing on the balloon one place and it comes out the other way. I mean it would seem in pursuing a policy like this that it would be important to try and evaluate just those kinds of behaviors that you don’t want to be in some ways incenting.

Man: Dan you’re absolutely correct. We have heard from the community that Neurontin is a favorite sleeper and Seroquel is a favorite sleeper. The nuance is we don’t know if that is driven by provider preference or by our

programs but you're absolutely correct. If we did anything like this we could track that and find out what's going on.

Vyn Reese: This is Dr. Reese. I do not also want to promote like any of the [inaudible] for long term use. And that's basically if they look at TV that's what they're seeing. And that's what patients are going to be asking for too, even in this program. And the pharmaceutical companies have been very good at marketing insomnia for a variety of reasons as a disease and it's – and if we have unlimited use these, there clearly has to be [inaudible] and limits on these for patients who basically don't turn the TV off and a variety of other behavioral reasons that they're not sleeping. So it's not – clearly needs to be an open door, but the door maybe is closed a little too tight, that would be my concern right now is that there needs to be a little bit of [inaudible]. Not wide open, there clearly needs to be controls in this because it's a very easily abused area.

Patti Varley: This is Patti Varley and I'd just a couple of points of clarification. I think I know the answer but I just for point of discussion. I'm assuming if you have someone who is chronically ill with or has cancer in hospice, this does not apply. We're not talking about those extremes, they don't – I'm assuming. Correct? The other is Dr. Pascualy, did you say that to change somebody's basic sleep habits or behaviors tends to be about six weeks with or without medication? Is that?

Ralph Pascualy: Right, because we are talking about habits and we're also talking about a biological process. So that once you start to change your habits it's not just your habit's that change, your brain and your arousal also change. So it's not surprising that it takes a number of weeks to do that and the studies that have been done for 20 years for some reason six weeks has turned out to be a number that keeps coming up. And typically probably because the 30 day number had been used in drug studies. So the question was if you kept going could you still see an improvement with behavioral therapy just a little longer, two more weeks.

Patti Varley: So, with that said do you agree that if you're going to use pharmacologic intervention, that that being said that again this behavioral logic along with pharmacologic logic that ten days versus six weeks that the six weeks is a better treatment than the ten days?

Ralph Pascualy: Well, so that's two different questions, because one is how long do you want to have someone on a behavioral program to understand its efficacy. And that has nothing to do with whether you prescribe a medicine. So I think that yes, if you're looking at a behavioral program and you're doing something very simple and inexpensive, a sleep diary. Now granted there are people who have a hard time with that, I mean from a biological medical point of it they can't write or they can't see or they can't organize

themselves. We're not talking about that. From the pharmacological side that yes, because you are dealing with potentially a mood disorder, bipolar disorder, anxiety, psychosocial stress is quite severe a divorce, a death, any number of things. In general I think that the ten day is your first shot out of the gate is probably what would be limiting the physicians a lot who are thinking of all these things. So I'm – I do think that the first prescription should allow enough time for those practitioners, whatever they are to kind of sort this out and then at the end of that period then is where the issue is. Well did you in fact put them on behavioral therapy. That's where the restriction piece should kick in. That would make sense I think. And make a lot of people happy about the quality of their care, but also protect everybody else, and then over several years elevate all the practitioners that would like to provide consultation, would like to provide behavioral care.

Man: Well and, just real quickly [inaudible] with Siri. We can relax the ten in 30, we can go up to six weeks, but then it becomes medically necessary to continue chronic more than six weeks and then if you want to go more than six months then another sort of second tier or third tier level. Doing this on the fly versus doing it with some more due diligence, your recommendations.

Alvin Goo: Hi, it's Alvin. Because a majority of the cases that we're dealing with is going to be secondary insomnia, and probably cognitive behavior is recommended, are there going to be sufficient amount of therapists and reimbursement for that? Can we refer for cognitive behavior?

Man: Well I think first off, cognitive behavior is at the purview of a mental health specialist, psychologist, primary care doctor, or is it... And I think just simple sleep labs or simple sleep diaries. I think that's the domain of the primary care doc is to document has there been an adequate trial of taking away their caffeine, looking at their substances that they may be abusing, looking at their sleep hygiene, other things. And then after that, with that let's say six weeks, then is there a medically necessary reason to continue between six weeks and six months, yes or no. And then after that then that should be an ample opportunity to basically mix and match pharmacologic therapy as well as sleep hygiene which I don't think is the venue of a mental health specialist. At least that's how I look at it.

Man: Yea, I think that some of the trials using sleep hygiene have been based on community practitioners. Essentially it's a very careful checklist but a checklist that a primary care physician can master easily. And the American Academy of Family Practice has those checklists available on their website. And those, just those techniques alone are tremendously effective in people who have a secondary insomnia in terms of helping to do that. I think the cognitive behavioral part however, that's something

that if a person has not responded initially to this straightforward sleep hygiene controlled sleep diary, then cognitive behavioral therapy is very effective, but that does require someone who is – who knows something. And that's not likely to be, as I said it may not even be your sleep specialist in the sleep lab who can do that. So you do have to think about that.

Dan Lessler: Are there anybody else in terms of stakeholder input? I want to make sure. Carol.

Carol Cordy: This is Carol Cordy. Number six, is there more information on that? How – it says a separate class of hypnotic agents which we talked about this morning but, separate limits and authorization criteria, what's that about?

Man: Well you've taken it off the preferred drug list now and so we are [inaudible]. How you would look at Rozerem differently than other drugs.

Vyn Reese: This is Dr. Reese. I would be interested to hear what the sleep specialist says about that. What do you think Dr. Pascualy?

Ralph Pascualy: Well, I think it's correct. I think it is correct to treat it differently. It really is completely novel in that it works, a true mechanism of sleep. The other drugs, all of them, essentially sedate in some way and they don't affect the biological principle like Ramelteon does. Now, that said, the problem with Ramelteon it has. Well there's a couple of problems. The first problem is that it is ineffective as far as we know with the data we have for sleep maintenance. So this is not a drug that improves broken sleep. And if we look at the client population you're describing, broken disturbed sleep is actually the predominant problem. Probably two thirds of it. And the other third are mixed, they don't fall asleep and they also can't stay asleep. So Ramelteon would probably not be a drug that would be used commonly and here's why. Your ideal person is someone who has trouble falling asleep but once they fall asleep, they stay asleep. Okay, so that means that we're talking about a different population. Second of all, I think the initial pass is that patients who have taken sedating agents, who have been on sleeping pills, are not likely to respond to this drug. So you're looking at people – this drug is wonderful of a new onset of insomnia, a person who can't fall asleep, is probably naïve to sedation, and so this again is a perfect primary care environment where someone comes in and says no staying up really late working on projects I'm having trouble falling asleep and you say well let's start with this because this has no abuse liability that we know of, it has no – it's not a sedative. And it does not have any of these substance and addiction issues with it at all. So it probably should be in its own category. And we also know that in fact it may work better as the weeks go on. There's some new stuff coming out saying that perhaps because it works on the timing system of the brain, that it might in fact be

better at week five and six than it was at week one and two which is unusual because the other drugs, although they may sustain the benefit, there is some drop off in efficacy when you go out on the tail.

Bob Bray:

This is Dr. Bray. I just wanted to check with you on your impression in a couple of impressions that I have about that drug. In the citing here it talks about how there was a statistically significant difference in sleep latency, but it wasn't perceived by the patients. And what I recall from looking at that information was that sleep latency in the placebo group was 2+ hours and the sleep latency in the treated group was 1+ hours which if I'm trying to get to sleep and the drug helps me to get to sleep after an hour, that's probably a reason that I can't figure out whether there's a difference because it's too darn long. So the information I looked at said, gee, it's kind of like the cognitive benefit of cholinesterase inhibitors. You can measure it, but you can't detect it very well because it's not necessarily the thing that the patient's after and I suspect maybe that's one reason why the benzo treated patients don't like this drug because they're probably more likely to have dramatically shortened their sleep latency.

Man:

Right. So what you're saying, okay so there's a couple of things that you're saying. The efficacy is clear and on the one study you're talking about that very prolonged sleep latency. No, the studies on this drug did show that it was better than that, but what'll happen is that if someone starts to use Ramelteon and they're using it on a population that has a chronic insomnia, they will very soon become discouraged with the drug. It won't work is my point. So I'm saying that I think Ramelteon is a great drug I think in the right population it has a lot of promise, but I don't see that drug becoming a drug of abuse or a drug that people will stay on. In other words there is – there aren't other factors that would encourage someone to use that drug. And there's no factor in the drug itself meaning any withdrawal from it like a benzo. Essentially if it's not working it'll feel like I'm not getting any sedation, I don't feel anything, and I'm also not falling asleep. So I think they would just quit. And that's my experience is patients will come back and say, you know that didn't work. I need something else, I've got my wife's Ambien and that knocks me out.

Dan Lessler:

Other comments or observations? So my sense is as we've been discussing here what the committee might feel most comfortable with. It sounds like there's general support for the recommendation but that there would also be a desire to change the limit in the first 30 days to 30 in the first 30 days with the option of getting ten on a subsequent. So we cover the first six weeks, consistent with the discussion. Is that true? Is there anybody who feels strongly otherwise in terms of this recommendation with that modification? The 30 for the first 30 days.

Jason Iltz: This is Jason. I guess the only question I would have is isn't that sort of what the recommendation says already? That they will authorize a one time?

Dan Lessler: Right, for special circumstances. That will require a PA though.

Jason Iltz: So what we're really talking about is easing the restriction within the first fill with no authorization.

Dan Lessler: Right.

Jason Iltz: So I guess the question I would have then is how do we ensure that it happens in the groups that you folks kind of labeled and described, that it's being used in that particular instance without the authorization. My sense is that not every patient.

Dan Lessler: I don't think there'd be – I don't think there'd be any way to do that. I mean it sort of would be a. We're trying to put in the flexibility and I mean at some point we have to allow clinician judgment.

Jason Iltz: And I guess that's my concern because it seems to be the reverse of what, in my mind should happen for the majority of people. I think you should be more restrictive upfront and then show if there's a need, loosen the restriction, as opposed to being less restrictive upfront and then going oh by the way for the second month you can only have ten.

Ralph Pascualy: I think that the clinical logic is the other way. I think that for the provider group, it is highly likely that they will find ten problematic in terms of even scheduling a patient to get back in. So what you end up is a patient who's doing well for ten days and then doesn't sleep for a week before they can get back. So I think from a clinical perspective it makes a lot of sense to allow that first 30 days. And that gives with the next ten the practitioner has time to bring that patient back once or twice. And at that point they should be able to go for an authorization or to take whatever steps are required if they want to extend it. I think it'll make the practitioners very happy to have that flexibility. I think the quality for the patients – because I've had patients come back and say well am I only supposed to sleep ten days a month? And I think that if you want to get the quality up on that first piece in the evaluation do that and then get the quality on the second piece by then restricting it and allowing other specialists to help with the evaluation and the care. I have to excuse myself, I'm sorry, I appreciate being invited. I have a three o'clock I have to get back.

Man: Could I make a recommendation. I mean just sort of on process. We could certainly do this on just new starts and then if people and so the way this

could work would be there's 30 days authorization for any new starts. And then to get to the six weeks if they want to do ten in 30 they can do that without an issue. We could do that. Then anybody that wants to go over essentially 30 days or six weeks, that requires medical necessity, and then we could say for anxiety, [inaudible], PTS, all these other aspects, we could authorize. But then at six months then you have to go see – and we'll work with the community on what would be an appropriate level of second review for six months or greater.

Vyn Reese: This is Dr. Reese. I think that's a great plan. I think that would really meet the clinicians' needs and it would be a lot – I think what Dr. Pascualy said is the way clinicians practice. If they're treating secondary insomnia which is the, that's the reason most of the time these drugs are used. And the newer drugs are safer, less addiction potential, and you're not going to use them long in patients who have secondary insomnia. It becomes a big issue when the patient's coming back again and again then you need to get a sleep specialist and you need to figure out what to do with that patient. I think it's a more sensible way – it's the way we practice.

Alvin Goo: This is Alvin. And again I think we have to remind ourselves that we have no data on these agents for secondary insomnia. And we really don't have any good data as far as abuse potential. I wish he was still here but Dr. Pascualy mentioned those few little studies in addicted patients well the agent that they used was Triazolam and we know we wouldn't do that – I mean that's not a fair comparison. And so we have no long term data to suggest, although I think it's less addictive and I hope it's safe, we don't have any data to support that.

Patti Varley: This is Patti Varley and to me, again I wish he was still.

Patti Varley: Physiological addiction but also psychological addiction which is why the behavior thing, because they are going to feel the sedative or the sedative quality with that where they won't with Rozerem. But I think that that six weeks gives you an opportunity to have them reset their – and that's when you talk about behavioral intervention with sleep is it's a changing of the pattern of your sleep. And I am concerned that the ten days, ten days, ten days it just makes them dependent on the pill as opposed to really being able to reset themselves.

Man: I just wanted to add a clarification on that. So are you saying that – let's say we authorize somebody for 30 days, no restrictions, they get an extra ten in 30, but the issue is the ongoing ten in 30 for people who don't want to – does that stay. And that's part of the nuance of how do you.

Patti Varley: I thought it's a one time thing and then you'd have to get. My understanding from what you said was the initial prescription for 30 days

with ten for the second month was automatic, no pre-authorization. If after that six weeks that patient by the clinicians assessment still required to stay on that med the prior authorization would need to be requested at that time. Is that correct?

Man: For more than ten in 30.

Man: And that was my question. Does ten in 30 get you anything and that would just make it six weeks, yes or no, but then the nuance as you said the unintended consequence. If it's no then do we go to Seroquel, Neurontin, benzodiazepine.

Janet Kelly: This is Janet Kelly. This is not my area of practice but I think that a lot of people get these medications because there's a situational thing. They've been traveling or whatnot. They don't need 30 days. And I think that the ten is an appropriate piece for that. There are a lot of people that have other more – disease states but I think that a fair number of these are because we're going across country and the sleep gets all mucked up and ten days is more than adequate to get them back on track for that.

Dan Lessler: But just because you can prescribe 30 doesn't mean you will prescribe 30.

Janet Kelly: Well, the data shows that because we can prescribe ten we prescribe ten.

Dan Lessler: Carol do you have a comment?

Carol Cordy: I wanted also to – and Jeff you said this would happen – make sure that when this six month time arrives that there really will be access for these patients. And I really question that if it's more than just seeing a person that helps with sleep hygiene versus giving CBT which I think would be impossible. But also I think there are those cases where patients – we often, we seldom check for functionality when we make these decisions. If this patient is more functional on their sleeping ten nights a month or getting ten a month, is there some way to say well they don't need to go through all this stuff, they don't need to try and get CBT or whatever. They're functioning. So why not say functionality is something that we're measuring as well? So you can go beyond the six months, you're functioning it's fine, just keep taking your...

Vyn Reese: This is Dr. Reese. I just wanted to say one thing about the ten and I think it's totally appropriate to give ten to somebody who's just come back and has a sleep disturbance from traveling through several time zones who suddenly had a death in the family, something that's big and maybe short lived. Something that's acute trauma. And I don't think everybody's going to prescribe 30 just because you can. I think ten is certainly reasonable for some people with acute self-limited event. And so I don't think that

everybody will automatically prescribe 30 just – I know I won't. I can't imagine doing that. If I think ten is going to suffice I'll prescribe ten. I'm not that manipulative.

Patti Varley: This is Patti Varley and I guess my question would be playing the devil's advocate here. So if most people with prudent judgment in those situations of travel acute insomnia due to travel or a traumatic loss or something didn't write ten, and for that one time wrote 30 with ten refill, what would be the horrible negative consequence of that? Because they're not going to keep refilling it. They're just going to do it that one time anyway. I'm just, again I'm playing devil's – what would be the horror of that versus to me, the fact of either writing double the dose and having people cut it in half or using Seroquel when you have somebody who truly has a secondary insomnia that needs to retrain that needs that six weeks.

Steve Hammond: This is Steve Hammond. I think we allow that that might happen if we just allowed new starts to get 30. But sometimes people might get more than they need. I just also wanted to remind you that one of the recommendations from the 1983 consensus conference was that for long term use for chronic insomnia, one recommended strategy was intermittent use. Perhaps one night in three. And so that is another recognized use of smaller amounts of these agents.

Vyn Reese: This is Dr. Reese. I think that's fine. I think if you wanted to do a ten in 30 after that that's fine. I think having 30 the first month would give us flexibility. And maybe we only prescribe ten the first month. If it's not, 30 isn't needed. And I think it's pretty rigid right now. And I would think that that's the way I would like to see it is to have that first month be a little more loose. We can tighten down then if it becomes a chronic problem. And plus people aren't – can they go to different doctors and get 30? You're going to see that in the claims data. Right? If they're going to go to three different doctors and get 30, it's going to pop up as red flags. If they're abusing it for some reason.

Dan Lessler: Actually that would be a good leading indicator of the extent to which this is an abusable drug.

Man: But my understanding is we can track new starts per client.

Siri Childs: The only reason that we would not be able to track it is if they paid cash. And they do do that.

Dan Lessler: I think we've pretty much covered this at this point and what I was going to say is it sounds like we're sort of back to where we started with good discussion and additional insight but that is that there's a general consensus that is in agreement with the recommendation assuming that

there's a change such that in the first 30 days that would be dispensing of 30 pills. And I guess what I would ask at this point is maybe I can actually take the chair's prerogative and make that as a motion that in terms of the support of the DUR for this policy with that one change. And is there a second? Alright, so that's second. And at this point all those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So I think there's – it's a good discussion and some modification and an endorsement.

Woman: Somebody was going to say something about the Rozerem or.

Man: Just one clarification, if any of the members want to inform Steve or Siri as to the indications for that 30 days to six months, we would certainly send your comments, what would be good indications for the prior authorization so you can inform us better.

Dan Lessler: I think Jeff as well just in terms of any kind of drug utilization review that you could possibly be looking at – trying to get a handle on what other medicines people are prescribing in place of these. I think just – I know education alone is not very effective with the medical community but to the extent that maybe there are opportunities to use more of an academic detailing kind of approach because I think the other thing that's come out of this conversation is just really the need to educate the medical community about best practice in terms of the use of these medicines.

Siri Childs: This is Siri again and I'd like to get permission from the board to delay any type of a review like that until we're well into our new computer system that tracks diagnosis because we don't have diagnosis information now. It'll be whenever we implement, and maybe six months or so after that. So we're looking maybe a year from now.

Man: I would look back at your own agencies though. The first time I ever – I mean I grew up in North Bend and so we're sort of out in the sticks and over the last six months to a year we've seen an increase in people that are wanting to stay locally for their mental health care because they've been encouraged by agencies in the city to sort of do that and not come in as often maybe because of hardship or... And the first time I ever ran across anybody switching to Seroquel to use for a sleeper at bedtime they were doing that at Seattle Mental Health. Because they didn't have any resources for their Trazodone didn't work and they only can get ten of this type of medication. And they were getting Seroquel samples from Seattle Mental Health to help them sleep at night.

Man: Were you all interested in hearing what we're thinking about Rozerem.

Dan Lessler: Yea that would be great.

Man: Again, just for clarity, the criteria and restrictions we were just discussing would apply to the sedative hypnotics and not to Rozerem. So Rozerem's off the PDL and we were contemplating having a prior authorization process which would initially be expedited prior authorization questions that the pharmacist can answer at the point of presenting the prescription. And the questions we were wanting to ask were does the patient have difficulty falling asleep, does the patient have trouble staying asleep, and if it were yes to that then Rozerem would not be appropriate. The patient must not be on stimulant medications and the patient has not tried and failed other sedative hypnotic medications within the past year. And that we would ask the pharmacists to provide, at the time of dispensing the initial prescription, educational materials on sleep hygiene and a sleep diary. If those criteria were met, we would authorize three months, 90 days of Rozerem. After 90 days if it were requested again we would require prior authorization and what Jeff calls medical necessity. And we would ask further have underlying disease contributors been evaluated and treated and is this being given in combination with sleep hygiene and some sort of attempt at cognitive behavioral therapy. And then if those were affirmative, we would authorize another three months. And then after six months if it were still requested that would be when we would require sleep specialty consultation or allow it if it were being prescribed by a sleep specialist.

Patti Varley: This is Patti Varley and I'm just curious as to the specific question about stimulants only since other medications can influence it and it's a well known fact that sleep onset problems, even before the use of stimulant is a primary problem of the ADHD population. So I'm curious how that came up as disallowing it.

Man: Well that was our first pass at it, we thought that that would be.

Woman: You're being prejudiced against...

Carol Cordy: This is Carol. I have another question on that. I wasn't clear on the when you said they have not tried and failed another or.

Man: Well again that speaks to what Dr. Pascualy pointed out is that those who have tried and failed other sedative hypnotics are not likely to respond to Ramelteon. We decided to make it within the past year. If they tried it maybe five years ago, that wouldn't disqualify. Again this was a first pass, we came up...

Carol Cordy: And so if they've tried and failed something else within the last year, they do not get the Rozerem.

Man: That's what we're thinking.

Man: We'll have to work on these. And this is because of your decision to take it off the preferred these were at least a first pass.

Dan Lessler: It seems like a very good first pass to me in terms of the clinical rationale behind it. From a practical standpoint I sort of wonder with the criterion that a person cannot have tried and failed an alternative which would be benzo like. Because I think in fact what's going to happen is that people are going to try those and if a patient fails then they're going to say why don't I try this. And maybe that's an opportunity to educate them at that point, but I think that's where, that's sort of where it's going to go.

Patti Varley: This is Patti Varley. I agree with you but I think that's bad practice. I mean what we're saying is that because the way we've done pharmacology in the past which as you try the most familiar agent, when that doesn't work and fails you try the new one. But the indication for this one is different. And I think if we allow that to happen, then we're reinforcing bad clinical judgment and information. So I don't have a problem with us restricting it to the population where clinically it is found to be efficacious.

Dan Lessler: The point is well taken.

Vyn Reese: This is Dr. Reese. But I think that the average doctor is going to reach for the more familiar drug first. And then they may have spoiled this poor person with primary insomnia who has trouble falling asleep and they sleep well once they get there and they give them Zolpidem or something and then bingo they can't use Rozerem which they should've been prescribed in the first place. That's the ridiculous thing about it. I think it's a very good stab at it. I think it has all the indications he said, I agree that maybe somebody who's been on methylphenidate for ADD for some time that they shouldn't be not be able to use this. They also have a problem with insomnia too and I don't know. I mean I don't know how you're going to tease that group out. That's a little bit tricky. I think it's an excellent start and I think it covers most of the issues that we discussed here today and what Dr. Pascualy said. So I think it's commendable.

Man: They can use Clonidine if they're on methyl stimulants, Clonidine.

Jason Iltz: This is Jason. So I'm a little naïve to the point of sales systems. So can you walk me through that process in terms of, I'm just trying to – from the pharmacist standpoint I'm trying to think of how this would work. Is this

something that pops up on the screen, is this a pre-printed questionnaire, have we even gotten to that point?

Siri Childs: This is Siri again. We have not gotten to that point obviously. Right now Rozerem has a ten for 30 limit on it just like all the other drugs. So if we are able to implement this, we'll be implementing in October. If not, we will be frozen out of our point of sales system for probably the next quarter. And so we may be talking about sometime in April before we could actually implement this because of our point of sale transition that's going on. But it would be EPA criteria that have been pre-published. And we always tried – the idea with our criteria, especially our EPA criteria is that it's a form of education. And you know we believe that we really do teach through the EPA criteria that we have.

Alvin Goo: Hi it's Alvin. I think the EPA criteria should be as simple as possible and I think you listed five questions the pharmacists have to ask. That's quite a bit. Usually it's one or two questions. And so I think you're right, it's an opportunity to educate and the pharmacist should educate, but I'm not too sure how it's going to go over and I think somebody mentioned education. I think there needs to be a very nice, simple, one page EPA criteria that you send to all the providers too that they should be giving diaries and doing the sleep hygiene too. The pharmacists can also do that but I don't know, I would caution and having the pharmacist ask five questions I think that's a little bit too much and I'm wondering if you could pare it down a little bit more.

Dan Lessler: How about you can ask the odd questions one month and the even questions another month?

Man: Based on their license plate?

Woman: What would happen if you asked one question was do you have trouble falling asleep. If the patient says no then you say, "I'm sorry, you can't have this drug. Your doctor doesn't know what they're doing."

Man: And that makes sense, if there was maybe there had to be a certain answer to question one before you answered question two. And if you got to that point there's a stop at some point. It might be just as simple as that. My concern is that we've all filled out that form that there's 20 questions and it says if you answer yes to any of these you can't – you're going to be denied. Well, how many people even really read the thing. We just all check no, no, no, no. So my concern is that their pattern will develop and the questions won't even be asked and we do a disservice to the patient in terms of education. And we all know that it's left, right, left, left, right on the little check boxes and it goes through. So the education piece is vital and the information that you talked about in terms of diaries and those

things, we have to make sure those are available to everyone and it's not just stuffed in the bag with the prescription that got filled. There's got to be some time taken to explain how to use the diaries and the appropriate tools that are in there.

Woman: And they've got to be in 20 languages.

Man: So I think what Siri and Steve and [inaudible] were trying to do is anticipate what your motion would be this morning. So we really – this is a first pass. I think taking all of this dialogue in, we can make it simple, we can make it work within the POS system and educating and we'll take that back. Obviously we'll be held accountable because you'll see it.

Dan Lessler: Right, okay.

Bob Bray: Bob Bray. The other thing I think that from how you initially conceive this to then the discussion that's taken place that's different is what constitutes a consultation with a sleep specialist. Because I think initially the concept was sleep labs. But Dr. Pascualy's comments were about folks who know about cognitive behavioral therapy and those patients that it's appropriate and other folks that may need to be involved besides just a sleep lab. And I think that in order for these kind of things to work, that's the other thing with the provider education that has to be there is – who, tell me who, what's their phone number and all that kind of stuff would be real important to make that work.

Man: And we have based on his recommendations five levels of providers and we can seek out those and put those actually on a web based and put that as part of the education. Where we draw the line will be something that we'll let everybody know.

Siri Childs: Actually, this is Siri again. I'd like to ask a question. MaryAnne Lindeblad, our director of the pharmacy program has said that if we are going to require a consultation then HRSA is going to make the arrangements for the doctors. Is that something favorable that you would support?

Dan Lessler: I'm not sure what you mean by make the arrangement for the doctor.

Siri Childs: Well she believes that if we're going to require a consultation that we should go through the hoops and not put all of you through the hoops. And so we would look with the geographical area of the patient and we would arrange with your office and the consultation, the referral.

Woman: That would be unbelievable.

Siri Childs: Unbelievably bad?

Vyn Reese: This is Dr. Reese. I'm all in favor of that, but make sure we know that there are patients being [inaudible]. It would be one less form we didn't have to sign, it would be good.

Siri Childs: But you see what her plan is is that she believes that the burden should be on us if we require it.

Woman: I totally agree and if Dr. Pascualy's statistics were right and he was saying 50% of people with insomnia – I don't know what kind he was referring to, do have sleep apnea and they'd also have to get the CPAP and go through that whole process too, and that would be wonderful if somebody else besides our clinics.

Dan Lessler: But hopefully, sleep apnea, we're not going to be treating it with sedative hypnotics. They're liable to die by the time they got to the sleep specialist. I mean they may get there in a box.

Woman: Sure, but I think a lot of those people out there treated do have sleep apnea and they're not recognizing it.

Man: So with your approval I think we have enough that we can build a program that on the front end is more flexible but on the back end makes sure that we provide customer service in medical necessity.

Siri Childs: One more thing, this is Siri again. And I know I heard from our pharmacists that they didn't like the five questions for EPA, but you wouldn't rather have PA, right? Okay.

Dan Lessler: So is there any other business at this point or you've got what you need from us? So I think then we can adjourn.