

**Washington State Pharmacy and Therapeutics Committee  
June 15, 2016**

Michael Johnson: Good morning. We're going to go ahead and convene the Washington State Pharmacy and Therapeutics Committee. I would like to welcome all of you here attending. We'll start with identifying ourselves. We'll start with Chuck and go around.

Chuck Agte: Chuck Agte with Washington Medicaid.

Allison Campbell: Allison Campbell, Washington Medicaid.

Christy Pham: Christy Pham with Labor and Industries.

Jaymie Mai: Jaymie Mai with Labor and Industries.

Mason Bowman: Mason Bowman, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Dale Sanderson: Dale Sanderson, committee member.

Michael Johnson: Michael Johnson, committee member.

Eric Harvey: Eric Harvey, committee member.

Christine Klingel: Christine Klingel, committee member.

Susan Rowe: Susan Rowe, committee member.

Po Karczewski: Po Karczewski, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Michael Johnson: I think that's the introductions. I'd like to remind everybody to introduce themselves when they start talking. So I think we have Marian on the phone. Is that...

Marian McDonagh: Yes, I'm here.

Michael Johnson: Okay. If you're ready to start I think we're ready.

Marian McDonagh: Great. Okay. Good morning, everyone. All right. So this morning I'm going to tell you about our report on newer oral anticoagulant drugs and this class does have... goes by a few different names. Novel oral anticoagulant drugs and also direct-acting oral anticoagulant drugs. So we'll be using the NOAD abbreviations.

[loud beeping]

Shall I go on?

Donna Sullivan: Yes.

Marian McDonagh: Okay. So let's go to slide 2. So slide 2 goes over our key questions, which are a little bit different format for this report. So here we have three key questions that are... each of them is about the benefits and harms in a specific population and then the fourth key question is looking at subgroups of the populations to see if any of the benefits or harms vary by subpopulation characteristics. Let's go to the next slide, slide 3.

So these are the populations that were included in the report. Treatment for a DVT or PE and then the second population, the second key question is for extended treatment to prevent recurrence. And then the third is prophylaxis for patients with non-valvular or atrial fibrillation or patients undergoing orthopedic surgery. Let's go to slide 4.

So these are the drugs that are included in the report. Dabigatran, which is available at a 75 and 150 mg doses, apixaban 2.5 and 5 mg, rivaroxaban at 10 mg, 15 and 20 mg doses, and then...

[loud beeping]

All right. Can you hear me all right? It doesn't sound very good on my end.

Woman: It's the microphone.

Maria McDonagh: All right. Tell me to stop if it's too difficult to hear me. So then edoxaban at 30 and 60 mg.

[loud beeping]

So I want to note that for some of these trials...

Woman: Hang on a minute.

Maria McDonagh: Okay. So for some of the trials dosing included doses that are lower than what are currently FDA approved for some of the indications. Some of our trials also included these lower doses and are now approved for patients with renal dysfunction. So it can be a little confusing because the original trials included those lower doses for patients who did not have renal dysfunction. So we try to make that clear where we can. So the next slide, slide 5.

This is our search strategies and I think the important thing to point is that these ended in September 2015. So if we go to slide 6 then.

So overall we included 53 studies and I think the important thing here is that we found no head-to-head trials for any of the included populations. So all of the evidence in this report is indirect meaning that the comparisons were of each of the [inaudible] drugs to warfarin or low molecular weight heparin or some other comparator that is not one of the other NOACs. So we probably included published network meta-analyses, so indirect statistical comparisons

of the drugs. If we found them and if they were good quality. If we did not find a network analysis we conducted our own indirect comparisons, network analyses and in one case the updated one where there was some new evidence. Another thing that I want to tell you at this point is about the major bleeding. It is the primary adverse event outcome that we are reporting today in the slide set. I think it's important to note that for this outcome the definition of the outcome has been very consistently used across all of the studies based on a 2005 International Society on Thrombosis and Hemostasis definition. So that's just one thing to be sure that all of the studies reporting on major bleeding used the same definition. So let's go to slide 7.

So this is key question 1. So the results... looking at the results for treating VTE in adults. All right.

So on slide 8 are the results. So here we did conduct a network meta-analysis of six trials. Again, these are indirect comparisons for all of the drugs. So this did include all of the drugs at approved doses for treating VTE and we found no significant differences in the VTE outcomes between the drugs. We considered this evidence to be insufficient; however, to draw conclusions partially because it is based on the indirect comparison. It's very difficult with an indirect comparison where there are absolutely no head-to-head trials to determine the consistency across the findings. And then also the point estimates here are very, very... the confidence intervals are wide so they are imprecise. So there is some hesitancy there for us to give this any kind of confidence in that finding. So for major bleeding we found that apixaban had a lower risk of major bleeding than edoxaban or dabigatran, but again the confidence intervals are wide. But we did rate this as low strength evidence. Additionally, we found some observational study that dabigatran and rivaroxaban did not differ compared to warfarin for GI bleeding, in particular, which was another outcome we were looking for, but we didn't find it reported very often. All right. So let's move on to the next key question. The next slide, slide 9.

This is looking at extended treatments to prevent recurrence of patients who had a DVT or PE. So let's go to the next slide.

This is slide 10, looking at the results. So here we based these results on a published network meta-analysis of three trials. They were placebo-controlled trials of apixaban, rivaroxaban and dabigatran. There were no trials of edoxaban for the extended treatment. The treatment lasted in addition to the usual treatment for DVT PE it treated an additional 6 to 12 months in these trials. This study found no statistically significant difference for VTE recurrence or all-cause mortality and similarly no difference in major bleeding. Again, we find the evidence here to be insufficient for very similar reasons as before that it's an indirect comparison, we can't evaluate the consistency and the precision is very low. Additionally, I do want to note that there was one trial comparing dabigatran to warfarin, not to placebo for extended treatment. Here there was, again, no difference between dabigatran and warfarin for the outcomes of VTE, DVT or PE mortality. Okay. So this review included a bleeding outcome that we did not include and it was clinically relevant non-major bleeding. So this is defined as overt bleeding, not meeting the criteria for major bleeding, but requiring medical intervention, unscheduled contact with a physician, interruption of or discontinuation of study or discomfort or impairment of activities of daily living. So we didn't include this as one of our primary adverse event outcomes because we think the major bleeding outcome is more consistently defined and more important, but in this case this review did find lower risk for this outcome with apixaban at the lower dose than compared to rivaroxaban or dabigatran. And the 2.5 mg dose is currently the FDA approved dose for extended treatment. We did give this a low strength of evidence.

So if we move to the next slide then this is the key question on looking at prophylaxis, preventing VTEs in patients with atrial fibrillation or patients who are undergoing orthopedic surgery. So we'll go to slide 12.

We'll start with the evidence on atrial fibrillation. There is quite a bit of evidence here. So we did find a published network meta-analysis

of these studies, but there were some newer studies that were not included in the network analysis so we updated that analysis and in the end we included 10 randomized controlled trials. Each of these were comparing the NOAC drug to warfarin. So here the range of duration of the studies was 3 to 24 months and some of the smaller, newer studies were really focused on reporting on bleeding outcomes and not benefit outcomes. There was an additional randomized controlled trial, apixaban versus aspirin, not warfarin, in patients who were unable or unwilling to take warfarin, which was stopped early for benefit. So I'll not that all of the findings here are low strength of evidence and again with indirect comparisons like this head-to-head comparisons can come up with different findings. So there was no difference in all-cause mortality between the drugs found in our analysis. That's not shown on the slide. So we'll start instead with the primary outcome measure for all of the trials that were looking at benefits. So all of the primary trials for each drug, which was a composite outcome of any stroke so ischemic or hemorrhagic or systemic embolism. So these were the primary outcome measures in the larger trials. So in preventing stroke or [inaudible] events in patients with non-valvular atrial fibrillation there are mainly no significant differences between the drugs particularly when we are looking at the doses that are commonly used in the U.S. now and in patients with normal renal function. So you can see on the slide that the significant... one of the significant differences we point out in this analysis was that edoxaban 30 mg had a greater risk of this composite outcome than apixaban 5 mg, rivaroxaban 15 mg, and dabigatran 150 mg. But the edoxaban 30 mg is not the approved dose for atrial fibrillation at this time. And the second finding, for this outcome was that rivaroxaban at 20 mg, which is the standard dose, had a higher risk for the stroke or embolic systemic embolism outcome than dabigatran 150 mg. We compared this... our finding to the analysis in the published network analysis and it was very similar. They also broke it down further and found that there was no difference between these two drugs, rivaroxaban and dabigatran for ischemic stroke, but that rivaroxaban had an increased risk for hemorrhagic stroke. And all the other comparisons between the drugs were not significant for this outcome. However, we did conduct a sensitivity analysis of the rivaroxaban data because the large trial, the Rocket AF

trial of rivaroxaban, while the inclusion criteria were quite similar across the studies, the population ended up being in enrolled in Rocket AF had a higher baseline risk for this outcome than the other trials, but in particular the main trial of dabigatran, the Rely trial. So we did some sensitivity analyses removing the Rocket AF study from the analysis as being different and the difference between rivaroxaban and dabigatran becomes not statistically significant in that sensitivity analysis. So we don't put confidence in the finding of the difference then. So for the outcome of myocardial infarction although subgroup analyses of the primary large trial of dabigatran, that's the Rely trial found the risk to be not statistically significant compared to warfarin. Our network meta-analysis found that dabigatran did have a significantly increased risk of MI compared with apixaban or rivaroxaban and that edoxaban 60 mg... or compared to edoxaban 60 mg when compared to the dabigatran 150 mg. We also found that the lower dose of edoxaban had a higher risk compared with the approved dose of edoxaban, but all other comparisons were not statistically significant and sensitivity analyses did not affect these findings. So looking at major bleeding outcome, the key findings here are that apixaban at the 5 mg dose has a lower risk than dabigatran 150 mg or rivaroxaban 20 mg. And the edoxaban has a lower risk at 60 mg... 60 mg has a lower risk than rivaroxaban at 20 mg. The other significant findings are less generalizable because they do involve lower than typical doses of edoxaban and dabigatran. Now, again here the primary trial, the large primary trial of rivaroxaban, Rocket AF there's another issue here that we had to explore with sensitivity analyses for the bleeding outcome as well. That study used a point of care INR testing device to adjust the warfarin doses in the control group and that device has since been withdrawn from the market due to concerns over inaccuracy or at least inconsistent results. So there is concerns that the warfarin was not being adjusted correctly in the control group that might affect the findings. So we conducted two sensitivity analyses of the rivaroxaban data here on major bleeding to assess potential impacts and the results for apixaban 5 mg and edoxaban changed slightly in the direction of smaller differences between the drugs, but the results still show a lower risk of major bleeding with apixaban or edoxaban than with dabigatran 150 or

rivaroxaban 20 mg and no other changes in statistical significance were found.

Oh, I'm sorry, we should have gone to slide 13 for the major bleeding outcome. So why don't we go to that for a moment and you can look at the findings on the major bleeding.

Woman: We're on that slide.

Maria McDonagh: Okay. Great. Thank you for keeping up with me there. Sorry. So that's the evidence for atrial fibrillation and now we'll move on to the next slide, which is orthopedic surgery.

So prophylaxis in patients undergoing knee and hip surgery primarily. So here we conducted a network meta-analysis of 21 trials without almost 40,000 patients and compared a NOAC fit primarily to [inaudible], but not exclusively. The evidence for all-cause mortality and symptomatic DVT was unfortunately insufficient for all comparisons. So it was not listed on the slide. The most common outcome reported in 19 of 21 trials was a composite outcome of any DVT, nonfatal symptomatic or objectively confirmed PE, and all-cause mortality. So a composite of all of those. So for this outcome we evaluated the evidence separately between hip and knee patients because the baseline risk between those populations is different. But overall the findings are very similar when you look at the relative risks. So apixaban had lower risk than dabigatran 150 and rivaroxaban had a lower risk than dabigatran at either dose studied. So looking at major bleeding then the only statistically significant finding was in patients undergoing knee surgery where apixaban at the 2.5 mg dose had a lower risk than rivaroxaban at the 10 mg dose. So let's go to slide 15, which is key question 4.

This is looking at all of the possible permutations of subpopulations. So let's go to slide 16.

This is a summary of the evidence. Now here we were limited to looking at subgroup analyses and post hoc analyses and a couple of observational studies. We did have over 30 subgroup analyses from

these very large trials to look at to try to address this question. So in general we see that the findings in the subgroups based on age, sex, or race and ethnicity in those subpopulations the findings are very similar to the overall study findings. So no differences were clear from those analyses. However, in patients who have diabetes, patients who are dialysis, patients who are concomitantly taking an anti-arrhythmic or anti-platelet drug with their NOAC therapy, the subgroup analyses indicate there is a need for further study—that there may be some issues there. Let's go to slide 17.

This is the summary. A quick summary of the evidence. So overall there's no direct comparisons, no head-to-head comparisons of the NOAC for any of the populations. So we're limited to indirect comparisons and again just a warning that we need to interpret those with caution and in this case because there are... network analyses were based only on indirect comparisons, there were no head-to-heads to add to the network we would only rating this... any of the evidence no higher than low strength. So in atrial fibrillation when we consider the FDA approved doses the baseline... and baseline risk issues, there's no real differences found between the drugs in the primary outcome of stroke or systemic embolism. And low strength evidence finds... suggests that apixaban or rivaroxaban have a lower risk of VTE and mortality in orthopedic patients compared with dabigatran and the differences in their effectiveness are not found between the drugs in either initial treatment for VTE or extended treatment of VTE. If we got to the next slide then.

Looking at the harms outcomes of bleeding, slide 18. Apixaban, edoxaban and dabigatran, particularly at lower doses have lower rates of major bleeding across the populations. And evidence on other comparisons or outcomes was insufficient to draw conclusions. That's the summary. If there are any questions I'd be glad to try to answer those.

Michael Johnson:

Thank you, Marian. Are there any questions from the committee members?

Susan Rowe: Marian, when there were the direct comparisons with warfarin that didn't show a difference, was the time and therapeutic range for warfarin 66% or was it different than that?

Marian McDonagh: That's a good question. I don't know the number... the percentage of the time they were in the correct range for each population. Yeah, sorry, Susan I can't answer that.

Susan Rowe: In the DPT PE studies there are some of the agents that require a low molecular weight heparin lead in or prior therapy and some that can be started kind of [inaudible]. Did this address that at all?

Marian McDonagh: Well, they wouldn't have addressed in the... I mean I guess I'm not sure. Maybe I'm not sure I follow your question. So I guess maybe the answer is no because the network would have simply incorporated however the drug was used in that early lead-in phase. So it wouldn't have been able to address differences based on that.

Susan Rowe: Okay. Thank you very much.

Michael Johnson: Any other questions? Okay. Thank you, Marian. You're welcome to stay on the line. I think we'll call for shareholder input next and I think we have six shareholders. The first up will be Chris Conner followed by Jason Talvera. We have three minutes. Go up to the podium at the front. Identify who you represent and we'll give you three minutes.

Chris Conner: Good morning. My name is Chris Conner. I'm with Bristol Myer Squibb and I'm here to ask that Eliquis be retained as a preferred drug on the Washington Medicaid PDL. Eliquis, as you heard, is indicated for a reduction in the risk of stroke and systemic embolism in patients with non-valvular AFib. It's indicated for the prophylaxis of DVT in patients undergoing hip or knee replacement surgery and it's also indicated for the active treatment of DVT and PE and in reducing the recurrence of the risk of DVT and PE.

Again, as you heard, I'm required to draw your attention to some important information in the black box warning for Eliquis.

Specifically, pre-mature discontinuation with Eliquis without coverage of another anticoagulant can increase the risk of stroke or thrombotic events. So if Eliquis is to be discontinued in any other setting but the setting of an active pathological bleed covered with another anticoagulant is strongly recommended.

In terms of adverse events the most common adverse events with Eliquis are related to bleeding. This bleeding can be serious or life threatening so it's important to keep that in mind. I have with me a copy of the package insert. So upon request I'd be happy to distribute or discuss with you further, again, upon request, in the interest of time I'm going to move on to say some things about our clinical trial.

In patients with non-valvular AFib we compared Eliquis with warfarin in the time to therapeutic range or time in therapeutic range the question came up, the median in that study was 66% and the mean was 62. In that particular trial Eliquis is unique across all the oral anticoagulants in that it showed not only a significant reduction in the risk of stroke or systemic embolism, but also a statistically significant reduction in the recurrence of major bleed. That again is our head-to-head trial versus warfarin. There are no head-to-head trials of Eliquis comparing Eliquis to the other newer oral anticoagulants, but as you heard, you know, there are meta-analysis, indirect treatment comparison analyses, there are even real-world observational studies looking at claims comparing all of these newer oral anticoagulants. Again, these are not head-to-head trials so keep that in mind.

I'd be more than happy to share what I've got with you on those data. Again, upon request. That's all I've got and again I'd just like to ask that Eliquis be retained as a preferred agent on the Washington Medicaid PDL.

Michael Johnson:

Thank you. Next up will be Jason Talavera followed by Mae Kwong.

Jason Talavera:

Dear esteemed colleagues, distinguished panel and committee members, I am Jason Talavera. I'm a physician, a cardiologist and a fellow of the American College of Cardiology and board certified in

cardiovascular diseases, echo, nuclear cardiology, cardiovascular CT, vascular ultrasound and internal medicine. I work at Western Washington Cardiology up in Everett, Washington and this is my first time at one of these meetings. I'm here really to advocate on behalf of my patients for access to the DOAC class. I was really impressed, Marian, with the analysis that you just went over. That was very, very comprehensive and really I commend you and your group on this.

Upon my review of the literature there's one in particular that stands out to me and that is apixaban. As mentioned, for the indication of non-valvular AFib. It was the only one to show superiority in terms of stroke, systemic embolism and the only one to show superiority in terms of bleeding. For the indication of PE DVT it was also the only one to show superiority in terms of bleeding.

I think our number one thing as clinicians is do no harm. And this whole class of medicines is an anticoagulant and the whole risk is bleeding. So really if you're reducing stroke and you're reducing bleeding you get the benefits of both. So for that reason I'd like to suggest that Eliquis be... I'm sorry, apixaban be retained as one of the preferred on the Medicaid formulary. And as you know my patient population up in Everett, the salaries are much lower than here in the major Seattle area and so this is... I appreciate having access to something other than Coumadin.

Michael Johnson:

Thank you. Any questions? All right. Mae Kwong is next followed by Steve Hall.

Mae Kwong:

Good morning. My name is Mae Kwong. I'm the [inaudible] liaison for Janssen and I would like to thank the members of the committee this morning for the opportunity to speak today on behalf of Xarelto, otherwise known as rivaroxaban. Based on data that's been presented I just wanted to clarify that the INR device that was presented by Marian, the sensitivity analysis have been done by the European Medicines Agency. The data has been published in New England Journal of Medicine by Duke Clinical Research and all analysis have not changed the label. The INR device was only in specific populations and the data is confirmed based on those sensitivity

analysis. Just to give you some background looking at the Washington State Department of Health, strokes are the leading cause of death... strokes and cardiovascular death are the leading cause of death here in Washington and in fact more patients die from strokes in the Northwest over any other part of the U.S. This underscores the need to add rivaroxaban to the PDL. As was stated it enrolled the highest risk patient population across the pivotal non-valvular AFib studies with a CHAD score of 3.5, which also contributes to potential for increase in bleeding.

Given the information with prior strokes and non-valvular AFib, as well as our post marketing data looking at both ischemic stroke rates, as well as intracranial hemorrhages the data continues to stand... to confirm the Pivotal studies both in the real world setting. Xarelto is a once daily oral direct factor 10A inhibitor that has the longest approval for all six indications for non-valvular AFib stroke prevention for orthopedic prophylaxis, as well as DVT and PE treatment, as well as extension of prophylaxis in those patients who are at risk for recurrence. So again I would like to request that Xarelto be considered for addition to the PDL and we have incorporated different sub groups looking across the continuum in patients with prior strokes, patients on hemodialysis. That information now is incorporated into our label with a dosing recommendation there. We've looked across different renal function impairment from severe renal impairment to normal renal impairment and again the data stands and it is confirmed.

Xarelto now has a start-up pack for VTE treatment which contributes to patients being able to have access to DVT and PE treatment for the first month of therapy, which is the timeframe in which the patients are at greatest risk of recurrence of their DVT and PE.

Looking at some claims analysis versus standard of care rivaroxaban continues to show efficacy and safety and shows length of stay decreases, as well as decreases in hospitalizations.

The real world safety, efficacy...

Michael Johnson: I have to ask you to wrap this up.

Mae Kwong: Okay. To close, Xarelto continues to be a safe and effective anticoagulation option. Real world data confirms its efficacy and safety both from an ischemic stroke perspective, as well as a hemorrhagic stroke perspective, which differentiates it from the other NOACs in the class. I respectfully ask that Xarelto be considered for addition to the PDL as a once-daily option that contributes to better adherence, better persistence, as well as better compliance with patients. So I think a once-a-day option is necessary to be available on the PDL. Thank you.

Michael Johnson: Thank you. Any questions from the committee? Next up will be Steve Hall followed by Dana Sox.

Steve Hall: Good morning. Steve Hall, Senior Associate Director at Boehringer Ingelheim Health Economics and Outcomes Research. I'd like to testify on behalf of Pradaxa or dabigatran and also request that it be retained on the formulary. I'd also like to spend a couple minutes talking about our reversal agent, iderusizomab or Praxbind. Dabigatran is the first and only NOAC with a specific reversal agent. It's indicated to reduce stroke in systemic embolism in patients with NVAf and per the earlier question in the landlord Rely trial the TTR warfarin in that trial was 64%. It's also indicated for DVT treatment and PE treatment in patients who have been treated with a parental anticoagulant for 5 to 10 days. It also is indicated to reduce the risk of recurrence of DVT and PE in patients who have been previously treated and our newest indication is for prophylaxis of DVT and PE in patients who have undergone hip replacement surgery. There is a new dose for that. It's initiate therapy at 110 mg and then continue on 220 mg for 28 to 35 days.

As is mentioned already in this category there is a black box warning. So I won't belabor that point, but premature discontinuation of any anticoagulant leads to concern and can increase the risk of thrombotic events and so if it's discontinued for any reason coverage with another anticoagulant should be considered. Also, it can cause epidural... I'm sorry, it can't cause, but epidural or spinal hematomas

may occur in patients that are treated with dabigatran and so we need to be cautious in that case as well.

It's contraindicated [inaudible] of pathological bleeding, known hypersensitivity reaction or mechanical prosthetic heart valve. And because it can increase the risk of bleeding we do now a new reversal agent available, iderusizomab, and it's indicated for patients who have been treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed both in emergency surgery or urgent procedures, as well as life-threatening or uncontrolled bleeding. The recommended dose is 5 grams given in 2.5 gram vials. No reconstitution is necessary. It's a humanized [inaudible] antibody fragment that binds to dabigatran and it's a [inaudible] with a higher affinity than the binding affinity of dabigatran to [inaudible]. So thereby it neutralizes the anticoagulant effect of dabigatran and its metabolites.

Most frequent adverse reactions with iderusizomab are headache in healthy volunteers and then in patients is hypokalemia, delirium, constipation, pyrexia and pneumonia. By itself it shows no pro coagulant effect measured as endogenous thrombin potential or ETP. And patients who do have underlying disease states that predispose them, obviously, to thrombin [inaudible] events and so reversal can expose them to thrombotic risk of their underlying disease and therefore resumption of anticoagulant therapy should be considered as soon as possible and dabigatran can be reinitiated within 24 hours of administration...

Michael Johnson: I'll have to ask you to wrap up.

Steve Hall: That's it. Thank you very much.

Michael Johnson: Any questions? So next up is Dana Sox and then Juan Guerra will follow. Remember there's a three-minute cap.

Dana Sox: Hi. My name is Dana Sox. I'm the Medical Science Liaison Daiichi Sankyo. I just want to thank you for the opportunity to present key data on our once-a-day factor 10A inhibitor, Savaysa. To briefly

review the two approved indications, Savaysa has been shown to reduce the risk of stroke in systemic embolism in patients with non-valvular atrial fibrillation. Per our label, in this population Savaysa should not be used in patients with a calculated threatening clearance greater than 95 mL per minute because of an increased risk of ischemic stroke relative to warfarin. Savaysa is also approved for the treatment of acute venous thromboembolism and has been shown to reduce the risk of recurrent DVT and PE.

Of note, Savaysa has three box warnings which are available for reference in the prescribing information and important safety information documents, which I have available for you if you'd like to look at them.

So as a result of the [inaudible] trial, which included over 21,000 patients and a warfarin group with a TTR of 68%. The FDA has designated Savaysa superior to warfarin in demonstrating fewer major bleeds in NVAf including reductions of intracranial hemorrhage and fatal bleeding by up to 50%. Based on the results of the [inaudible] trial Savaysa also received superiority to warfarin in demonstrating less clinically irrelevant bleeding in acute symptomatic VTE with a 19% relative risk reduction. In addition to the clinical merits I'd also like to share highlights of some recently published health economic studies.

It's important to note that the cost-effective thresholds were recently recommended by ACC and AHA in which therapies with incremental cost-effective ratios or ICERS of less than \$50,000 were deemed high value and highly cost effective. Based on the Engaged trial an estimated lifetime healthcare costs Savaysa was shown to be highly cost effective in NBAf with an ICER of less than \$37,000 per quality gained. A separate [inaudible] model using data from the [inaudible] trial was also shown to be highly cost-effective for the treatment of VTE over one year. Using a network meta-analysis of published clinical and safety data comparing cost effectiveness of Savaysa and rivaroxaban in NBAf Savaysa users had lower overall costs and better outcomes in terms of [inaudible]. Savaysa was overall determined to be dominant and highly cost-effective alternative to rivaroxaban.

Finally, using a budget impact model, if added to Medicaid formulary, Savaysa would represent less than 1 cent per member, per month assuming a 3% initial uptake. So it's important to note that all modeling techniques have limitations, which are described as part of the Savaysa dossier and is available through your PDM.

In summary, Savaysa is the only one today NOAC superior to warfarin with fewer major bleeding events and less clinically-relevant bleeding in NVAf and VTE respectively. Savaysa has also proven cost-effectiveness and has added benefits of no meal time restrictions or CYP3A4 drug interactions. So that concludes my presentation.

Michael Johnson: Any questions?

Mason Bowman: Could you restate the [inaudible] with the creatinine clearance again?

Dana Sox: So Savaysa is not... for NVAf... patients with NVAf Savaysa is not to be used with a creatinine clearance... calculated creatinine clearance of greater than 95 mills per minute.

Mason Bowman: Thank you.

Michael Johnson: Thank you. Next up will be Juan Guerra.

Juan Guerra: Hi. My name is Juan Guerra. I'm a doctor, primary care, at Swedish Medical Group working in the trenches as it were and I'm here to simply ask that the pre-auth process for medicines like Xarelto be streamlined improved or be rid of because in the case of DVT PE a medicine like Xarelto is an emergent medicine that needs to be used right away. The pre-auth process puts a block in that and limits my patient's ability to get the medicine quickly. In my patients it is my experience that most of them get it approved, but when I need that medicine to be given that day, that minute usually, for a DBT to prevent PE having that block also puts a block in my mind that if it's 4:00 I may not prescribe that medicine because I'm not going to get that pre-auth until the next day. If it's 8:00 maybe we will go through the process, we'll get the medicine in the next few hours, maybe the next day also. The pre-auth process for a medicine like Xarelto that is

easy to use, no side effect, once-a-day, high compliance medicine where patients will have to come in for an INR makes my job a lot easier and makes a patients' health outcomes, especially DVT PE much better. Thank you so much.

Michael Johnson: Any questions from the committee? Okay. Thank you. Are you still on the phone, Marian?

Marian McDonagh: Yes.

Michael Johnson: Do you have any comments? Thank you. We can let you go.

Marian McDonagh: Okay.

Michael Johnson: We'll go ahead and get started on the committee business. So I think the first item I think is to approve the report, the final report. No? It's not. It's not a scan. Okay. We'll go to the slide that's up. Any comments?

Christine Klingel: I think one thing that we could maybe add. We say non-valvular atrial fibrillation and I believe one of the agents now is approved for valvular. So we just included valvular and non-valvular atrial fibrillation or we could just say atrial fibrillation, as well. Either one I would be okay with.

Donna Sullivan: I would suggest, since they are not all indicated for that, and I believe one was actually... might have been contraindicated or specifically not to be used. Because you say that they are safe and effective... you say all the drugs are safe and effective for these indications. It might be better to just say that they are safe and efficacious for their FDA labeled indications.

Michael Johnson: I think that's the way to say it.

Christine Klingel: Or it could just be removed non-valvular and then... because they all are approved in some respect for atrial fibrillation. It just demands if it is valvular or non-valvular, so if we don't specify does that...

Donna Sullivan: That would be okay.

Christine Klingel: Okay.

Donna Sullivan: Just take out non-valvular.

Eric Harvey: I think we need to add edoxaban.

Michael Johnson: Any other comments from the committee? I think this actually looks pretty good. I'll go ahead and read this for my proposal.

After considering the evidence of safety, efficacy and special populations for newer anticoagulant drugs for the prevention of stroke and systemic embolism in patients who are medically ill, undergoing surgery or with atrial fibrillation, and the prevention and treatment of VTE/PE, I move that apixaban, dabigatran, edoxaban, and rivaroxaban are safe and efficacious for their approved indications. Apixaban, dabigatran, edoxaban, and rivaroxaban cannot be subject to therapeutic interchange in the Washington preferred drug list.

Eric Harvey: I'll second.

Michael Johnson: All right. All in favor say aye.

Group: Aye.

Michael Johnson: Opposed same sign. All right. The motion carries.

Donna Sullivan: I believe Shelley is on the phone already. Leta is pulling up the slides.

Michael Johnson: Are you ready to go, Shelley?

Shelley Selph: Yeah. Can you hear me okay?

Michael Johnson: Yes.

Shelley Selph:

This is the review on disease-modifying drugs for multiple sclerosis and this is the third update of the MS drug report. The last update was in September of 2013. Next slide.

Here are the key questions. Key question 1 is a standard effectiveness question. Key question 2 examines the relationship between neutralizing antibodies and clinical outcomes. Key question 3 looks at comparative effectiveness in the clinically isolated syndrome or first [inaudible] event. Key question 4 is a standard harms questions and key question 5 is a standard subgroup question. Next slide.

We included adults with any form of MS or clinically-isolated syndrome and included the listed outcomes for benefit. Next slide.

The included harms are listed. This review is unusual in that we had previously excluded placebo-controlled trials as this was a streamline review for the last update. However, we needed to go back and identify all placebo-controlled trials and include new placebo-controlled trials that were to perform a network meta-analysis using placebo as the common... the primary common comparator. In general there is little mention of placebo-controlled trials in the text of the report unless it involves a new drug and there is lack of head-to-head evidence. Our searches are through the end of last year.

Here's a list of included interventions. After the key questions were approved ocrelizumab was granted breakthrough therapy for primary progressive multiple sclerosis for which there is no currently approved pharmacotherapy. Although not originally an included drug we did the extra work to include in this update. Most of the evidence for ocrelizumab is actually in relapsing remitting multiple sclerosis patients which we also included. Also since this report was completed daclizumab was approved for relapsing forms of multiple sclerosis in May of this year. Next slide.

We identified 25 new publications of which 10 were included in trials for this update. Next slide.

In going through the slides we underlined drug names when the evidence was new and bolded when the comparison was significant. Also we listed rates when possible. When reporting relative risk estimates that were calculated by study authors, the rates may not have been reported. In patients with relapsing or remitting multiple sclerosis treatment with ocrelizumab 600 mg resulted in similar risk of relapse as interferon beta-1a or Avonex. Where there was a lower risk of relapse and disability progression with ocrelizumab than with Rebif based on head-to-head evidence. In our network meta-analyses we only included approved drug doses and doses of unapproved drugs going forward in the approval process. And if you look in your... in the report, table 3, that gives you the estimates for relapse and the relapse and remitting population. In our network ocrelizumab was calculated or estimated to be the drug most likely to have the lowest risk of relapse, but caution must be exercised in determining calculations that are at least partly based on indirect comparisons. Our network generated a relative risk for all included drug comparisons, but we consider such evidence as low strength. Next slide.

Daclizumab is another humanized monoclonal antibody, which like ocrelizumab is... well, except it is now approved, whereas ocrelizumab is not. Initials HYP stand for high yield process as daclizumab was reformulated for long-term subcutaneous administration with less site [inaudible] toxicity than in earlier forms. Daclizumab 150 mg was associated with less disability progression and lower risk of relapse than Avonex. Next slide.

Alemtuzumab was associated with improved disability and in risk of relapse when compared with Rebif. In both our network meta-analysis and a recently published network meta-analysis conducted by Cochrane Alemtuzumab is the approved drug calculated to have the lowest risk of relapse. Next slide.

We only had placebo-control evidence on teriflunomide before. For this update we identified one head-to-head randomized controlled trial which indicated that relapse outcomes were worse with 7 mg of

teriflunomide compared with Rebif, but results were similar when the teriflunomide dose was upped to 14 mg. Next slide.

There was no new evidence regarding the comparison of dimethyl fumarate or BG12 with glatiramer and the previous update found the frequency of relapse to be similar. With fingolimod evidence was also not new, but relapse was approved with .5 mg versus Avonex. Next slide.

Glatiramer 40 mg given three times a week is a new dosing for which there was only placebo-controlled evidence. Not surprisingly annualized relapse rates were superior with glatiramer compared with placebo. And there was no new evidence for glatiramer 20 mg versus interferons and from the old report we found relapse outcomes to be similar. Next slide.

We also found glatiramer similar to Avonex, Rebif and betaseron as noted in the previous report. Next slide.

Pegylated interferon is a newcomer to this report. There was no head-to-head evidence for this drug, which was better than placebo in effectiveness. Next slide.

Treatment with betaseron Rebif results in better relapse rates than Avonex. Next slide.

Now moving on to comparative effectiveness evidence in the non-relapsing remitting multiple sclerosis population. In patients with primary progressive MS there was moderate strength evidence that ocrelizumab delayed disability of progression better than placebo. In a combined group of patients with MS or clinically isolated syndrome there was no difference in annualized relapse rate between betaseron and glatiramer. Next slide.

In patients with a progressive form of MS, and that would be primary progressive, secondary progressive, or progressive relapsing MS, treatment with betaseron improved relapse rates over placebo and in patients with all types of MS persistence raised with betaseron was

similar or less than rates with Avonex, Rebif and glatiramer. Next slide.

Moving on now to key question 2, which examined the effects of neutralizing antibodies in clinical outcomes. So there's no new comparative evidence for this key question. From the previous update we know that Avonex is the lowest immunogenicity and neutralizing antibodies were seen the soonest with betaseron. Next slide.

Key question 3 looks at the comparative effectiveness of disease modifying therapies in clinically-isolated syndrome. In the actions of any head-to-head evidence we relied on our indirect treatment comparisons to help address this key question. Our calculations indicated that risks of progression from clinically-isolated syndrome to an MS diagnosis were similar with any of the interferons in either dose of teriflunomide. Next slide.

Looking at the comparative harms of disease-modifying treatments in patients with relapsed and remitting multiple sclerosis. Patients treated with ocrelizumab were less likely to leave the study due to adverse events than patients treated with Rebif. All the rates of serious adverse events were similar. Next slide.

When compared with Avonex ocrelizumab had similar rates of withdrawals due to adverse events and serious adverse events. Next slide.

Although a great proportion of patients left the study due to adverse events with daclizumab versus Avonex the result... the risks of experiencing any serious adverse events were similar. Next slide.

Alemtuzumab treatment was associated with fewer withdrawals due to adverse events than Rebif. And in our network meta-analysis alemtuzumab was the only approved drug with an estimated lower risk of study withdrawals due to adverse events than placebo. This is also consistent with Cochran's network meta-analysis. But again results must be interpreted with caution. Next slide.

Treatment with dimethyl fumarate increased the likelihood of experiencing any adverse event, but without difference in withdrawal due to adverse events or serious events compared with glatiramer. Next slide. Teriflunomide treatment resulted in fewer withdrawals due to adverse events than Rebif, but no difference in risk of having any serious adverse event. Next slide.

Treatment with fingolimod and Avonex resulted in similar study withdrawals and serious adverse events. Next slide.

However, as we note from the previous update, fingolimod is associated with less risks of pyrexia myalgia and flu like illness compared with Avonex, but increased risk of elevated liver enzymes, specifically ALT with fingolimod. Next slide.

Glatiramer the new dose was associated with borderline increase withdrawal due to adverse events compared with placebo. Next slide.

Withdrawals due to adverse events were similar with glatiramer compared with a beta interferon, but glatiramer was associated with increased injection site reaction on lipoatrophy, but less flu-like illness and decreased risk of hepatotoxicity. Next slide.

People left the study due to adverse events more often with pegylated interferon and were more likely to have severe adverse events than placebo, but no difference in risk of experiencing serious adverse events. This study was unique in that it pulled out that separate category of severe adverse events, which we don't generally see. And in this case severe was defined as symptoms that cause severe discomfort in capacitation or significant fact of daily life that could cause stopping... necessitating stopping treatment, treatment for symptoms, or hospital admission. Next slide.

Our network meta-analysis indicated no differences between the beta interferons including pegylated interferon in withdrawals due to adverse events. But evidence from the prior update indicated that

Avonex was associated with the least injection site reaction, but the most flu-like illness of the beta interferons. Next slide.

Changing population now from relapsing remitting MS to primary progressive MS overall withdrawals were less likely with ocrelizumab versus placebo, but withdrawals due to adverse events were not reported. Serious adverse events were not increased, however. Next slide.

In patients with clinically isolated syndrome, patients treated with Avonex were less likely to leave the study due to adverse events than patients treated with 7 mg of teriflunomide, glatiramer or betaseron. Next slide.

However, in patients with clinically-isolated syndrome there were fewer study withdrawals due to adverse events with teriflunomide compared with glatiramer. Next slide.

Moving on now to key question 5, our subgroups question. A significant piece of new information for this question is that in utero exposure to fingolimod may be associated with increased risk of poor fetal or neonatal outcomes. That affected about 10% of the pregnancies had serious problems. Next slide.

So to summarize, this review included 25 new publications, which 10 were new trials. We conducted a network meta-analysis in patients with relapsed and remitting multiple sclerosis for risk of relapse and withdrawal due to adverse event. And for clinically isolated syndrome patients in risk of disease progression to MS in study withdrawal due to adverse events. We included ocrelizumab and also daclizumab. At the time neither one of those were approved, but since then daclizumab has been approved. And we included placebo-controlled evidence for glatiramer 40 mg and for pegylated interferon. Next slide.

Some of the take home points that are new to this review, ocrelizumab and daclizumab are promising new therapies. But alemtuzumab still performs well in network meta-analyses and

performs the best of all the approved therapies. Due to limited head-to-head evidence network results do need to be interpreted with caution and we consider them of low strength evidence. Caution should also be exercised to prevent pregnancy in women of reproductive age being treated with fingolimod. That concludes the report.

Michael Johnson: Thank you, Shelley. Can you stay on the line while we have stakeholder input?

Shelley Selph: Sure.

Michael Johnson: So for the stakeholders, again, you have three minutes and please identify who you represent. First will be Margaret Olmon followed by Emily Stevenson. Can you go up to the podium?

Margaret Olmon: Hello. My name is Margaret Olmon. I'm with U.S. Medical Affairs with Abbvie. Thanks so much for allowing me to come in and talk to you today about our new drug, daclizumab high yield process. The brand name is Zinbryta. This will be a summary only today. I have my prescribing information with me. If you have any questions I'd be happy to answer them after we finish talking.

In patients with multiple sclerosis nerve cell damage accumulates over time leading to permanent, irreversible disability and no course of the disease is typical. Each patient may need several different treatments over the course of their disease. The unique mechanism which Zinbryta exerts therapeutic effects in MS is presumed to involve modulation of the IL2 mediated activation and blimp sites. Through the binding of the CD25 subunit of the high affinity IL2 receptor. Cells that require high affinity IL2 receptor signaling such as the activated T cells that play a central role in MS pathology are selectively inhibited. Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis in adults. Because of its safety profile the use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for MS treatment. It is administered as a self-injected subcutaneous monthly injection. Zinbryta has a box warning for

hepatic injury including autoimmune hepatitis and other immune mediated disorders and is available only through the Zinbryta REMs program. Zinbryta can cause severe liver injury including life-threatening events, liver failure and autoimmune hepatitis. Physicians should obtain transamination bilirubin levels before initiation of Zinbryta and monitor and evaluate transamination bilirubin levels monthly and then up to six months after the last dose. Zinbryta is contraindicated in patients with pre-existing hepatic disease or hepatic impairment including ALT or AST at least two times the upper limit of normal because Zinbryta could exacerbate existing liver dysfunction, a history of autoimmune hepatitis or other autoimmune conditions involving the liver. The efficacy on safety of Zinbryta was demonstrated in two randomized double-blind controlled studies.

I will focus my attention today on the Decide trial, a head-to-head trial of Zinbryta against Avonex. When compared to Avonex Zinbryta demonstrated a statistically significant 45% relative reduction in annualized relapse rate, which was the primary endpoint.

In summary, I'm requesting the committee consider adding Zinbryta to the PDL so that patients and physicians in Washington may have another treatment option for relapsing forms of MS, one with a unique mechanism of action, proving efficacy over Avonex and with monthly subcutaneous dosing. Thank you so much for your consideration.

Michael Johnson: Thank you. Do you have any questions? Next up will be Emily Stevenson followed by Lynda Finch.

Emily Stevenson: Hi. My name is Emily Stevenson and I'm a Medical Science Liaison with Sanofi Genzyme. I'm here today to review clinical information Aubagio or teriflunomide. Please see the full prescribing information listed in the package insert to use Aubagio safely and effectively in patients. Aubagio is a [inaudible] synthesis inhibitor indicated for the treatment of patients with relapsing forms of MS. It's available as a 7 mg or 14 mg tablet taken orally once daily with or without food. Four randomized controlled double-blind clinical trials established the

efficacy of Aubagio in patients with relapsing forms of MS. Study 1 and study 2 evaluated the two doses for up to 26 months or 40 months respectively. The studies found a statistically significant reduction in primary endpoint of annualized relapse rates for patients in both Aubagio groups compared to patients who received placebo. Additionally, there was a statistically significant reduction in the relative risk of disability progression at week 108 sustained for 12 weeks in the Aubagio 14 mg compared to placebo. Study 1 also showed that patients in both Aubagio groups also had significantly fewer gad-enhancing lesions as compared to placebo. Study 3 evaluated Aubagio 7 mg and 14 mg for up to 108 weeks. Patients in these studies were required to have had a first clinical event consistent with acute demyelination occurring within 90 days of randomization and MRI features that were characteristic of MS. The proportion of patients free of relapse was greater in both Aubagio groups than in the placebo arm. The effect of Aubagio on MRI activity was demonstrated in study 4. The mean number of unique active lesions per MRI brain scan during the 36-week treatment period was lower in both Aubagio groups than in the placebo group and the difference being statistically significant for both Aubagio groups. Aubagio has a box warning of hepatotoxicity and a risk of [inaudible]. Aubagio is contraindicated in severe hepatic impairment, in pregnancy, and in patients currently on [inaudible] treatment. The most common adverse events are headaches, diarrhea, nausea, alopecia, and increased ALT. If required, elimination of Aubagio from the plasma can be accelerated by the administration of cholestyramine. Aubagio may decrease white blood cell count. A recent CVC should be available before starting Aubagio. Patients should be monitored for signs and symptoms of infection and Aubagio should not be started in patients with active infection.

Pregnancy must be excluded before starting Aubagio. If the patient develops symptoms consistent peripheral neuropathy they should be evaluated and discontinuation should be considered. Aubagio may increase blood pressure. Blood pressure should be measured at treatment initiation and then monitored during treatment. Please refer to the package insert for complete Aubagio prescribing

information. Thank you for your consideration. I'm happy to answer any questions you may have.

Michael Johnson:

Thank you. Next up will be Lynda Finch followed by Mary Kemhus.

Lynda Finch:

Hi. I'm Lynda Finch. I'm a Medical Value Liaison for Biogen. I'm going to cover, just very briefly, two of our products today. So Plegridy, it's one of the products that was mentioned in the update and just a key piece of information that's missing from the update is that the neutralizing antibody formation rate for Plegridy, which what we saw in our clinical trials is less than 1% of patients developed neutralizing antibody. I think that's an important point because it is the lowest neutralizing antibody rate of all the interferons. It was approved in August of 2014 as the first pegylated beta interferon with a prolonged half-life for treatment of patients with relapsing forms of MS. It's administered subcutaneously once every 14 days.

So very brief for Plegridy and I'm going to spend most of my time talking to you today about Tecfidera. Tecfidera was approved in March 2013 and it has since been prescribed to over 190,000 patients. It is the most frequently prescribed oral medication for MS. That number, 190,000 is as of December 2015. So it's a little bit out of date. The main thing I want to talk to you today about is some of the clinical considerations for using Tecfidera.

So as I'm sure many of you are aware, there have been reports of... rare cases of PML with Tecfidera. We've had four cases of PML and this is in the setting of prolonged lymphopenia. The severe prolonged lymphopenia is a known risk factor for PML. It does occur with other products in this class as well. So I'm sure you're aware. The three cases that we had in the setting of severe prolonged lymphopenia, and then one case occurred in the setting of moderate prolonged lymphopenia. So healthcare providers should assess the benefit and risk in patients that experience moderate lymphopenia for more than six months and consider interruption of treatment in patients who have lymphocyte counts of less than 500 persisting for more than six months. The lymphocyte monitoring that is in the label, and the label was revised in December, it provides an effective means for early

identification of patients at risk for developing moderate to severe and prolonged lymphopenia.

The overall risk benefit for Tecfidera remains favorable and aside from these rare cases of PML there's no overall increased risk of other opportunistic infections in patients taking Tecfidera.

And then lastly I want to say that Biogen is highly committed to patient safety and it continues to be our first priority. We have a comprehensive effort dedicated to understanding the impact of Tecfidera on lymphopenia in the development of PML and we will continue to keep you up to date in the most relevant information for this severe adverse event. Thank you.

Michael Johnson: Thank you. Any questions?

Lynda Finch: Thank you.

Michael Johnson: Thank you. Last up is Mary Kemhus.

Mary Kemhus: Hi. Good morning. I'm Mary Kemhus and I am a pharmacist with Novartis Pharmaceuticals. So I'm speaking on behalf of Gilenya today. I'm requesting that Gilenya continue to have... or that patients continue to have access to Gilenya on the Washington Medicaid PDL and I'd like to just highlight a few key things that set Gilenya apart from the other agents available.

Multiple published clinical trials have shown Gilenya efficacy across all four MS measures, including disability, which is included in the labeling, relapses, MRI activity, and brain volume loss. Gilenya is the only oral drug that has head-to-head superiority data comparing Gilenya to an injectable product, specifically Avonex. Based on published extension data in that trial versus Avonex patients who switched to Gilenya had a 29% improvement in annualized relapse rate. What I'd like to emphasize about that, though is that in patients who are required to use an injectable agent first they never achieve the same benefit that we're seeing in patients who are on Gilenya from the very beginning.

In a recently completed phase 4 real world comparative trial versus injectable disease modifying agents, including Copaxone and interferons, a patient could be on any of the injectables. The study enrolled over 800 patients from the U.S. and at the end of a year over 80% of patients that had started on Gilenya remained on therapy versus only 30% in the injectable arm remained on therapy at 12 months.

Gilenya has been on the market for over five years now and has extensive real world experience with over 148,000 patients treated and more than 316,000 patient years of experience. There was a label change in February of this year, which includes updates to the warnings and precaution sections of the labels and I would refer you to the PI for those details.

So in summary, Gilenya is the only oral disease modifying therapy that has demonstrated superior efficacy to an injectable agent. It is shown consistent in sustained efficacy and is a well-tolerated agent for MS patients. So for these reasons I respectfully request that you maintain Gilenya as a preferred agent on the Washington PDL. I'm happy to answer any questions you have.

Michael Johnson: All right. Thank you. Are you still on the line, Shelley?

Shelley Selph: Yes.

Michael Johnson: I think we have some questions.

Eric Harvey: My question was regarding the comparative study between fingolimod and interferon beta-1a. I think the previous speaker did clarify that that was a direct head-to-head comparison and not a network comparison. Is that correct?

Shelley Selph: Um, oh, are you speaking from the report or from the slide?

Eric Harvey: It's highlighted on slide 11.

Shelley Selph: Let me see what you're looking at here. Yes, that's from a direct comparison.

Eric Harvey: Thank you.

Michael Johnson: Any other questions from the committee for Shelley? Well, thank you, Shelley.

Shelley Selph: You're welcome. I also have Ian standing by.

Michael Johnson: All right. We'll shift our focus to a motion.

Donna Sullivan: I just wanted to point out that the drug down on the bottom, the ocrelizumab, is not yet on the market. So it won't be eligible for inclusion, but the daclizumab was approved in May so it is eligible to be included in the motion.

Susan Rowe: Since we've reviewed ocrelizumab, when it comes on the market is it eligible without another review?

Donna Sullivan: It would be eligible... it would... when it does come out on the market it would be considered non preferred, but already reviewed.

Susan Rowe: Okay.

Michael Johnson: Do we need to accept... so we'll look at the motion.

Chuck Agte: Donna, do we need to pull the natalizumab from that list since it wasn't in this report?

Donna Sullivan: No. Mitoxantrone and thesabre were not included in this update. I would have to ask Shelley exactly why. I don't recall off the top of my head, but they were included in previous reports and they are indicated for MS. So you can decide to exclude or you can just continue to carry them forward. But it is my understanding that they will not be included in further updates on this particular class.

Shelley Selph: They weren't included due to the state's decision to remove them for the previous update due to size and also due to adverse events. So they can be returned to the list whenever the states decide to do that.

Donna Sullivan: Do we still need Shelley on the phone? Shelley, thank you for refreshing my memory, but you are excused. Thanks. Ian, we will be just a few more minutes.

Ian Blazina: Great. Thanks.

Eric Harvey: I will read the motion. After considering the evidence of safety, efficacy and special populations for the treatment of multiple sclerosis, I move that daclizumab, HYP, mitoxantrone, natalizumab, dimethyl fumarate, teriflunomide, fingolimod, glatiramer, interferon beta 1B SC, interferon beta 1A IM, and interferon beta 1A SC are safe and efficacious. A product that is safe for use during pregnancy should be made available. The multiple sclerosis drugs cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment. An oral agent should be included in the list of preferred drugs on the PDL.

Christine Klingel: I think we just need to add alemtuzumab to the list. It's at the very top. We did not have it in the motion. Then I will second.

Eric Harvey: I'm comfortable with the modified motion.

Man: I don't know if it's technically relevant, but there is the peg interferon beta 1A SC. So the 1A SC agent is pegylated and it might be worth adding that to the motion. Yeah. I wish we could cut and paste when we're reading.

Donna Sullivan: So that would be a third one because there's a non pegylated 1A, as well.

Christopher Smith: There are three interferons, but you didn't have the peg before the beta 1A SC.

Michael Johnson: Do we need to read this again?

Donna Sullivan: I don't think so.

Michael Johnson: The motion was seconded. With those revisions all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. So I think we have Ian on the phone. Is that it?

Donna Sullivan: Yes.

Michael Johnson: Ian? Okay. Give us a second, Ian. We're just moving the slides over.

Ian Blazina: All right. I'm ready whenever you are.

Michael Johnson: All right. I think we're ready.

Ian Blazina: I'm sorry. I don't have the agenda in front of me. Are we starting with the macrolides slides?

Donna Sullivan: We have the skeletal muscle relaxers up.

Ian Blazina: Okay. So this is the preliminary scan number 6 for the skeletal muscle relaxants report. This was conducted in May 2014 and it's a scan for the last update report which was in May 2005. This is scan number 6 and scan number 5 was in May 2013, which is on the next slide, slide 2.

Then the next slide, slide 3, lists the population inclusion criteria for adults or children with spasticity or muscular skeletal condition or nocturnal leg cramps and we excluded patients with restless leg syndrome, nocturnal myoclonus and obstetric or dialysis patients. Next slide.

This is a list of the included drugs. Next slide.

Efficacy and effectiveness outcomes. Relief of muscle spasms or pain, functional status, quality of life, and we excluded non-clinical outcomes. Next slide.

The searches were from Medline from 2013 through May of 2014. And we also searched AHRQ, CADTH and some other sites for comparative effectiveness reviews, as well as drugs of FDA or new drugs, indications, and black box warnings. Next slide.

So this search identified no new drugs. A few drugs were identified in prior scans. Next slide. We also identified no new indications or black box warnings in the current scan. The previous scan had identified one black box warnings related to Dantrium finding a higher proportion of hepatic events with fatal outcome in elderly patients. Next slide.

The current scan identified no new comparative effectiveness reviews, head-to-head trials or placebo-controlled trials. Prior scans have identified four placebo-controlled trials, but no new CERs or head-to-head trials. Next slide.

This table lists the four placebo-controlled trials available since the last report. Next slide.

So since the last report there were two new drugs, no new comparative effectiveness reviews, no new head-to-head trials, and four new placebo-controlled trials. That's all the evidence from this update. If there's any questions...

Michael Johnson:

Any questions from the committee? All right. There are no stakeholders for this topic. All right.

Donna Sullivan:

This particular class we're going to archive so I'm going to ask Leta... we're going to do a little bit of shuffling around. So we have a different motion that we need to pull up for the archiving, but this is the motion from the last meeting that you had. So, we'll okay the scan and then we'll do the archive motion at the end of the three different classes.

Christopher Smith: I move to approve the scan as adequate.

Mason Bowman: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. We'll go to the next topic. Ian?

Ian Blazina: All right.

Michael Johnson: I think we have macrolides on our...

Donna Sullivan: So Leta is reminding me of the rules of order. Go ahead and accept your motion as previously stated and then we'll do the archive motion at the end.

Eric Harvey: I would like to reiterate the prior motion.

Man: I second.

Michael Johnson: All approved say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The motion carries. Now we can go ahead and start with Ian. Okay, Ian, you can go ahead and start with macrolides.

Ian Blazina: All right. This is the macrolides update. This is update number 5 from July 2014. Next slide.

The original report was in August 2006 and there were four previous scans. The most recent being September 2013. Next slide. We searched trials from Medline from 2006 through June 2014, as well as

looking for comparative effectiveness reviews and new drug indications and black box warnings. Next slide.

The population was community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, Otitis Media, pharyngitis, and mycobacterium avium complex. Interventions were Azithromycin, Erythromycin and Clarithromycin and we were including head-to-head trials and good quality comparative effectiveness reviews. Next slide.

This slide lists the efficacy and harms outcomes. Next slide.

We identified no new drugs since the prior report and no new indications. A previous scan had identified a safety alert with Azithromycin related to abnormal changes in electrical activity of the heart. Next slide.

We identified no new comparative effectiveness reviews in this scan. Previous scans had identified three Cochrane reviews, two of community-acquired pneumonia and one of Otitis Media. Next slide.

We reviewed 40 new citations for this scan and identified no new potentially relevant head-to-head trials. Previous scans had identified three potentially-relevant head-to-head trials. Next slide.

This slide is just a table of those three trials. Next slide.

So in summary there were no new head-to-head trials identified in this scan. Three from previous scans and no new comparative effectiveness reviews, also three from previous scans, no new drugs or indications, and no new safety alerts in this scan with one previous safety alert from 2013. Are there any questions?

Michael Johnson:

I'm not seeing any questions. There are no stakeholders so I'd like to propose that we accept this scan as adequate.

Christopher Smith:

I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries.

Eric Harvey: I'd like to reiterate the prior motion from October 2013.

Mason Bowman: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. Give us a moment, Ian.

Ian Blazina: Okay.

Michael Johnson: All right, Ian, you can go ahead and start.

Ian Blazina: All right. This third slide set is for TZDs for diabetes. This is preliminary scan number 1 of update number 2. This was originally conducted all the way back in August 2009. Next slide.

The last report was update number 1 in August 2008. Next slide.

The population was adults and children with type 2 diabetes and adults and children with pre diabetes, as well as adults and children with metabolic syndrome. Next slide.

The included interventions were pioglitazone or rosiglitazone and comparators were within class or between class. They included pioglitazone or rosiglitazone versus placebo, no treatment, or other oral hypoglycemic agents. Next slide.

We included glycemic control HVA1C as well as effectiveness outcomes of incidents of type 2 diabetes for the pre-diabetes

population. Durability of control progression or occurrence of long-term microvascular complications and macrovascular complications, as well as all-cause mortality and quality of life. Next slide.

For harms we included total adverse events, withdrawals due to adverse events and some specific adverse events. Next slide.

The searches were from November 2007 to August 2009 and we identified 243 citations. Next slide.

Of those citations there were 22 new potentially relevant trials. Fifteen were placebo or active control and 2 were head-to-head efficacy trials. Next slide.

We also identified 2 new effectiveness trials and 3 post hoc analyses of previously included trials. Next slide.

We identified no new drugs or indications. And that is everything. Are there questions?

Michael Johnson: I see no questions from the committee members. There are no stakeholders. So I'd like to propose that we accept this as adequate.

Susan Rowe: I will second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries.

Donna Sullivan: Before you reiterate the motion from this class I just wanted to point out what's not in this scan is that the FDA has removed the labeling restrictions on rosiglitazone and removed the requirement that it be involved in a REMs program. So I would maybe recommend that you not make it be non-preferred on the PDL, which will allow us to not require prior authorization for it when doctors want to use rosiglitazone versus pioglitazone. I can tell you right now that we

have had no requests for it since between January and April 2016. So I just wanted to point that out before you just reiterate the same motion. Thank you.

Christopher Smith: So again the date range is limited to 2009 because that's... it's an archived class?

Donna Sullivan: Yes. The DERP governing board archived this class I think several years ago and so that was the last time that it was updated and I believe it might even be the last time we reviewed this class here at this committee.

Susan Rowe: I believe on the harms side of it there was a review of the bladder cancer evidence against pioglitazone and somewhat refuted or, again, considered less scary. Just that's kind of another update to this class.

Christopher Smith: That's what Donna was referring to.

Donna Sullivan: Yes.

Christopher Smith: Do we have anything, any literature to look at or review regarding that?

Donna Sullivan: I didn't bring anything with me specifically. I did not look at the date of this particular scan before we had the meeting and did not realize that it was from 2009. You can decide not to archive this class and we can bring some DUR, you know, more DUR information for you. But this class won't be updated through DERP. So other than us synthesizing the data ourselves then there's nothing for me to bring to you.

Susan Rowe: I do want to clarify, so the bladder cancer concern was on pioglitazone, not rosiglitazone. So the REMs removal has nothing to do with pioglitazone, but I think... I don't think we have to necessarily not archive this class. I think what we've seen is an improvement in the safety profile. So there's nothing in terms of a safety for our patient population that would necessarily make us not archive the class is what I'm seeing.

Christopher Smith: I agree. I think that the... as Donna was saying the evidence that made people concerned about the use of pioglitazone is less and in particular that hard to deal with the heart failure risks and so the... that occurs less often with the pioglitazone than with the rosiglitazone and that therefore it would be a safer option among the two and less concerning than had previously been thought.

Donna Sullivan: Actually that's what the labeling has been changed. So pioglitazone is now... also has the contraindication of congestive heart failure. So I think what they found is that rosiglitazone... there wasn't the difference between the two, that they were both equally risky for patients with CHF.

Susan Rowe: I agree. Heart failure is still a risk with this medication and I guess what I would say is if there are patients who have been on it without, you know, were on it without problem then you don't necessarily take it off, but you wouldn't choose this as a medication to start if you had a patient with diagnosed heart failure.

Christopher Smith: So how does this information, this concern, impact our actions today? This is not new information that we're acting on. If anything, as you said, it tends to be a lower risk than we had previously thought in our prior motion.

Michael Johnson: I think this is almost now a class effect. Both of these agents have the same risks and so I think it would be hard to choose one over the other. So I think we should, you know, I propose we remove that one sentence if everyone is agreeable to that.

Susan Rowe: I agree.

Michael Johnson: Yeah. You want me to read that? So I'm going to make a motion. So after consideration of the evidence of safety, efficacy and special populations for the treatment of type 2 diabetes, I move that pioglitazone and rosiglitazone are efficacious options as second line therapy. Thiazolidinediones can be subject to therapeutic interchange in the Washington preferred drug list.

Eric Harvey: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. Any... I think Ian is off the line now. Are you still there Ian?

Donna Sullivan: He's free to leave if he hasn't hung up already.

Michael Johnson: Do you want to take a break? Oh, we have to archive. Exactly. Any comment on the proposed motion up on the slide?

Susan Rowe: I move to propose this motion as stated on the screen. Do you want me to read it?

Donna Sullivan: Yes, please.

Susan Rowe: Okay.

Donna Sullivan: It is printed in the back of your handout in the back of that archived drug class.

Susan Rowe: Oh yay! All right. After considering the scans presented today I move to archive the following drug classes from further regular review by the P&T Committee: diabetes, TZDs last reviewed 6/15/2016, macrolides last reviewed 6/15/2016, and skeletal muscle relaxers last reviewed 6/15/2016. The drug classes will remain on the PDL and the committee's last motion will remain in effect until changed by the committee. The agencies may conduct updated cost analyses of these drugs without additional committee approval so long as any resulting changes in the preferred status of a drug remains consistent with the committee's last motion for that drug class. The committee may review the archive status of a drug class upon its own initiative or by request of the participating agencies at any time.

Amber Figueroa: I second that.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. So now a break.

Donna Sullivan: Yes. And the P&T Committee will adjourn.

Michael Johnson: All right. What time do you want to reconvene?

Donna Sullivan: We will reconvene at 11:00 for the DUR board.

Michael Johnson: Thank you. You are dismissed.

Okay. We are going to reconvene. So welcome back. We're going to reconvene the Drug Utilization Review Board at this time. We're going to change our order a little bit. We're going to start with denosumab first with Ryan. We'll let Ryan start.

Ryan Pistorosi: Thank you for the introduction. I'll be presenting the denosumab medical policy. So the objectives of this presentation are to review some of the background information and that will set the foundation for this medical policy and then we'll move into the actual medical policies for denosumab.

So for the background information, denosumab is a monoclonal antibody that targets the RANKL ligand receptor. The RANKL is an essential protein for the formation, function and survival of osteoclasts. And the osteoclast are essential for the... in the cycle of bone health because they reduce the... sorry, so the RANKL by inhibiting it, it decreases the osteoclast activity and decreases the bone resorption, which is the main function of the osteoclasts. And so by preventing that it improves bone health. RANKL is also a mediator of bone pathology in solid tumors with osteo metastases. So when a solid tumor attaches to the bone and begins to grow

RANKL is expressed on those cells. And RANKL is also expressed on the stromal cells in giant cell tumor of bone.

So with that information we can move on to the FDA approved indications. As you can see they match closely with the pathobiology of denosumab. So the first four are the approved indications for Prolia and then the last three on that first list are the approved indications for XGEVA. Just to review, Prolia is for the treatment of osteoporosis in post-menopausal women to increase bone mass in men with osteoporosis for the treatment of bone mass in breast cancer patients with aromatase inhibitors and for the treatment to increase bone mass in prostate cancer with ADT. So for those it is more of the osteoporosis indications. For XGEVA its approved indications are for the prevention of skeletal-related events in bone metastasis from solid tumors for the treatment of giant cell tumor of bone and for the treatment of hypercalcemia of malignancy refractory to bisphosphonates. I just wanted to highlight that. There are a few similar uses that denosumab is not approved for and for those are for the prevention of osteoporosis for the prevention or treatment of glucocorticoid-induced osteoporosis and for the prevention of skeletal-related events in multiple myeloma.

So when reviewing this medical class I focused mainly on the national guidelines for each of the approved indications. For osteoporosis they favor initiating pharmacotherapy for anyone with T-scores of negative 2.5 or lower measured at the femoral neck, total hip, or lumbar spine. And there's actually significant variation between the national guidelines for the treatment of osteoporosis and so I listed three different ones here. I do want to highlight that it is a bit misleading on that third one. So the National Guidelines Clearinghouse, which is run by ARHQ actually compiles different guidelines. So this is not an individual guideline from ARHQ. The guideline was actually for the Institute of Clinical Systems Improvement, which is a group that reviews medical policy for medical groups, physicians, hospitals and health plans in Minnesota and the northern Midwest. And so that should be changed there. I apologize. So the AACE would recommend alendronate, risedronate, zoledronic acid and denosumab as first line therapy for the

osteoporosis. National Osteoporosis Foundation recommend any FDA approved pharmacotherapy as first line and then the Institute for Clinical Systems Improvement was the guideline that recommended the bisphosphonates. The national guidelines for breast cancer for patients with the aromatase inhibitors they generally recommend bisphosphonates as the initial therapy, but they may also consider denosumab based on individual characteristics. I didn't list them, but those were the NCCN and ASCO(?) and those are typically the guidelines that I would use for reviewing the cancer indications. For the prostate cancer recommendations most of the guidelines I reviewed recommended the bisphosphonates. So alendronate, zoledronic acid, and denosumab, but the Institute for Clinical Systems Improvement specifically recommended zoledronic acid and in reviewing NICE they recommended bisphosphonates as well.

The national guidelines on the metastatic cancer to the bone to prevent skeletal-related events generally recommended the IV bisphosphonates and denosumab as first line therapy although the oral ibandronate has been studied in this setting with positive results in the UK, but the NCCN and ASCO recommended the IV bisphosphonates and denosumab as first line. The guidelines for the giant cell tumor of bone that is unresectable or is resectable with unacceptable morbidity are recommended to be treated with denosumab, chemotherapy with interferon or radiation therapy. This was pulled from the NCCN guidelines. Prior to the approval of denosumab the bisphosphonates were used in this area, but recent studies have shown that because of the RANKL activity on the giant cell tumor that denosumab does have superior outcomes than actual tumor activity whereas the bisphosphonates have some tumor activity. And then the national guidelines on hypercalcemia of malignancy generally recommended the IV bisphosphonates, particularly zoledronic acid since it did have [inaudible] over the other bisphosphonates in this class. And due to the labeling the denosumab is labeled to be in patients who were refractory to bisphosphonates.

So with that information we're moving on to the medical policy. And so I split the medical policy between Prolia and XGEVA since they do

have different indications and there is different level of evidence based on the use, but the intended... or the proposed medical policy would have patients be eligible for Prolia when they meet all of the inclusion criteria for the treatment of FDA approved indications. So if the patient has at least one of the following indications, which is they are a man or post-menopausal woman with a T-score of -2.5 at the femoral neck, total hip, or lumbar spine, they are a man receiving ADT or non-metastatic prostate cancer, and if they are a woman receiving aromatase inhibitor for the treatment of breast cancer. If the patient is considered high risk for fracture. So if they have a history of osteoporotic fracture or if they have multiple risk fractures... multiple risk factors for fracture defined as WHO FRAX 10-year probability of hip fracture greater than 3% or a 10-year probability of a major osteoporosis-related fracture of 20% based on the US adapted WHO algorithm.

And the final inclusion criteria is that the patient has tried and failed with failure defined as intercurrent fracture following one year of treatment or a significant decrease in bone density while on treatment after ruling out other causes such as adherence, malabsorption, or calcium or vitamin D deficiencies, or is intolerant to or has a contraindication to at least one oral bisphosphonate and zoledronic acid. So the exclusion criteria for this medical policy is that denosumab is being prescribed for the prevention of all osteoporosis or for the treatment of glucocorticoid-induced osteoporosis. If the patient has any of the following contraindications, which is uncorrected pre-existing hypocalcemia, if the patient is pregnant, and if the patient is currently receiving XGEVA. I will leave that. So that's the end of the proposed policy for Prolia.

The proposed policy for XGEVA is that they are being treated for the... for any of the FDA approved indications with any of the following criteria. So it can be any one, two or three not like the Prolia medical policy, which required one, two and three. So for this policy you can look at it as three different indications. So the first way to receive XGEVA would be that if a patient has bone metastases from solid tumor and the patient has tried, is intolerant to, or has a contraindication to intravenous zoledronic acid. Number two is if the

patient is an adult or a skeletally mature adolescent with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. So no trial and failure of bisphosphonates there or other therapies. And lastly if the patient has hypocalcemia of malignancy, defined as an albumin-corrected calcium of greater than 12.5 mg/dL due to malignancy after ruling out other causes, and the patient has tried and failed with failure defined as refractory hypercalcemia after at least 7 but no greater than 30 days of IV bisphosphonate therapy per episode of hypercalcemia. And is intolerant to or has a contraindication to intravenous zoledronic acid or intravenous pamidronate.

The exclusion criteria for XGEVA mirrors the exclusion criteria for Prolia in that denosumab is being prescribed for the prevention of skeletal muscle events in patients with multiple myeloma for the prevention of all osteoporosis or for the treatment of glucocorticoid-induced osteoporosis. And the other contraindications are the same where it's uncorrected pre-existing hypocalcemia, patient is pregnant, or if the patient is currently receiving Prolia. And that ends the proposed medical policy for denosumab. So I will turn it over to the committee for questions and discussion.

Michael Johnson:

Any questions from the committee? So, again, we do have one stakeholder. So Dr. Sylvia Churchill. So we'll have her come to the podium for three minutes.

Sylvia Churchill:

Good morning. My name is Sylvia Churchill. I'm a Pharmacist here in Washington State and I work for Amgen as a Health Outcomes Pharmacist. Good summary there. There are just a few things I wanted to point out and one is that there is different dosing for the two formulations of denosumab. For Prolia it's 60 mg sub q once every six months and for XGEVA it is 120 mg sub q every four weeks. I did want to point out that XGEVA did show superiority to zoledronic acid in our clinical trials. Amgen conducted three randomized double blind head-to-head trials comparing XGEVA to zoledronic acid in patients with breast cancer, prostate cancer and other solid tumor cancers and an integrated analysis of these three trials showed an increase in the time to the first skeletal related event. The time was

19.5 months with zoledronic acid and 27.7 months with XGEVA so it extended the time by 8.2 months and it also decreased the total number of SRE events in this population. There was about 2,500 patients in each arm. The incidents of skeletal-related events with XGEVA was 1360 and with zoledronic acid was 1628. So these numbers can be a big deal to patients and especially if you've got a cancer patient who can extend the time to their first fracture by 8.2 months.

I also wanted to highlight the importance of considering renal function in this population of patients. These are cancer patients. They are generally older and often on nephrotoxic chemotherapy. A US study showed the incidence of renal impairment is 49% in these patients with solid tumors. With bisphosphonates and zoledronic acid you do want to be very cautious of using these agents in renal insufficiency. There's a dose adjustment required for a creatinine clearance of 30 to 60 and it is contraindicated in a creatinine clearance less than 30.

XGEVA on the other hand is not cleared by the kidneys. It is not affected by kidney function. So this is a drug that you can use in this population and that is probably one of the important things I wanted to point out. And then lastly I just wanted to let you know that in regards to Prolia we do have 10 years of long-term safety data that has just recently been completed and that's from the long-term extension of our Phase 3 Freedom trial. Over 2,600 patients completed 10 years of treatment with Prolia. The safety profile remained consistent over those 10 years and new fracture rates remained low. In addition, patients showed a progressive increase in their bone mineral density from baseline over that 10 years. That increase was 21.7% from baseline at the lumbar spine and 9.2% increase in BMD at the hip.

I have package inserts available if you'd like the complete information, but besides that is there any questions? All right. Thank you very much for your time.

Michael Johnson:

Thank you.

Ryan Pistoresi: If the committee has any further questions or discussion we can make a motion to accept this as is or if you have any amendments that you'd like to make.

Man: I have some questions. I'm just not sure about the use of the term "all osteoporosis". What do you mean by using that adjective "all"?

Ryan Pistoresi: So for the... one of the indications when we were using all osteoporosis is that we are also including the glucocorticoid induced osteoporosis. So if you'd like me to change the definition and redefine it as osteoporosis as defined as negative... a T-score of -2.5 or other...

Christopher Smith: In the exclusion criteria in slide 10 couldn't you just say for the prevention of osteoporosis or for the treatment or prevention and treatment of glucocorticoid-induced osteoporosis?

Ryan Pistoresi: We could change it to that.

Christopher Smith: That might be more clear.

Ryan Pistoresi: Okay. Thank you for the note. I will go ahead and change that. And so that will be noted for both the Prolia and XGEVA.

Christopher Smith: Looking at the inclusion criteria for Prolia I think I heard you say must meet one, two and three.

Ryan Pistoresi: Correct.

Christopher Smith: So one is really the definition, you know, you include the definition there of osteoporosis. Two then refers to... you've got the osteopenia in there. Would you need to have two if you already had one? Can you explain to me why you'd have to meet criteria two if you've already met criteria number one? If you've got osteoporosis as defined in category one I don't see why you would need to have history of fracture or have significant osteopenia which is 1B.

Amber Figueroa: I think inclusion criteria in number 2 is maybe addressing the B and C parts of number 1. Because these people are not necessarily people that have osteoporosis, but they need to be at high risk for fracture to qualify for this medication.

Ryan Pistoresi: In reviewing your comment... or your question, I do see the point that you're making that if someone has a T-score of -2.5 for 1A they likely would already meet the qualifications for 2B, which is defined as the WHO FRAX 10-year probability scores.

Christopher Smith: My understanding of the FRAX scores is it is not relevant to those with osteoporosis. By definition if you have osteoporosis you've got... you meet criteria for treatment and the FRAX score is used for those who have osteopenia to determine if it is severe enough to warrant therapy. So it is those that when you enter that into the search tools it is those with significant osteopenia and it's a way to calculate is it bad enough to warrant therapy? So their T-score is usually less... is between -1 and -2.5 when you use that tool. So I think the only change I would suggest is that you don't need to have the word and. I think it should be items... inclusion criteria 1 or 2 plus 3.

Ryan Pistoresi: Do any of the other members agree?

Susan Rowe: I like Christopher's change a lot.

Ryan Pistoresi: I can remove the AND. So it can be either 1 or 2 to meet...

Christopher Smith: Let's make sure everybody agrees with that. You may have had some reason for stating it that way, but my understanding is that would be more accurate. I think otherwise set up a bar that would not necessarily... it would be somewhat redundant. By having osteoporosis you are at high risk for fracture. So I don't think you really would need to go onto inclusion criteria 2 if you already met it with one of the first category definitions.

Ryan Pistoresi: I believe that when developing this the 2 was more relevant for 1B and 1C so patients who are on ADT or on a aromatase inhibitor who do not meet, you know, multiple risk factors for fracture do not

necessarily need to be treated with denosumab or a bisphosphonate. I think that was my original intention, but when drafting this outline I may have blurred the line between 2 and 1A. So one way that we could re-do it is that I could change it so that 1A is a criteria by itself and then 1B and 1C are linked to A and 2B. And so I can re-write that so that it shows 1A as a separate indication and then 1B and 1C must link to 2A or 2B.

Christopher Smith: So specifically if you're a man receiving... if you're treating a patient who is receiving androgen deprivation therapy for non-metastatic prostate cancer that in and of itself is an inclusion criteria?

Ryan Pistorosi: If they have the multiple risk factors for fracture or have a history of osteoporotic fracture.

Christopher Smith: You still have to meet one of the other criteria.

Ryan Pistorosi: That's correct.

Amber Figueroa: But isn't the whole reason this is indicated for groups in 1B and C is because they would be at high risk of fracture?

Ryan Pistorosi: I believe that when I was drafting this, this is how the inclusion criteria for the clinical trials defined the patients at risk for high fracture. And so this was derived from the inclusion criteria.

Christopher Smith: Maybe items B and C should be in this second category of inclusion criteria as items C and D? In other words they should be separated by the word OR from the other indications. Is that what you're saying?

Donna Sullivan: So Christopher, this is what I understand you saying is that 1A would just become 1 and then all of the others would be... 1B would become 2A, 1C would become 2B, etc., and then 2A would be 2...

Christopher Smith: In any order there. Yeah, they would all be separate definitions of a high risk for fracture other than osteoporosis.

Donna Sullivan: So they were all ORs and not ANDs?

- Christopher Smith: Correct.
- Donna Sullivan: So it would be 1A that patient is a man or post-menopausal women and diagnosed with osteoporosis defined as T-score of -2.5 or lower at the femoral neck, total hip or lumbar spine or the patient is at high risk for fracture defined as patient is a man who is receiving androgen deprivation therapy for non-metastatic prostate cancer or is a woman who is receiving adjuvant aromatase inhibitor for breast cancer or history of osteoporotic fracture or multiple risk factors for fracture defined as WHO FRAX 10-year probability of a hip fracture greater than or equal to 3% or a 10-year probability of a major osteoporosis-related fracture greater than or equal to 20% based on US-adapted WHO algorithm and then we move down to number 3. Correct. Okay.
- Christine Klingel: So one more point then. If we have the exclusion criteria then being prescribed for the prevention of all osteoporosis you could potentially have someone who is receiving androgen deprivation therapy, has not had a fracture, or it would be diagnosed with osteoporosis yet. Or you could have someone with multiple risk factors for fracture, but not technically diagnosed. Would that then exclude them because you can't use it for prevention?
- Ryan Pistorosi: That is correct. It has not been approved for the prevention of osteoporosis. Only for the treatment of osteoporosis and for the other approved indications.
- Christine Klingel: So if we had someone is receiving androgen deprivation therapy, but has not been diagnosed with osteoporosis but is at high risk then he wouldn't qualify based on being excluded because he's... we're preventing osteoporosis and we're not treatment it?
- Ryan Pistorosi: So that's where the FDA indication... it's a little funny how it's written. So it's for the treatment to increase bone mass. So not for the prevention. So one way that you can look at this is that you're not treating it indefinitely to prevent osteoporosis from occurring, you're

treating it to actually increase the bone mineral density or the bone mass in those patients to prevent fractures and other events.

Donna Sullivan: I think Christine what you're asking for is that somebody might have met criteria for treatment with denosumab in 1 or 2 that we just read, but then it's excluded because of this statement here. So I think what we could say is that denosumab is... denosumab for prevention of osteoporosis in people who do not meet criteria 1 or inclusions criteria 1 or 2 is not approved or is not authorized.

Christine Klingel: I got that. I think that would cover my concern.

Ryan Pistorosi: We can add that.

Chuck Agte: I have a question in regard to the proposed shift of 1B and C under 2. If we do that then it makes one of our criteria... basically B and C are the FDA indications. Correct?

Ryan Pistorosi: That is correct.

Chuck Agte: So if we just make 1A an OR and then move B and C into 2 as a list of things then it makes one of our approval criteria just history of osteoporotic fracture. And I don't think it's our intent to allow Prolia for anyone who has a history of osteoporotic fracture if they aren't meeting one of the FDA indications in B and C. So I'm not sure we can make that move as proposed so far. I think we need to manipulate the outline in our ands and ors a little bit, but I don't think we would want to do that as suggested because it makes A and B approval criteria unto themselves.

Donna Sullivan: I'll ask this to the clinicians, if somebody has a history of an osteoporotic fracture wouldn't they have a diagnosis of osteoporosis?

Christopher Smith: It meets crit... the who diagnosis, but it is not defined then by the T-score. So it's another definition of osteoporosis. It's another way of meeting the criteria for osteoporosis.

Donna Sullivan: So I guess the question to the committee is, is... do you feel a history of an osteoporotic fracture in and of itself is enough justification for the use of denosumab? I think is that what you are asking, Chuck?

Chuck Agte: Yes.

Man: Chuck's point is that it is not an FDA approved indication. Is that right?

Chuck Agte: My point was that it is, as originally written, it was not intended to be an approval criteria in and of itself. It was linked to the prior ones and I just wanted to make sure that the board saw that in terms of just the... the order of operations in the way it was being written there. So it's less, but it's not an FDA indication and more that I wanted to verify that they understood that it would make A and B approval criteria unto itself and verify that that was your intent.

Susan Rowe: Chuck, I think we would be... we would be okay on this because they still have... we've got the AND in there for the exclusion criteria and they have to have been... or not... number 3 they have to have failed a bisphosphonate. So I think that use of denosumab when a patient has had a fracture and has failed bisphosphonates I think is very reasonable.

Chuck Agte: Again, I wasn't expressing a clinical concern, I just wanted to make sure that that matched the board's intent. Because not knowing the clinical significance I was not sure where those lined up or did not line up. So thank you.

Amber Figueroa: Just to kind of clarify for the non-clinicians in the room. My thought of what that history of osteoporotic would mean is someone comes in, they have fallen and broken their wrist, they have... they are high risk for osteoporosis, but they refused to do a DXA scan or a diagnostic test to diagnose them to get a T-score with osteoporosis. So just to kind of help understand why that is part of the inclusion criteria, in my opinion.

Christopher Smith: You can have an osteoporotic fracture and not have a T-score greater than -2.5 and still be eligible for treatment. So they don't necessarily have to refuse a DXA.

Donna Sullivan: Again, in that fracture would be, as Dr. Rowe pointed out, in a patient that was on a bisphosphonate at the time of the fracture and that therefore that's a failure of the bisphosphonate.

Michael Johnson: Is there any further discussion? Anyone ready to make a motion? Do you want to change the wording on the screen or how do you want to do this?

Ryan Pistoresi: I can change the wording on the screen.

Christopher Smith: What about if you had the indications match the FDA-approved indications? Is there a reason why you wouldn't just have that list serve as your indications?

Ryan Pistoresi: Would you propose that I just leave it as one and then have the high risk for fracture be incorporated into the other FDA approved indications? Or just leave it as FDA approved indications without this section?

Christopher Smith: Just looking at their slide, number 5, and wondering whether that serves as inclusion criteria as well. Is there a reason why that wouldn't be your inclusion criteria?

Ryan Pistoresi: That was the intention for that 1A, B and C was for the inclusion criteria to have the osteoporosis in post-menopausal women, men with osteoporosis, breast cancer patients with AI and then prostate cancer with ADT.

Christopher Smith: And so then more generally you wanted to include some categories of patients that wouldn't specifically meet the FDA approvals and that would be those with the significant osteopenia or history of fracture? That's why you had a separate group of item 2?

Ryan Pistorosi: So I believe my original intention was to have item 2 be linked to the patients on ADT and AI because someone can have a T-score of +2 and be receiving an aromatase inhibitor and then would qualify based on that alone. And so based on what the inclusion criteria for the clinical trials were people at risk of fracture or people who have previously had an osteoporotic fracture and then were put on an aromatase inhibitor.

Christopher Smith: That's just the FDA approved indications. I get back to my original suggestion and that is just to change the AND to an OR after 1C. I would ask you to consider that as an option and tell me why that wouldn't suffice. Either inclusion criteria number 1 as originally written or number 2. It seems like that would be the most succincted.

Donna Sullivan: I think if we do that I'm okay with it. I think the question is, do we need a 1 and a 2? Or do we just have a list of things that are approvable?

Christopher Smith: It's just that it is broken down by those that are clearly FDA approved versus those that are not, but considered to be high risk. Is that correct, Ryan? Items in number 2 are not FDA approved indications.

Ryan Pistorosi: So yes, number 2 are not FDA approved indications, but are risk factors for patients that met 1B and 1C. So if I'm hearing you correctly one of the ways to solve this conundrum would be to just remove section 2 and just to have patients that meet the FDA approved indications and then patients' trial and failure of the bisphosphonates. I think that would clarify this medical policy and help answer... or help address your concerns.

Christopher Smith: But you do want to include those indications from item 2. Those are certainly relevant and those are patients who would be considered for treatment with Prolia. So I don't think you want to remove those. I really think it is quite clear the way it is written, you just want to say inclusion criteria 1 or 2.

Donna Sullivan: Then what I'm hearing you say, Christopher, is that you want all of these to be standalone by themselves approvable conditions. So what I would recommend instead of saying that patients that meet at least one of the following FDA approved indications, we just say patients that meet one of the following indications and list all five. Okay.

Amber Figueroa: I still think that that messes with the exclusion criteria of prevention of osteoporosis because if 2A and B become standalone then if you have someone who has multiple risk factors for fracture, but they are not diagnosed with osteoporosis then you're preventing osteoporosis.

Donna Sullivan: I think we already accepted the friendly amendment to... that denosumab is... the exclusion criteria is for those people who do not meet one of the above indications. We don't approve it for prevention of osteoporosis. I mean if you really... the more I think about it, it might be a little redundant because we say we approve it if you have one of these and we don't approve it if you don't have one of these. So we could potentially just get rid of that one, that first exclusion criteria. Does that make sense to you, Ryan?

Man: [inaudible]

Ryan Pistorosi: I'm just thinking that it is not approved for the prevention or treatment of glucocorticoid-induced osteoporosis. And in fact patients that were on glucocorticoids had I think a higher risk of abnormal fractures.

Donna Sullivan: So what I would recommend Ryan is that just delete denosumab as being prescribed... I would just change number 1 to say denosumab prescribed for the prevention of osteoporosis in... or for the prevention of glucocorticoid induced osteoporosis and get rid of the first part. So denosumab is prescribed for the prevention of glucocorticoid-induced osteoporosis.

Amber Figueroa: I think it should be for the treatment of glucocorticoid-induced osteoporosis.

Ryan Pistorosi: Okay.

Christopher Smith: I think we discussed that before. I think we said prevention or treatment of glucocorticoid-induced. You don't want people to use it to prevent it, either. Right? So you would just remove of all osteoporosis as an option. You don't want people prescribing it just to prevent or to treat.

Ryan Pistorosi: Okay. I added it so how does that currently sound? Denosumab is prescribed for the prevention or the treatment of glucocorticoid-induced osteoporosis?

Christopher Smith: That looks good to me.

Ryan Pistorosi: Do the other members have any further comment or questions?

The way that it is currently written now is shown up on the screen and I can pull it up in the PowerPoint presentation. So it would be listed as one of the following with the first three being the FDA approved indications, D being the history of osteoporotic fracture and E being the multiple risk factors and then number 2 is the trial and failure of the bisphosphonates. And now the new exclusion criteria would be for the prevention or treatment of glucocorticoid-induced osteoporosis.

Were there any additional changes you wanted to make on the XGEVA or is that okay except for maybe the exclusion criteria to reflect the exclusion criteria for Prolia? The XGEVA was not approved for osteoporosis since there is different dosing strategies between Prolia and XGEVA.

So if there is no further comment is there a motion to accept the medical policy as rewritten or as it currently stands?

Susan Rowe: I move to accept the policy as we have rewritten it.

Christopher Smith: I second.

Michael Johnson: All approve say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The motion carries.

Donna Sullivan: We are going to run through the current existing limitations on some of the PDL classes that we just reviewed and update those recommendations. So the first class that I want to go through is the anticoagulant drug products. Currently we have apixaban or Eliquis as preferred in addition to dabigatran, brand name Pradaxa. The current limitations are with your new motion still no therapeutic interchange and right now all of these medications are on prior authorization and they are limited to their FDA approved or compendia supported indications that are listed below and dispensed as written does not allow the override of that authorization. I do have an update that I want to make to our recommendation and I want to actually remove the prior authorization for preferred drugs. I'm sorry, I didn't get this updated beforehand. And then for the non-preferred drugs just require that the patients use both... or all of the preferred agents before they can go to a non-preferred agent. And the reason why when I was doing my research and looking at this particular class kind of to support what the gentleman said earlier, is we had roughly 40 authorizations for... or requests for the anticoagulants and I think we denied 2. And so it's just... since we have such a high approval rate it doesn't make sense to continue prior authorizing it, that they don't seem to be being used inappropriately and I think to some extent the indications have expanded since these drugs were first put on prior authorization. So that is my recommendation for this particular class.

Susan Rowe: I would endorse that actually, Donna. I think when we originally put the prior authorizations they were fairly new. We were using the prior authorization somewhat educationally to point out the need to be checking renal function. And I think they have been in use long enough that I think we can really safely remove that. So I would endorse removing the prior auth.

Donna Sullivan: Any other questions? Was there any stakeholder input?

Michael Johnson: No.

Donna Sullivan: Okay. So just a motion to approve would be...

Susan Rowe: I do have a question. So I'm looking at our preferred agent and non-preferred and again this is... bids are put in prior to our... sealed bids are put in prior to our meeting and then after we meet they can... are opened and negotiated. Is that?

Donna Sullivan: Yes.

Susan Rowe: So our preferred agents could change?

Donna Sullivan: That is correct.

Susan Rowe: Okay.

Eric Harvey: I'd like to make a motion that the Medicaid Fee for Service Program implement the limitations for the anticoagulant drug class listed on the previous slide as recommended in their recommendations.

Christopher Smith: I have a question. If someone is looking at this and wanting to understand it, would people know what "must step through all preferred drugs" means? Is that a term that is commonly used? Is there another way we should phrase that? Or does the rest of the committee feel that does not require clarification? Is it a term that speaks for itself?

Donna Sullivan: If you don't understand what it says then I would say that maybe other providers wouldn't either. So we could say must try... must have an adequate... and then we might have to define adequate.

Christopher Smith: That's the issue. Is it try and fail? Or is it... not like the way it smells. How are we defining this?

Amber Figueroa: That also doesn't address contraindications, which I'm trying to remember back a couple of hours ago when we were discussing it. If there were to be a contraindication to one of the preferred drugs...

Donna Sullivan: I added that in there. So they must try all preferred drugs with the same indication before a non-preferred drug will be authorized unless clinically... or unless not clinically appropriate or contraindicated.

Christopher Smith: I think that helps to clarify.

Michael Johnson: I think we have a motion with that addendum and I would second that as written.

Donna Sullivan: Okay.

Michael Johnson: So all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. This carries.

Donna Sullivan: The next class is the skeletal muscle relaxers as they are listed here and in this particular group most of the generic products are preferred at this point in time with the exception of carisoprodol, which the committee has made non-preferred for safety and potential misuse reasons. So the cyclobenzaprine... so baclofen, cyclobenzaprine, methocarbamol and tizanidine are all preferred for their generic formulations. The current limitations are that they must try one preferred generic before any brand is authorized. Carisoprodol requires prior authorization and it must be prescribed for one of its FDA approved indications of acute musculoskeletal condition and they must have tried and failed... or tried all preferred and non-preferred drugs within a skeletal muscle class before they can have carisoprodol. In addition to that the DAW does not override that prior authorization requirement. So we're recommending that we continue generics first, which is what is currently in place and that they continue the prior authorization on carisoprodol as it is.

Amber Figueroa: I don't know if we could reword the carisoprodol one, but it says limited to the diagnosis of acute musculoskeletal condition. Acute generally means kind of a two-week time period in my mind and if you've had to try eight meds before you can use that it just... I don't know.

Susan Rowe: Actually the feeling of the committee in the past is that we don't want it on formulary at all or even the option of it, but what... we're not able to do that because there is a federally mandated rebate on it so we're not allowed to exclude it. So this was effectively a way to not have our patients on it. That's just the history.

Donna Sullivan: I mean if the committee... what you're saying then is by then it's not... no longer acute. I understand that. If that is the intent then we can leave it. Or if the committee warrants, if they still need to try all of the other medications first we can remove the word acute if the committee feels that that is the direction you want to go.

Christopher Smith: I think it's good the way it is written. It's possible you could have a patient who has had multiple acute conditions and previously tried and failed the others and so now with their tenth ankle sprain they are asking for carisoprodol. So the situation could come up, but they might still somehow qualify, but I think that the restrictions sound like it is quite a good barrier in place.

Susan Rowe: If there are no other questions I move to prove the motion as written. Do I need to read it or do you have another question?

Christopher Smith: No, I was just going to second your motion.

Susan Rowe: Okay.

Donna Sullivan: I want to clarify. You said you want to approve the motion as written. I think what you meant to say is you want to approve the recommendation as written?

Susan Rowe: I move to approve the recommendations as written.

Donna Sullivan: Thank you.

Christopher Smith: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries.

Donna Sullivan: Okay. So the macrolide products, the azithromycin, clarithromycin and erythromycin, all of the generic products in this class are preferred. There's no limitations on the macrolides. There's no therapeutic interchange as well and I don't recommend any. I'm standing in the way of you and lunch. Make a motion.

Michael Johnson: So I move that the Medicaid Fee for Service Program implement the limitation... or the above, no limitations, for the macrolide drug class listed.

Mason Bowman: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. All right. The motion passes.

Donna Sullivan: And then the next class is the TZDs the Actos and Avandia. The current limitations is that rosiglitazone requires prior authorization to ensure that it is not used in congestive heart failure, and that they must try and fail metformin or another drug for diabetes, and pioglitazone. Between January and April 2016, as I mentioned earlier, there have been no requests for rosiglitazone. So my recommendation is to remove the prior authorization requirement on rosiglitazone.

Susan Rowe: I move that we accept the recommendations as written.

Eric Harvey: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. That passes.

Donna Sullivan: And we are finished.

Michael Johnson: That concludes the DUR Board. We are adjourned. Have a good day.