Washington State Pharmacy and Therapeutics Committee
June 21, 2017

Amber Figueroa: Good morning, everybody. My name is Amber Figueroa. I'm a committee member and I'm going to be chairing today. This is a new experience for me. So I'd like to convene this P&T Committee meeting and I think we'll start with introductions. It looks like we are a limited number today. So we'll go around and introduce ourselves.

Charity Harris: Charity Harris, Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Dale Sanderson: Dale Sanderson, committee member.

Catherine Brown: Catherine Brown, committee member.

Susan Flatebo: Susan Flatebo, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Po Karczewski: Po Karczewski, committee member.

Nancy Lee: Nancy Lee, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Amber Figueroa: All right. So let's jump right in. Our first order of business is looking at the expanded scan for ADHD.

Leta Evaskus: Ian, are you on the phone?

Ian Blazina: Yes, I am.

Amber Figueroa: Excellent. All right. Go for it.

Ian Blazina: All right. So this is the expanded scan report for pharmacologic treatments for attention deficit hyperactivity disorder from January of this year. The last report was update number 5 in July of 2015 and the last preliminary update scan was June 2016. The dates of searches for the current scan are January 2015 through December 2016. You can go to slide 3.

This is the inclusion criteria. We included studies of attention deficit disorder and attention deficit hyperactivity disorder in children and adults. The outcomes we were looking for were functional capacity, quality of life symptoms and abuse, misuse or diversion. We were including head-to-head randomized controlled trials, systematic reviews and we are excluding placebo-controlled trials following a decision from the last full update report to limit the scope. Next slide.

This is a table of included interventions, which I do not need to read. Next slide.

So we are looking for head-to-head trials. We did dual review of the quality of the studies and we did limited data abstraction in this expanded scan format. So we abstracted symptom response and functional capacity for benefits outcomes and overall adverse events and withdrawal due to adverse events for harms outcomes, as well as the author stated conclusions, but we did not do our own synthesis. Next slide.

So since the last update report we identified a few new drug formulations, two of amphetamine and two of methylphenidate. Next slide.

We identified no new serious harms and one ongoing Agency for Health Care Research and quality review of diagnosis and treatment

of ADHD in children and adolescents. The draft was posted in 2016. The final report is expected soon, but as of this morning it's not yet available. Next slide.

Since the last report update we identified five new publications, two were of primary head-to-head trials, and three were secondary analyses of two of the previously-included trials. Next slide.

This shows a table of these trials. Notice that all were in children or adolescents. Next slide.

So we identified two new trials of atomoxetine versus methylphenidate and these trials found no difference between the drugs in symptom outcomes. Both groups improved significantly from baseline and there are also no differences in withdrawals due to adverse events from one trial. Next slide.

We also found secondary publications of a trials of lisdexamfetamine. The primary publication reported time to response and response according to the CGI scale. The new secondary analyses included response for reductions of 25, 30 or 50% by nine weeks. So a dichotomous outcome, as well as sustained response over weeks four to nine, remission according to the CGI scale and parent-assessed functions. Next slide.

We also found two new analyses of a trial comparing extended release mixed amphetamine salts with extended release dexmethylphenidate. The primary analysis found no difference in symptoms between the drugs but better improvement at higher doses. New analyses finds that there were no significant differences in sleep durations, sleep start time, nocturnal awakenings or sleep end time and this was not affected by dose. The higher doses as a group reduced sleep duration compared to the lower doses by a mean of 21 minutes. Next slide. So since the last report in 2015 there have been four newly approved drug formulations, no new boxed warnings, one ongoing comparative effectiveness review and five new head-to-head publications. Next slide.

In summary the two primary… two new primary trials comparing atomoxetine to methylphenidate both… found that both drugs significantly decreased symptoms and symptom severity, but there was no difference between the groups in symptoms outcomes or withdrawal due to adverse events. Next slide.

And the secondary analyses found that lisdexamfetamine compared to atomoxetine more children taking lisdexamfetamine achieved response and they had more sustained response over week four to nine, as well as greater improvements in family, social and school functioning according to a parent assessment of the changes were very small. For the comparison of mixed amphetamine salts versus dexmethylphenidate both extended release there were no differences in sleep outcomes, but higher doses resulted in shorter sleep times for both drugs. And that's everything I have. Are there questions?

Dale Sanderson: A couple questions. Any differences between pediatric and adult populations in terms of effectiveness in the studies that you've seen and also differences between hyperactivity versus the inattention?

Ian Blazina: So all of the newly identified trials were all in children or adolescents. So we don't really have any information comparing to adults. They were also all in children with attention deficit hyperactivity disorder.

Amber Figueroa: Just clarifying, with the ADHD there's two subtypes – the inattentive and the hyperactive, but you guys… they didn't separate it out in any of those studies? It was just the ADHD in general?

Ian Blazina: Well, the way we do those expanded scans is we weren't digging deep into the papers for the population characteristics and things. So we would have to look more carefully at the papers to see if they stratified by the type.

Amber Figueroa: Great. Thanks again. Any other questions? Okay. We will move on to… we have a few stakeholders here today. So we'll call up Dr. Steven Fuchs. Next will be Ms. Christina Heiner. Just a reminder you will have three minutes to present.

Steven Fuchs: Good morning. My name is Steve Fuchs. I'm a field medical director for Pfizer. I'm here today to ask that Quillivant XR and QuilliChew ER be added to the Washington drug list as preferred agents. Both contain methylphenidate, a schedule 2 controlled substance. Their package inserts discuss important safety information including a boxed warning for abuse and dependence. The full prescribing information including the medication guide is available for each at their website. Both medications are indicated for the treatment of ADHD in children ages 6 years and above. Quillivant XR is the only approved extended release methylphenidate oral suspension. QuilliChew ER is the only approved extended release methylphenidate chewable tablet. The delivery system uses proprietary technology to create particles with various coating thickness which governs the extended release of methylphenidate.

Quillivant XR contains approximately 20% immediate release and 80% extended release methylphenidate. It is banana flavored. The QuilliChew ER contains approximately 30% immediate release and 70% extended release. It is cherry flavored. The efficacy of Quillivant XR was established in a two-week placebo-controlled cross-over trial in 45 children age 6 to 12 years old. The cumulated efficacy data from other methylphenidate products were also considered. The efficacy of QuilliChew ER was established in a double blind randomized placebo-controlled laboratory classroom study in 90 children age 6 to 12. Their safety profiles are similar to those of other methylphenidate products.

A [inaudible] equivalent study showed a similar pharmacokinetic profile for QuilliChew ER whether it was chewed or swallowed whole. The recommended starting dose of each is 20 mg once daily in the morning and may be titrated up or down weekly in increments of 10, 15 or 20 mg. Daily doses above 60 mg have not been studied and are not recommended. In an observational cohort study 54% of children ages 6 to 11 years reported they cannot swallow a pill. Having extended release methylphenidate available as a liquid as chewable tablets offers long-acting treatment options to clinicians for their

patients with ADHD who have difficulty swallowing capsules or tablets.

In conclusion, I would like to thank the committee for listening to my testimony and urge that Quillivant EX and QuilliChew ER be added as preferred agents to provide a unique treatment option for appropriate patients. I'd be happy to respond to any questions.

Amber Figueroa: Thank you.

Dale Sanderson: I have a question.

Amber Figueroa: Sorry.

Dale Sanderson: If someone swallows the chewable thing, how does that work?

Steven Fuchs: So, um, you know, it's made to be chewed, but if someone would swallow it, you know, we've had cases of that coming up. So they did a pharmacokinetic study and saw that the kinetics on that are the same so we expect, you know, we didn't study the… all the efficacy on it, but the kinetics on it were the same so you'd have the same absorption, you know, same length of time and all. If they do go and swallow it by mistake you are still going to get the action there.

Amber Figueroa: Thank you. Next is Christina Heiner and after her is Michelle Tori.

Christina Heiner: Good morning. I'd like to thank the members of the committee for the opportunity to ask for your consideration to add Adzenys XR ODT to the preferred drug list. My name is Christina Heiner. I'm the vice president of pharmacy for Viking Health Care Solutions. We represent NEOS Therapeutic, a pharmacy company based in Grand Prairie, Texas.

Adzenys XR ODT is the first and only extended release orally-disintegrating tablet indicated for the treatment of ADHD in patients age 6 and above. It's a long-acting tablet. It lasts around 11 to 12 hours. So this covers the patient during school and after school. The ODT technology uses drug-loaded amphetamine micro particles. The

uncoated particles are the immediate release particles, the coated particles are extended release and those are immediate release are released within the stomach and the extended release within the intestine.

As an orally-disintegrating tablet Adzenys XR ODT requires no water for administration. There's no need to swallow an intact capsule or tablet. It can be taken with or without food. It has an orange flavor and it disintegrates in the mouth between 30 and 45 seconds. This unique formulation was developed to meet the unmet significant demand for those patients who have difficulty swallowing. As you know, most ADHD patients are diagnosed at the ages of 6 and 7 and prior to that time they probably haven't had an opportunity to try an intact capsule or a tablet and studies have shown that up to 54% of patients in the pediatric population have difficulty swallowing and up to 40% in the adult population have difficulty swallowing.

Adzenys XR is a new formulation option that offers a viable and needed alternative to current dosage formulations. It's given as a single dose. There are clear dosing instructions. You know exactly how much medication the patient has taken. There are six different strengths. So that makes titration easier. I'd like to thank you for your consideration and I respectfully request that Adzenys XR ODT be added to the preferred drug list and happy to answer any questions.

Amber Figueroa: Dale, do you have any questions? Anybody else? Thank you. All right. That's it for stakeholders.

Leta Evaskus: Ian, are you still on the phone?

Ian Blazina: Yes, I am.

Leta Evaskus: Okay. We can let you go now. Thank you.

Ian Blazina: All right. Thank you.

Amber Figueroa: Do you guys have any questions or discussion at this point?

Ryan Pistoresi: As you look through the motion the first thing will be to accept the scan as adequate and then to go through the motion.

Amber Figueroa: I'd like to move that we accept the scan as complete.

Ryan Pistoresi: This is an expanded scan so it's different than the typical scans that we usually see. So this allows us to look at new information and add these new drugs as eligible to be preferred on the preferred drug list. So I think what we would say is that the scan is an adequate update and then you can reiterate the prior motion or make a new motion depending on your assessment of the new information.

Leta Evaskus: I need someone to second the acceptance of the scan.

Susan Flatebo: I second the motion.

Ryan Pistoresi: If you spend a second you can have any discussion or you can vote to whether it's approved or not and then after that we can go onto the different motions for the subclasses. Now it's the vote and then the motion.

Amber Figueroa: Okay. So then we need to vote because we have moved and seconded that we are accepting this expanded scan as adequate. All in favor say aye.

Group: Aye.

Amber Figueroa: Any opposed? I'm going to get the hang of this.

Ryan Pistoresi: Great. Thank you.

Amber Figueroa: All right. Go ahead.

Po Karczewski: On the safety and efficacy part on the alpha agonists. I know a lot of folks feel that the clonidine and guanfacine are very… quite a bit different in their actions and rather than having one included I would suggest that we should have both included.

Dale Sanderson: I would agree.

Amber Figueroa: I agree as well. Did anybody have any other discussion about the motion?

Dale Sanderson: One thing that has not been discussed here is the terms of abuse potential and, you know, packaging these different medications and which ones are more likely to be potentially abuseable. Is that something we should be considering?

Donna Sullivan: I think to some extent that's a little bit out of the scope. I don't know how you would distinguish which ones would be abuseable or not. I mean you can still swallow them so they are technically all abuseable. I'm not exactly sure if you're talking about diversion there's not a whole lot we can do about that.

Dale Sanderson: In terms of breaking the capsule and using it in ways other than, you know, more of the extended release things that may less likely to be abused.

Ryan Pistoresi: That may be more of a DUR type question rather than whether it can be preferred on the preferred drug list or not, but I think maybe that can be something that we can maybe evaluate at another time when we get more information.

Amber Figueroa: I have one question in this and it may be DUR related, but prior to now, what did we do for kids that couldn't swallow a capsule or a tablet? I mean I guess this is for the practicing people here. If these new drugs are the orally-disintegrating and the suspension and the chewable, what did we do before?

Donna Sullivan: So there has been a chewable methylphenidate, but its immediate release and I could be wrong, but I believe the Adderall is in the little pellets that they can open up the capsule and put it in like applesauce or something like that and take it.

Nancy Lee: So this is a question. So this is a scan to see whether or not a full report would also be something to pursue. Is that correct, as well?

So there's kind of two questions – one is whether to accept it as adequate or to pursue a fuller, more in depth update. Is that correct?

Ryan Pistoresi: So this is an expanded scan. So the typical scans are just an overview of what has been published just to say, you know, there's 5 new studies or 10 new studies just to give us an assessment of what new information is out there. This was an expanded scan so it's not at the same level as a full report where they go into the in depth information, but they do present some of the results that they find through the abstracts and they go through and look at kind of a high level so that they can present some new information whereas with the full report they go into all the details so they would have been able to answer the earlier question whether it was the inattentive ADHD or the hyperactive ADHD. So this is what we could get from DERP for this medication class and it will allow us to add these new products to be eligible to be on the preferred drug list, but it's not to the point where we could get a full report and I'm not sure if we would be able to get a full report on this class given some of the interest in some of the other drug classes with the other states.

Donna Sullivan: And you guys did just vote to accept it.

Amber Figueroa: In the motion it doesn't list them out. We're going to need to say the new ones if we want to include them, correct?

Ryan Pistoresi: Based on that the previous motion just listed methamphetamine-based and amphetamine-based agents I'm guessing that it includes those subcategories and so for this one we wanted to split it out to show that there were new amphetamine products and methylphenidate products and then to also help clarify which ones were the non-stimulants, the atomoxetine and then the alpha agonists.

Leta Evaskus: So do they not need to call them out because usually we list them out individually, but in this case can they just say everything in the amphetamine class and everything in the methylphenidate class?

Ryan Pistoresi: I think that would be fine. I'll leave it up to you to say if you want to name all of the individual drugs or if you want to just say the amphetamine, the dextroamphetamine, and know that we are including them on the column to the left.

Donna Sullivan: The reason why we do that is normally we don't call out brand names in the motions. So if you were just to name the drugs as they are listed, you know, in the motion just knowing that now they do include the new brands that are eligible to be preferred.

Amber Figueroa: I move that after considering the evidence of safety and efficacy and special populations for the treatment of ADHD I move that methylphenidate-based and amphetamine-based agents of both long- and short-acting formulations are safe and efficacious. A long- and short-acting formulation of each stimulant should be preferred drugs on the Washington State Preferred Drug List. No single stimulant medication is associated with fewer adverse in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington PDL.

After considering the evidence of safety, efficacy and special populations for the treatment of ADHD I move that the non-stimulant atomoxetine is safe and efficacious and should be included as a preferred drug on the Washington State Preferred Drug List.

After considering the evidence of safety, efficacy and special populations for the treatment of ADHD I move that the alpha agonists clonidine and guanfacine are safe and efficacious and that one of these agents should be included as a preferred drug on the Washington State Preferred Drug List.

Diane Schwilke: I'll second that.

Amber Figueroa: All in favor say aye.

Group: Aye.

Amber Figueroa: Opposed? All right. Moving on. Okay. Next we are going to move on to antiemetics. Do we have our presenter ready?

Ryan Stoner: Yes. This is Ryan Stoner.

Ryan Pistoresi: Great. We are getting the slides up and we will let you know when we are ready.

Ryan Stoner: All right.

Ryan Pistoresi: We're ready. All right.

Ryan Stoner: This is the expanded scan report for newer antiemetics completed in February 2017. Slide 2.

This is the history of this report and scan and the search dates for this current expanded scan were June 2016 through January 2017. Next slide.

This lists our inclusion criteria with our populations being adults and children undergoing surgery receiving moderately or highly emetogenic chemotherapy or radiation therapy or are people… women… pregnant women. Our interventions here that were included in the most recent update scan in July 2016 are listed below and that was the scan previous to this current report. Next slide.

Note on the methods in this particular expanded scan we looked for head-to-head trials of new drugs and if that was not available we also included placebo-controlled trials. We also screened secondary analyses for results if they… and then included them if they differed from the overall trial. Again, for the expanded scans we reported study quality and we included selected outcomes. For this report there were two efficacy outcomes, one being complete response and the other being the use of rescue medications and two harms, overall adverse events, and withdrawals due to adverse events. Again, as with the previous expanded scan we included the author's conclusions and results, but we did not do any synthesis on our own. Next slide.

The interventions included in this expanded scan are listed on this slide and these drugs and formulations of newer antiemetics approved since the last full DERP report, which was in 2009. The last two drugs on this list were found… are new since the last scan and they were found while we were doing searches for this current report. Next slide.

Our results of our search found 13 randomized controlled trials and this is a list of those broken down by the drugs and the populations and the comparisons. To get into the details, next slide.

For the granisetron transdermal system we found three randomized controlled trials. One was a poor quality and is not listed here. It was in adults with emetogenic… undergoing emetogenic chemotherapy and it found that this transdermal formulation was not inferior to other 5HT3 antagonists. Next slide.

Also the granisetron extended-release subcutaneous injection we found one randomized control trial and again this injection was found to be non-inferior to palonosetron IV. Next slide.

For rolapitant in the chemotherapy population we found four randomized controlled trials, three good, one fair and we found that… or these studies rather all concluded that rolapitant added to a 5HT3 antagonist was superior to the 5HT3 antagonist alone. Next slide.

We also found one good quality randomized controlled trial of rolapitant in women undergoing abdominal surgery and we found that rolapitant… or the study found that rolapitant alone was similar to ondansetron alone at preventing post-operative nausea and vomiting in this group of women. Next slide.

We also looked at netupitant and palonosetron combinations. We found first here a randomized controlled trial of fair quality where they used separate drugs together. This is not the fixed dose combination product. We included this because we did not have

other head-to-head evidence. But this combination alone was better than palonosetron alone. Next slide.

For doxylamine/pyridoxine fixed dosed combination products we found one placebo controlled trial in women with nausea associated with pregnancy. This was the product with 10 mg each of both drugs. We did not find any studies that examined the fixed dose combination product that had 20 mg of each drug. But for the combination of 10 mg of doxylamine and pyridoxine we found it to be superior… the study found it to be superior to placebo in reducing nausea and vomiting in pregnant women over two weeks. Next slide.

Because we found only this placebo-controlled trial for doxylamine and pyridoxine we also included one randomized control trial that we found that gave these products together, not in a fixed dose combination, but they were slightly different in terms of the amounts given, 25 mg and 12.5 mg of the drugs respectively. And this was found to be inferior to ondansetron in reducing nausea and vomiting in pregnant women over five days in this small trial. Next slide.

And finally this slide is just a summary of the evidence we found based on 12 fair and good quality randomized control trials for your reference. That's it. Are there any questions?

Amber Figueroa: I know in the last few years there's been concern about some studies showing, I think, birth defects with ondansetron used in first trimester. I didn't see anything about any boxed warnings or anything in here. Can you comment on that at all?

Ryan Stoner: It just wasn't something that was in the scope of this particular report, but it is something that would be looked at in further scans of the normal preliminary update scans. We would look for boxed warnings.

Amber Figueroa: Okay. Questions for Ryan? Okay. Thank you, Ryan, for the presentation. You can go ahead and go.

Ryan Stoner: Thank you.

Donna Sullivan: I just looked up ondansetron in MicroMedics and there is nothing in MicroMedics saying anything about birth defects or black box warnings. So I don't know if it is raised to that level yet with the FDA.

Amber Figueroa: We do have one stakeholder, Mr. John Dufilho.

John Dufilho: Good morning. My name is John Dufilho. I'm the senior medical science liaison for Heron Therapeutics for the western United States. I'm here today to review a couple of items that were not included in the current scan, one antiemetics. So a couple of items that may not have been available for inclusion. The first is a second phase three randomized study that was done in highly emetogenic chemotherapy specifically looking at the delayed phase of CINB day's two to five. This was a randomized, double blind, double [inaudible] study that was done with Sustol compared to ondansetron in combination with [inaudible] and dexamethasone in patients receiving highly emetogenic chemotherapy.

The unique thing about this study is that this was the first registrational trial that's been done using guideline recommended three-drug regimen in both arms. So the patient's received in the Sustol group they received 10 mg subcutaneously. In the ondansetron group they received the package insert label indication dose of 1.15 mg per kg IV and both patient groups also received [inaudible] 150 mg and dexamethasone according to the guideline recommendations.

The primary endpoint of the study was complete response meaning the patient had no amidic episodes and there was no use of rescue medication during the delayed phase, days two through five. 942 patients were enrolled and randomized equally between the two groups. The primary endpoint was reached with a CR rate for Sustol of 65% in the delayed and ondansetron CR8 of 57% for an absolute difference of 8% equating to a 14.2% relative improvement.

There were also significantly greater proportions of patients receiving Sustol who reported no rescue medication use in the delayed and

overall phases and also there was a significantly longer time to first use of rescue medications in the Sustol group. The patient's also reported a highly significant satisfaction with nausea and vomiting control which was reported for Sustol over ondansetron. There were no new safety signals in the study as compared to the 5HT3 receptor antagonist class and injection site reactions were noted in about 60% of both arms of the study with the most common injection site reactions being bruising and pain at the injection site. So this study represents the first time a 5HT3 [inaudible] antagonist has demonstrated superiority over another in highly emetogenic chemotherapy.

The second item for possible inclusion, which was published in the beginning of 2017 were the new NCCN antiemetics guidelines. In these guidelines Sustol received a category 1 recommendation for the prevention of CINV in patients receiving either highly emetogenic or moderately emetogenic chemotherapy.

Amber Figueroa: Mr. Dufilho, I'm going to have to cut you off there. Your time is up. Thank you.

John Dufilho: Any questions?

Amber Figueroa: Thank you. There is a question about the adequacy of the scan. I move that the expanded scan for antiemetics be accepted as adequate.

Dale Sanderson: I will second.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? Since there are so few of us, speak loud. Okay? That was a weak aye.

Nancy Lee: For the motion I suggest a change in wording. The second sentence, the preferred drug list must include at least one medication that has

instead both oral and intravenous routes, considering that have alternative routes approved in both adults and children since there is also transdermal patch available.

Ryan Pistoresi: Do you mind actually saying how you want it to read out as if you were reading the motion? That way we can copy it.

Nancy Lee: From the beginning?

Leta Evaskus: No, just that sentence.

Nancy Lee: Okay.

Ryan Pistoresi: Unless you want to do the whole motion and propose it?

Nancy Lee: So the sentence that I would like to propose changing – The preferred drug list must include at least one medication that has alternate routes approved in both adults and children.

Ryan Pistoresi: Do you mean to say that more than one route must be approved? Because the way it is read the preferred drug has one medication that has alternative routes. So do you want to maybe rephrase that to say that includes?

Nancy Lee: Yes, that includes multiple… yes.

Ryan Pistoresi: Thank you.

Amber Figueroa: So there are three medications on here that are not in the previous motion. So what we're deciding the doxylamine, the netupitant/ palonosetron and the rolapitant as if those should also be included in the preferred drug list. Discussion? Thoughts?

Susan Flatebo: Currently, is there not a neurokinin 1 antagonist approved or on the preferred drug list? Is the aprepitant or fosaprepitant are they on the preferred drug list?

Ryan Pistoresi: I'm just going to pull up the antiemetic section of our PDL and see what we have as preferred. So for our PDL we have granisetron solution and tablets. We have ondansetron ODT tablets and ondansetron solution and tablets. Did that answer your question?

Susan Flatebo: Yeah. As I'm seeing how this is worded the preferred drug list includes the 5HT3 antagonists only of the ones mentioned here, granisetron, ondansetron, dolasetron, and palonosetron.

Donna Sullivan: I'm looking at the PDL and it looks like the committee excluded aprepitant from the class. So it's not necessarily not preferred, it's just not part of the class. So it might be in the motion. It's the last sentence in the motion. It's up to you to decide if you want to lump all of the different antiemetics together that have the different mechanisms of action. The last time we reviewed it though the committee decided not to, but I think now there are a few other alternatives that have different mechanisms of action other than the 5HT3s.

Amber Figueroa: Clarification. This grouping is antiemetics, but then the subgrouping is 5HT3 antagonists?

Donna Sullivan: When we first added these drugs to the PDL years and years ago there were only the 5HT3s on the market. Then one… when new drugs came out the governing board for the Drug Effectiveness Review Project, you know, voted to include the drugs… the newer drugs in the class that had different mechanisms of action because they were being used. And so… however, the committee, when we reviewed it, chose not to include the aprepitant because it had… I don't remember exactly the indications, but it had a more refined use, I believe, at the time. So you didn't want it to be subject to therapeutic interchange or with the 5HT3s and so you chose not to put it on the… to include it in the class. But now, you know, you can reverse your decision and add, you know, add it as well as all of the new ones that were discussed today if that's what you choose to do.

If you feel that aprepitant or fosaprepitant, one of those, you know, needs to be included, you know, you can put in your motion, you

know, one of each mechanism of action or that we have to have something other than a 5HT3 in addition to any 5HT3 you can make those recommendations as well and then we'll consider those when we're doing the final selection of the products.

Susan Flatebo: I recommend that we add a drug in that class or have that option in there of aprepitant and fosaprepitant to be included in the medications used to treat radiation therapy, chemotherapy to include a neurokinin 1 antagonist.

Ryan Pistoresi: The way it is currently written it says that they are not included. So would you want to propose language that says, you know, the preferred drug list must include one medication and then after that you can propose a new sentence that the preferred drug list must include at least one medication for what you just said or however you want to phrase it?

Susan Flatebo: Yeah, I would propose language saying the preferred drug list also to have an option to include a neurokinin 1 antagonist.

Leta Evaskus: Do you want to add aprepitant and fosaprepitant to the list of drugs that are safe and efficacious?

Susan Flatebo: Yeah. I would like to include specifically fosaprepitant and aprepitant to the preferred drug list.

Donna Sullivan: So I'm going to just recommend a change then. Do you want to… because we don't know all of the different indications do we want to change this? Instead of calling out nausea and vomiting related to chemotherapy, radiation and post operatively, do we want to change that to their labeled indications so that FDA approved indications… and it is neurokinin 1? I just want to make sure we spell it right in the motion.

Susan Flatebo: Yeah, it's neurokinin 1 antagonist and I would say specifically for highly emetogenic chemotherapy and radiation therapy. They should be a preferred to treat.

Donna Sullivan: Okay. So would you call that a special population? Just for us how we operationalize this, so we put status indicators on when we do our cost analysis. So would you say that the aprepitant and fosaprepitant should be really limited to those people that have the significant emetogenic nausea, vomiting or treatment?

Susan Flatebo: Yes.

Donna Sullivan: That way we can… it's not open for everyone. So we can put it on prior authorization or put it on… actually not PA, but like an expedited authorization code. So if the pharmacy, you know, puts in the code then we can… it will be approved for just the severe chemotherapies and radiation that causes significant nausea and vomiting and not be open to, you know, somebody that just has nausea from post-operative or something like that.

Susan Flatebo: Yeah. I would maybe word it to say have the Washington preferred drug list to include fosaprepitant and aprepitant for treatment of patient's undergoing highly emetogenic chemotherapy or radiation therapy. So that kind of limits so that it can't just be used for other indications.

Donna Sullivan: Are those the only two neurokinin 1 antagonists?

Susan Flatebo: No. They talked about… today this expanded scan also covered rolapitant and netupitant as well.

Donna Sullivan: Instead of calling out a particular drug do you want to… would you want to say that neurokinin 1 antagonists… there must be a preferred neurokinin 1 antagonist for highly emetogenic chemotherapy and radiation?

Susan Flatebo: Yes, yes.

Ryan Pistoresi: Okay.

Donna Sullivan: I would make that specific too for patients with… receiving highly emetogenic chemotherapy or radiation therapy.

Amber Figueroa: What we're listing out in the second sentence, all the meds that are efficacious then we need to also include the netupitant, rolapitant, and the doxylamine. Correct?

Donna Sullivan: Correct. I'm just going to make a grammatical change. Can we put… where it says in the very first sentence, special populations for their FDA approved indications. Can you cut for their approved indications and then move that to… after efficacious at the end of that sentence? Thank you.

Susan Flatebo: The line that says granisetron, ondansetron and palonosetron can be subject to therapeutic interchange. Should you also include dolasetron since that's also a 5HT3 in that sentence?

Woman: Yes.

Susan Flatebo: And then further down for the neurokinin 1 antagonists, which are the netupitant, aprepitant, fosaprepitant and netupitant. I'm assuming at another meeting we'll probably discuss which would be the preferred. We would talk about which would be the preferred agent or…

Donna Sullivan: No. What would happen is we do a cost analysis and so we will look to see, you know, we will put… look at the supplemental rebate bids, if any from the manufacturer's, and then we'll do a cost analysis and pick which one is the preferred based on cost if you assume that they are all equally safe and efficacious. So the question would be is, do you want the aprepitant, netupitant and rolapitant, are those interchangeable in your opinion?

Susan Flatebo: My personal experience I have the most experience with aprepitant and fosaprepitant. I'm not as familiar with the other ones.

Donna Sullivan: Meaning like if somebody prescribed rolapitant would you feel comfortable if the doctor wrote, you know, may substitute that they could switch it to fosaprepitant? So that's what interchange would happen.

Susan Flatebo: Yes.

Donna Sullivan: Okay. So I would suggest that you include something that the anti… instead of listing out the drugs say something like the drugs can be… the antiemetics can be interchanged within their mechanism of action so that we can do the 5HT3s. We can do the neurokinin 1 antagonists separately and kind of treat them as two subclasses within this.

Susan Flatebo: Okay.

Ryan Pistoresi: Did you want to also leave in routes of administration within mechanisms of action or just within mechanisms of action?

Susan Flatebo: Just within mechanisms of action.

Ryan Pistoresi: Okay.

Donna Sullivan: So now if somebody could just read it.

Nancy Lee: Can I add a comment or question about doxylamine/pyridoxine? So in the expanded scan there was a placebo-controlled trial and then there was another randomized control trial that basically… the combination was inferior to ondansetron in reducing nausea, vomiting. So I don't know if the committee wants to reconsider that one in the first sentence?

Donna Sullivan: You can still include it if you want to say it is efficacious and you could… if you don't want it to be preferred you could say it should not be preferred or you can, you know, completely exclude it from the class if you want to do that. That's up to you. Just wanted to let you know kind of how you can handle it in the motion if you need to.

Amber Figueroa: Any comments about that, guys? I would back away from excluding anything when the study has an N of 36 and it's done over five days in one class of people. It may not work for that, but it may work great for post-op nausea.

Donna Sullivan: Is that one only indicated, we think, in pregnancy? And so maybe restrict it for use in pregnancy.

Nancy Lee: Aren't we kind of saying that in the sentence of efficacious for the FDA-approved indications?

Donna Sullivan: Yeah.

Susan Flatebo: I'll go ahead and… after considering the evidence of safety, efficacy and special populations I move that aprepitant, doxylamine, pyridoxine, netupitant, palonosetron, fosaprepitant, granisetron, ondansetron, rolapitant, dolasetron and palonosetron are efficacious for their FDA-approved indications. The preferred drug list must include at least one medication that includes alternate routes approved in both adults and children. The antiemetics can be subject to therapeutic interchange within their mechanism of action on the Washington preferred drug list. The preferred drug list must include a neurokinin 1 antagonist for patients receiving highly emetogenic chemotherapy and radiation therapy.

Catherine Brown: I'll second.

Amber Figueroa: All in favor.

Group: Aye.

Amber Figueroa: Opposed? All right. We totally reconstructed that one.

Ryan Pistoresi: I just wanted to say that we have scheduled a break a 10:00 a.m., but that was at the assumption that we would get through all the scans. So the anticoagulant scan and the multiple sclerosis scan by 10:00 a.m. Just wanted to bring that up in case you were planning on having a break at 10 or if you wanted to finish the P&T session, have a break and then reconvene as the DUR.

Amber Figueroa: Let's do it then. Next we have the anticoagulant scan. Do we have our presenter on board?

Brittany Lazur: Hi, this is Brittany.

Amber Figueroa: Go ahead. We have the slides ready.

Brittany Lazur: Great. Thank you. So this is the first preliminary update scan since the last report on this topic of new oral anticoagulant drugs. This scan was completed in April of this year. Next slide.

So the previous report was the original report which was completed in May of 2016 with searches through September 2015 and the searches for this scan were August 2015 through March of this year. Next slide.

So we included adult populations for the treatment of deep vein thrombosis or pulmonary embolism for extension of treatment for DVT or PE in patients at increased risk. For prophylaxis to prevent VTE in patients undergoing orthopedic surgery and also for prophylaxis in patients with a-fib. Next slide.

We included the following interventions: so one direct thrombin inhibitor, dabigatran and then the direct factor Xa inhibitors – apixaban, rivaroxaban and edoxaban. Next slide.

So slide 5 illustrates the comparators that we included in the scan. Next slide.

In terms of new drugs we did not identify any new anticoagulant drugs that have been newly approved since the last report and although reversal agents were not currently included in the scope of the report we note that the following new reversal agent for dabigatran has been approved. This is idarucizumab. This was approved in October of 2015. There are also two other reversal agents that are not yet approved, andexanet alfa, which is in phase 3, B or 4 development, and ciraparantag, which is in phase 2 development. Next slide.

So we identified no new serious harms that have occurred… or have been posted since the last report. Next slide.

So we've identified no newly completed reviews or comparative effectiveness reviews on this topic. However, there is one ongoing review by the Agency for Health Care Research and Quality pertaining to venous thromboembolism prophylaxis in patients undergoing orthopedic surgeries and as of this presentation this review is still ongoing at this time. Of note there is one CADTH review or review from the Canadian Agency for Drugs and Technology and Health for the newly approved reversal agent idarucizumab and this was published in January 2017. Next slide.

So since the last update report we have identified three active controlled trials. As you can see on this slide we have one for each population – atrial fibrillation, orthopedic surgery and pulmonary embolism. You can see that two trials compare rivaroxaban and enoxaparin to each other and once trial compared edoxaban with the enoxaparin/warfarin combination. Next slide.

We've also identified a number of secondary analyses of active controlled trials included in the prior report, 22 to be exact. So as you see on this slide the number of studies is broken down by the population and then by the primary study. Next slide.

So since the last report we've identified no newly-approved oral anticoagulants, no serious harms for these drugs, and no new completed reviews of anticoagulants. We have identified three new active-controlled trials and 22 new secondary analyses of active-controlled trials included in the last DERP report. Any questions?

Catherine Brown: On the new trials I'm not seeing that you listed whether they are good, fair, poor. Do you have that information?

Brittany Lazur: For scans we don't do quality assessments, but if we were to do a report and we included [inaudible] the quality assessment.

Catherine Brown: Thanks.

Amber Figueroa: Do we have any other questions for the presenter? Okay. Great. Thank you. Go ahead and go.

Ryan Pistoresi: I believe Brittany is also doing the next scan after this.

Amber Figueroa: So stay, Brittany, please.

Ryan Pistoresi: Thank you. Thank you, Brittany.

Brittany Lazur: Let me know when you're ready.

Amber Figueroa: Okay. We do have one stakeholder. Dr. Chris Conner. Could you come and present? You have three minutes.

Chris Conner: Good morning. Thanks for the opportunity to make a brief statement. I'm here with BMS to provide a statement in support of…

Ryan Pistoresi: I'm sorry. Could you state your name and also…

Chris Conner: Sorry. Yes, Chris Conner with Bristol Myers Squibb. I'm here to make a brief statement on behalf of Eliquis or apixaban. I'm support of its position on the Washington Medicaid PDL. I'm required to state first that Eliquis is indicated for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular A-fib. It's indicated for the treatment of DVT and PE and for the prevention of recurrence after initial treatment. It's also indicated for the prophylaxis of DVT in patients who have undergone hip or knee replacement surgery.

I'm also required to remind everyone that there is a black box warning for apixaban similar to the other direct oral anticoagulants. In regards to two items, two main items, one is the increased risk of [inaudible] with premature discontinuation and with risk of spinal hematoma with [inaudible] anesthesia or spinal puncture.

Lastly I do have to mention that the most common adverse events for apixaban are related to bleeding so providers are advised to evaluate the symptoms of blood loss promptly. For full safety information I'll refer you to the product package insert, but in closing I'd like to state

that as you've heard there are no randomized controlled head-to-head trials that compare these [inaudible]. However, there are observational studies and indirect treatment comparisons that do exist. Most importantly, of note, there have been three recently published that are non-industry sponsored. These studies were conducted by a group of researchers at the Mayo Clinic and before… I'd like to tell you briefly about the results of one of those studies, but before I do that I do have to also remind you that these kinds of observational studies obviously they are designed not to address causation, but they are designed to discover associations and the results of these observational studies are not meant to imply interchangeability or comparative clinical efficacy or safety. You really do need randomized controlled trials to establish that.

Now all that said and with all those caveats in mind I do think that these observational studies are important. Specifically, for policy makers like you where you're in a position to really think and evaluate the benefits of harms of these medications as they are used in clinical practice population versus the select kinds of patients that even quality for enrollment in clinical trials. With all that in mind I'd like to really briefly cover the results of one of these studies conducted by these Mayo researchers and the lead author here is noteworthy. This particular piece was published in Chest in December of last year. In this particular analysis the Mayo researchers used United Healthcare Optum Labs data, which is a combined medical pharmacy claims data set that compared a match cohort of non-valvular a-fib patients who were prescribed either apixaban, dabigatran or rivaroxaban and while they didn't find any difference in stroke or systemic embolism at primary efficacy endpoint, they did look at inpatient major bleed events and what they did find there was that there was a 50 and a 61% relative reduction in the rate of inpatient major bleed versus dabigatran and rivaroxaban respectively. Therefore…

Amber Figueroa: I'm going to have to cut you off there. Sorry.

Chris Conner: Okay. Thank you. Are there any questions?

Amber Figueroa: Any discussion about the scan adequacy? Then I move to accept the anticoagulant scan as adequate.

Dale Sanderson: I'll second.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Any opposed? Okay. I do have a question about the reversal agents. Is that considered somewhere else? If we're going to be approving drugs that have reversals we need to make sure that we have a way to reverse them.

Ryan Pistoresi: Right. So this is just looking at what's on the preferred drug list. So these products are available outside of the preferred drug list. So if a medication is needed they can request it much like all the other drug classes outside of the PDL. Now I don't know if those reversal agents will necessarily be included in these in terms of the future reports, but we would have to expand the scope of this class to include those. So right now they are not part of this class but they are still available just outside of the PDL.

Donna Sullivan: I don't know how those administered. Is that something that a patient would go to a pharmacy and pick up and take it on a regular basis or is that something that would be administered in the doctor's office or the hospital because it's an emergency? So that's kind of the scope of our preferred drug list in general. Administered in an emergency room or in the hospital setting we would never see that come through our pharmacy system.

Susan Flatebo: I just had a question on that last sentence, the apixaban, dabigatran, edoxaban and rivaroxaban cannot be subject to therapeutic interchange. So even though three of them are in the same class the dabigatran is a direct thrombin inhibitor, but aren't they taken as a class? So there's no interchange among them at all? I guess that's my question.

Ryan Pistoresi: So that was the previous motion. It was decided just to keep them all separate so that there would be no therapeutic interchange across this whole class. But if you'd like to change that since you mentioned that dabigatran has a different… is a direct thrombin inhibitor compared to the apixaban, dabigatran and rivaroxaban, you're more than welcome to do that.

Susan Flatebo: I would recommend changing the wording such that… as a separate class they should be subject to therapeutic interchange, specifically I mean dabigatran is a direct thrombin inhibitor, but the other three, you know, should be… since they are in the same class, I think they should be subject to therapeutic interchange.

Ryan Pistoresi: Right. So Leta just deleted the dabigatran from that list and the rest of the sentence… yeah, can be. Yes. So I think that… Is that what you were looking for?

Susan Flatebo: Yeah. Or just say, you know, based on mechanism of action or something like that. Or the other ones are factor 10A inhibitors. I don't know how you want to word it, but in such a way that I think they should be subject to therapeutic interchange.

Ryan Pistoresi: The way it is written up there is adequate for what you were looking for?

Susan Flatebo: Yes. Perfect. Thank you.

Amber Figueroa: After considering the evidence of safety, efficacy and special populations for newer anticoagulant drugs for the prevention of stroke or 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, edoxaban and rivaroxaban can be subject to therapeutic interchange in the Washington preferred drug list.

Jordan Storhaug: I second the motion.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? All right. Moving on to the multiple sclerosis scan.

Ryan Pistoresi: Brittany, we are getting the slides up. We will let you know when we're ready. Okay, we're ready.

Brittany Lazur: Okay. Thank you. So this is the first preliminary update scan since the last report on disease-modifying drugs for multiple sclerosis and this scan was completed in June of this year. Next slide.

So the last report was update number 3, which was completed in May of 2016 with searches through January of that year and the date of searches for this scan were November 2015 through May of this year. Next slide.

We included adult outpatients with multiple sclerosis including relapsing-remitting, secondary progressive, primary progressive and progressive relapsing multiple sclerosis. We also included adult outpatients with clinically isolated syndrome. Next slide.

In this slide we have the drugs that were included in this scan in order of approval. So the first drug on this list was approved most recently. Next slide.

On this slide we list the effectiveness outcomes for both populations of interest. Next slide.

On slide 6 we have the harms outcomes for these populations and for a full list of study designs they are available in the full scan document. Next slide.

So in terms of new drugs we identified two newly-approved drugs since the last report. The first is daclizumab, which was approved in May of 2016 and then second ocrelizumab, which was approved in March of 2017. And of note both drugs were under FDA review at the

time of the 2016 DERP report and so we included evidence for both these drugs in that report. Next slide.

So we identified one new serious harm. Or actually it's a revision to a prior boxed warning for teriflunomide and it refers to the risk of teratogenicity and this boxed warning was edited in November of 2016; however, this risk was known at the time of this drug's approval in 2012. Next slide.

And we've identified no newly published comparative effectiveness reviews since the last report. Next slide.

So on slide 10 we have identified four new head-to-head trials since the last report, two trials of the new drug ocrelizumab in relapsing-remitting multiple sclerosis. We've identified two new placebo-controlled trials both in primary and progressive multiple sclerosis and one each involving ocrelizumab and fingolimod. We've identified five new secondary analyses since the last report, three head-to-head and one of the new drug daclizumab, two placebo-controlled secondary analyses and three publications, and one of the new drugs daclizumab. Next slide.

So on slide 11 we have the study characteristics of the new head-to-head trials that have been published since the last report.

And on slide 12 we have the study characteristics of the new placebo-controlled trials published since the last report.

And then on slide 13 we have the study characteristics of the secondary analyses of prior included trials since the last report and it's broken down by the head-to-head trials and then also you can see the placebo-controlled trials listed on this slide. Next slide.

So since the last report we've identified two new drugs – ocrelizumab and daclizumab, both included for approval in the last update report. We've also identified four new head-to-head trials, two placebo-controlled trials in primary progressive multiple sclerosis and of note the study of fingolimod as new evidence to the prior reports. We've

also identified five secondary analyses in relapsing remitting multiple sclerosis. Are there any questions?

Amber Figueroa: Doesn't look like it. Thank you, Brittany.

Brittany Lazur: Great. Thank you.

Amber Figueroa: We have some stakeholders to talk to us today. I'd like to call Dr. Margaret Olmon and then Dr. Dan Allen will be next. Please remember to state your name and you have three minutes.

Margaret Olmon: Hello. My name is Dr. Margaret Olmon from Medical Affairs at Abbvie. Thank you so much for the opportunity to come and talk to you about daclizumab, also called Zinbryta today. This is only going to be a really short summary. So if you have more questions about efficacy and safety I have the package insert available with me today.

I'm here to request that the committee consider Zinbryta to the preferred list of drugs so that patients in Washington may have another treatment option for relapsing forms of MS, one with a unique mechanism of action, proven efficacy over Avonex and with monthly subcutaneous dosing. As you know, patients with multiple sclerosis have nerve damage that accumulates over time leading to permanent irreversible disability and no course of the disease is typical. Symptom type and severity vary between and within individuals. Each patient may need several different treatments over the course of their disease, especially in patients with highly active disease it is important for there to be multiple options of therapy. Zinbryta is indicated for the treatment of relapsing forms of MS 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's administered as a self-injected, subcutaneous monthly injection. Zinbryta has a boxed warning for hepatic injury including autoimmune hepatitis, and other immune mediated disorders and is available only through Zinbryta REMs program. This program includes certification of prescribers and pharmacies and patients must enroll in the program and comply with ongoing monitoring and evaluation

of monthly liver testing before each dose. Zinbryta is contraindicated in patients with pre-existing hepatic disease or hepatic impairment. Because Zinbryta could exacerbate existing liver dysfunction, a history of autoimmune hepatitis or other immune conditions involving the liver it is contraindicated.

As was mentioned in the scan the efficacy on safety of Zinbryta was demonstrated in two randomized double-blind control studies. I'll focus my attention today on the Decide trial, a head-to-head trial of Zinbryta in 1,841 patients. 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 that the committee include Zinbryta on the PDL so that there is at least one product in each mechanism of action available for the treatment of MS patients in Washington. I want to thank you very much for your consideration and answer any questions you might have at this time.

Amber Figueroa: Questions from the committee? Thank you very much. Dr. Dan Allen and then Dr. David Graden.

Dan Allen: Good morning. My name is Dan Allen. I'm a medical managed care director at Sanofi-Genzyme Pharmaceuticals. I'm here today to review the clinical information for Aubagio teriflunomide in support of its PDL inclusion. I presented the Aubagio clinical highlights. Please see the full prescribing information in the package insert to use Aubagio safely and effectively.

Aubagio is a [inaudible] inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis. It is available as a 7 mg or 14 mg tablet taken orally once daily with or without food. I need to remind you that Aubagio has a boxed warning for hepatic toxicity and the risk of teratogenicity. Aubagio is contraindicated as severe hepatic impairment, pregnancy and in patients currently on leflunomide treatment. There were four randomized control double-blind clinical trials to establish human efficacy of Aubagio in patients with relapsing forms of MS. I'll be reviewing two of those today.

Study one was a double-blind placebo-controlled randomized clinical trial evaluating daily doses of Aubagio 7 mg or 14 mg for up to 26 months in patients with relapsing forms of multiple sclerosis. The study found a statistically significant reduction in the primary endpoint of annualized relapse rate for patients who received Aubagio 7 mg or 14 mg compared to those who received placebo. Additionally, there was a statistically significant reduction in the relative risk of disability, progression at the end of… at week 108 sustained for 12 weeks and the advisory of 14 mg group compared to placebo. Patients in both the Aubagio groups had statistically fewer gadolinium enhancing lesions for T1 weighted MRI scan compared to the placebo group.

Study two was a double-blind randomized placebo-controlled trial evaluating once-daily doses again of Aubagio 7 mg or 14 mg which ranged up to 40 months in patients with relapsing forms of multiple sclerosis. There's a statistically significant reduction in the primary endpoint of ARR for patients who received Aubagio 7 or 14 mg compared to those who received placebo. Yet again there's a statistically significant reduction in the risk of relative disability progression at week 108 sustained for 12 weeks in patients receiving 14 mg of placebo. The most common adverse events occurred more often than 10% and 2% greater than placebo are headache, 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 complete blood count 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 with peripheral neuropathy the patient should be evaluated and discontinuation should be considered.

Aubagio may increase blood pressure. Blood pressure should be measured at the treatment initiation and monitored during treatment. Please refer to the package insert for complete Aubagio

prescribing. Again, thank you for your consideration. I would be happy to answer any questions you may have.

Amber Figueroa: Question? Okay. Thank you. Dr. Graden and then Dr. Tammy Towers Parry will be next.

David Graden: Good morning. My name is Dave Graden. I'm employed by Genentech Medical Affairs and I want to thank you for the opportunity to provide comments on Ocrevus or ocrelizumab. Ocrevus is a CD20 directed antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis. It is the only FDA-approved product for primary progressive forms of MS. During development Ocrevus was granted breakthrough therapy designation by the FDA for being a novel agent in this therapeutic area. As you well know, MS is one of the most common causes of neurological disability in young adults affecting approximately 400,000 people in the U.S. Approximately 85 to 90% of patients are diagnosed with relapsing forms of MS or RMS at onset. Primary progressive MS, PPMS is a relatively rare form accounting for approximately 10-15% of all people with MS.

Two identical randomized double-blind, double-dummy phase 3 studies, Opera 1 and Opera 2 were conducted comparing the efficacy and safety of Ocrevus head-to-head versus [inaudible] in more than 1,600 patients with RMS in the two studies combined. Both studies met their primary endpoint with relative reduction of 46% and 47% respectively in the annualized relapse rate at 96 weeks. Secondary endpoints were also met. A pulled analysis of the proportion of patients with 12-week confirmed disability progression showed a 40% risk reduction and key MRI endpoints showed relative risk reductions of 94 and 95% respectively in Opera 1 and Opera 2 and the mean number of T1 gadolinium enhancing lesions and relative risk reduction of 77% and 83% respectively in the mean number of new and/or enhancing or enlarging T2 hyper intense lesions.

PPMS patients were studied in randomized double-blind placebo-controlled phase 3 Orotorio(?) study. The primary endpoint of proportion of patients with 12-week confirmed disability progression

was met with a relative risk reduction of 24%. Secondary endpoints were also met. There was a 25% risk reduction in the proportion of patients with 20% worsening of the timed 25 foot walk confirmed at 12 weeks and the MRI endpoint of mean change in volume of T2 lesions from baseline to week 120 was also met.

The most common adverse reactions for Ocrevus were seen in greater than 10% of patients in RMS or upper respiratory infection and infusion reaction. In PPMS those are upper respiratory infection, infusion reaction, skin infection and lower respiratory infection. For further details on ADRs please consult the Ocrevus product package insert. Ocrevus is a…

Amber Figueroa: I'm going to have to cut you off there. I'm sorry. Thank you. Do we have any questions for Dr. Graden? Okay. Thank you.

David Graden: Thank you.

Amber Figueroa: Dr. Towers Parry and then Dr. Maria Agapova.

Tammy Towers Parry: Good morning. Thank you for the opportunity to be here. My name is Tammy Towers Parry and I'm a family physician. I worked at Swedish Greenlake for 17 years and I have relapsing remitting multiple sclerosis. So although I'm here as… although I am a physician I'm here as a patient and I want to tell you what my goal is by trying to help you to understand what my goal isn't.

My goal isn't to pitch the agent that I'm on. My goal is to see if we can agree on three things because I feel like if we can agree on three things everything else will fall into place and of course I'll share with you what agent I'm on and why. I hope that in this brief period of time I can help you understand how the decisions that you make today and the agents that you choose to keep on your formulary can have consequences that sometimes are far reaching and can impact more than just one person—sometimes hundreds or in my case thousands.

So can we agree that no two patients with MS present with the same set of symptoms or with the same lesion size? I hope we can because that's just a fact. Can we agree that brain and nerve tissue is excruciatingly vulnerable? I hope we can because it is and time is of the essence. And can we agree that longitudinal studies, many, many of them, have shown that at least 50% of MS patients have measurable cognitive difficulties? And that's also true. And I have an acronym. I think a lot of us in medicine do and in pharmacy. I have an acronym to help me to remember the things I can't remember and it's PRIMP. This is my education for you guys. PRIMP – problem solving. For me I have difficulty with reasoning, intellectual and informational functioning including information coming in from the five senses which most of you know about; very common in MS. Difficulty with memory. So making new memories and retreating old ones and difficulty with planning and prioritization. So if we can agree on those things then I think we're set.

And now I'd like to briefly explain to you my story so that I can help you to understand why I'm advocating for a broad formulary based on what we've agreed on, which is that treatments need to be individualized and time is of the essence and that cognitive difficulties are real and that many times when patients have to appeal for a drug it falls on them and to me it's a little bit like asking a blind person to read fine print if they expect to get the best pair of eyeglasses for themselves.

Dr. Lilly Jung Hansen, you might be familiar with her, is my neurologist and she prescribed for me Tysabri as a first line agent because hands down individually with time being of the essence and massive intellectual decline it was the best choice.

Amber Figueroa: Doctor, I'm going to have to interrupt you there. Thank you.

Tammy Towers Parry: Thank you very much.

Amber Figueroa: Any questions?

Tammy Towers Parry: You can ask me anything.

Amber Figueroa: All right. Great. Thank you. Dr. Agapova.

Maria Agapova: Hello. My name is Maria Agapova. I'm a medical outcomes liaison at Teva Pharmaceutical and I would like to thank this committee for giving relapsing remitting multiple sclerosis patients in Washington state access to Copaxone 40 mg per mL three times weekly administration and ask the committee to continue that access.

Glatiramer acetate has shown to be safe and effective, effective defined as roughly greater than 30% reduction in annualized relapse rate. Well beyond clinical trial experience extending 20 years and 2 million [inaudible] of exposure. To add to the thorough scan that you've provided today I'll draw your attention to the 2017 publication by calling it out in multiple sclerosis journal. It's an extension study of the Gala Pivotal trial of Copaxone 40 mg in which one thousand patients from the placebo and the treatment arm were observed on 40 mg per mL for an additional two years. Copaxone showed durability of efficacy and safety with sustained low annualized relapse rate and no new safety signals. This adds further evidence to the specific 40 mg per mL three times weekly administration of glatiramer acetate and I urge the audience to consider that glatiramer acetate should be an option for patients, especially those who are risk reverse to side effects of some of the other competing therapies or to uncertainty. At this time I'm happy to answer any of your questions. Thank you for your time.

Amber Figueroa: Questions? All right. Great. Thank you. All right.

Make sure and state your name when you get up there.

Lynda Finch: I'm Lynda Finch. I'm a medical value liaison with Biogen. I've been in the MS field for 10 years. Prior to that I worked in research in immunology and I entered the MS field 10 years ago because I have a family member that was diagnosed with MS.

Over the last 10 years many new options have been introduced for MS, but there is still no one single drug that's perfect to treat all

patients. As you heard today it is a heterogeneous disease, treatment is highly individualized. It requires multiple products with multiple mechanisms of action. Biogen has brought to market five different products for MS to address the needs of this diverse population, but we're still working on it. We're still trying to bring new things forth to address the need.

MS is also associated with a significant economic burden both for indirect and direct costs and today I'd like to share the results of a recent study that I think is relevant to this committee. It quantified the differences in health care consumption looking at 20,000 MS patients looking at the differences between privately insured patients and Medicaid patients and what they found is that Medicaid patients had as much as much as five times higher health resource utilization for inpatient and ER costs and this was despite the fact that those patients had an average younger age and the same study showed that only one-third of those patients were on a disease-modifying treatment as compared to half of the patients that are in commercially-insured population. So this is a particularly at-risk populations. Individuals with MS already face significant barriers in managing their disease. As Dr. Towers mentioned the cognitive barrier is significant. So adding an additional barrier of getting access to the medication that the physician and they have decided is best to treat their disease it can sometimes be unsurmountable and lead to these patients not being treated. It increases the risk of permanent irreversible disability, but also ultimately increases the economic burden of MS.

So I'm asking you to consider the complexity of MS treatment today and preserve open access to all the available therapies so that access to medication doesn't become one more barrier that individuals with MS must overcome. Thank you. And I support Avonex, Plegridy, Tecfidera and Tysabri. So if you have any questions regarding those products I'm happy to address those as well today.

Amber Figueroa: Doesn't look like it. Thank you. I move to accept the scan on multiple sclerosis drugs as adequate.

Diane Schwilke: I'll second that.

Amber Figueroa: Who is feeling brave in the world of pronunciation today?

Man: You have to vote.

Amber Figueroa: That's right. Darn it. Okay. Let's vote on this. All in favor?

Group: Aye.

Amber Figueroa: Opposed? All right.

Susan Flatebo: I just have one comment about this next motion. If we could just maybe word it somewhere in there something along the lines of the MS drugs at the very bottom, second to the last sentence, MS drugs with like mechanisms can be subject to therapeutic interchange because as they are developing new and new agents for treatment of MS there's going to be like mechanisms out there and maybe that should be considered?

Ryan Pistoresi: Let's open it up to discussion. So if the other members, you know, agree we can add that language or if you want to… but we'll type it out.

Susan Flatebo: I have to say most of the agents listed on the left are all different mechanisms too by the way, but I'm just thinking we should probably have that wording in there.

Amber Figueroa: I don't use these on a regular basis in clinical practice so I wouldn't be able to comment on like similar mechanisms of action. So who makes that determination? I mean I think my concern is what we've heard today and we all know that MS does look different for different patients and they respond differently at different stages in their disease to different drugs. If a doctor wants a specific medication I would definitely want that patient to have access to it specifically.

Susan Flatebo: I also think we need to include ocrelizumab in the wording in the motion because I don't think it's in there. Is it in there?

Ryan Pistoresi: The drug was reviewed in last year's update. So we did have the evidence that was presented then, but it was not FDA approved as it was still undergoing its review. But because it is now approved and we have reviewed the evidence it is eligible to be included in the PDL at this time. So it kind of is bold because it's a newly available drug, but the evidence was presented by OHSU last year so it is eligible. So we can add it into the motion.

Jordan Storhaug: I agree with Dr. Figueroa's comments there that I think at this point with MS kind of being so unique in its presentation that I would prefer to wait until we kind of have some good examples of similar drugs to substitute with each other before we change the language to include that.

Diane Schwilke: I agree with that.

Nancy Lee: Question – can we bring that up to the DERP as a possibility to look into for the next review?

Ryan Pistoresi: We can certainly bring that back to them, but it depends on what the other states are voting for, but we can see, you know, as more evidence for this class continues to come out; especially with some of these newer agents and biosimilars, you know, on the horizon we can certainly look at what the new evidence will show us.

Donna Sullivan: What specifically would you want them to look for?

Nancy Lee: I guess just to address the question of similar mechanism like medications to see if there is a difference in efficacy and harms and outcomes if they were to group them as more and more medications come out on the market.

Donna Sullivan: So you're basically asking them to kind of do a network analysis if they could.

Nancy Lee: If it's possible.

Donna Sullivan: Okay. And it would depend on… we could ask them. Usually they will do that if the studies are similar enough. But if there, you know, a lot of heterogeneity between the studies they can't, but we can ask if there is anything out there. We can ask them to look for it as well.

Amber Figueroa: Any other discussion? Do you want to go for it?

After considering the evidence of safety, efficacy and special populations for the treatment of multiple sclerosis, I move that alemtuzumab, daclizumab HYP, mitoxantrone, natalizumab, dimethyl fumarate, teriflunomide, fingolimod, glatiramer, ocrelizumab, interferon beta 1B SC, peginterferon beta 1A 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 MS drugs cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment of multiple sclerosis. An oral agent should be included in the list of preferred drugs on the PDL.

Jordan Storhaug: I'll second the motion.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed. Okay. Great. Wow. All right. Well, what time is it?

Leta Evaskus: 10:50. We could take a 15-minute break.

Amber Figueroa: Let's just go until 11:00. We'll adjourn the P&T Committee meeting and we'll come back in 10 minutes at 11:00.

Let's take our seats and we're going to convene the Drug Utilization Review Board.

Ryan Pistoresi: I'm going to be going through our DUR presentations today. So for the first four will be the same four classes that we reviewed at the P&T and then we have two additional topics brought to you today

which one is on the FDA warning on codeine and tramadol in pediatrics and then the later one is on the bisphosphonates. So we'll go ahead and get started with our recommended changes to the limitations to drugs on the PDL.

So for our first section we're going to do the ADHD drugs and for our first slide we have the current PDL status as of our last review. So these drugs that have been reviewed today are now eligible to be preferred, but this is currently what our PDL shows. And in terms of our utilization for the amphetamines most of the utilization, as you can see, is with the amphetamine dextroamphetamine combination product. The green bar is 2016 and the blue bar is 2015 so you can see some change over time between these years with pretty much every drug class showing an increase in the number of users and an increase in the amount spent. Also worth noting that the amphetamines are the relatively new drugs per the PDL and those were some of the ones that we reviewed today.

In terms of the methylphenidate products we have two new ones that have been reviewed and can be eligible to be preferred, but pretty much for this class, as you see, just all the generics are preferred for all the different products. And in terms of the utilization we've actually seen this one go down. So whereas we've seen the amphetamine products go up, the methylphenidate products have gone down from 2015 to 2016.

In terms of the non-stimulants this was our current PDL status as of last time we reviewed the class. So with the new recommendation the new motion will have the clonidine and the guanfacine and the atomoxetine all be preferred going forward. In terms of the utilization and spend you can see that the number of utilizers for the clonidine for ADHD is very low and that is because it has not been preferred, but we anticipate that to go up as it is now going to be preferred. The spend on it is relatively low compared to the atomoxetine although that has recently gone generic as of the last month.

In terms of our ADHD criteria we do have a maximum daily dose set by the age limit and that was set by the Pediatric Mental Health Work Group and when we presented that a number of years ago to the DUR board we accepted that and since then it hasn't change and this information is also available in our billing guides for providers to reference to see what the maximum dose is for these patients. And then it is grouped up in color by the methylphenidate, the amphetamine and the non-stimulants.

In terms of the alpha agonists we do have a dose criteria so it can be a total dosage for either one or both products together and it is set here whereas .1 mg of clonidine is equal to 1 mg of guanfacine and so for the 0-3 PA but then for all the other age groups they can get up to that dose.

In terms of ADHD duplication we have a PA required for combinations of the ADHD medications when they are across subtypes. So as you see in the chart below if you have a methylphenidate and an amphetamine that would go for PA or if you try to do a methylphenidate with a Strattera that would also trigger a PA, but if you tried to prescribe it with an alpha agonist it would not. And this was also a recommendation from the mental health work group that was used to establish the previous ADHD criteria.

Po Karczewski: Is that exclusive of cross tapering?

Ryan Pistoresi: So for cross tapers I believe it would have the PA. April Phillips is our SON pharmacist who does the reviews and she may be able to answer that better than I can.

April Phillips: I believe there is a 60-day… our system allows 60 days of overlap so that the cross taper can go through without hitting for prior auth.

Ryan Pistoresi: Thank you. For adult… for the ADHD adult diagnosis it is restricted. So the diagnosis restrictions are a cross section of uses legal in Washington and uses that can be considered medically-accepted indications. So this means that it is limited to the ADHD by expedited authorization. That PA requests must be submitted for all other

diagnoses and that there is no off label use currently supported in the compendia. So here is the actual law as it is written in the revised code of Washington and it says that it is unlawful for a practitioner to prescribe, order, dispense, administer, supply, or give to any person a schedule 2 amphetamine or schedule 2 non-narcotic stimulant except for the treatment of the following. So for the ADHD we have the EA and then for the other ones we would accept the PA criteria for review.

So our current limitations are we are using generics first. We have the age and dose limits that we just reviewed. We do have the prior authorization required for the use of two or more agents from different subclasses after the 60-day period and we have the adult diagnosis limitations based on the RCW language and we have the patient's must step through all preferred drugs with the same indication before a non-preferred drug would be authorized. And so our recommendation today is to continue all of the current limitations that we have already in place.

Do we have any stakeholder comments?

Amber Figueroa: There's no stakeholders.

Ryan Pistoresi: Great. So we can open it up to discussion for the DUR members and I have a recommended motion for you to use if you will keep the recommended limitations.

Amber Figueroa: Discussion or comments there regarding the current limitations?

Diane Schwilke: If there is no discussion then I move the Medicaid Fee-for-Service Program implement the limitations for the attention deficit hyperactivity drug class listed on slide 13 has recommended to include…

Ryan Pistoresi: Sorry, you don't need to include the include. Sorry, it's confusing.

Diane Schwilke: Sorry… as recommended.

Susan Flatebo: I second the motion.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? All right.

Ryan Pistoresi: So our next class is the antiemetics and this is the current PDL status for these drugs and as we just reviewed with the P&T we will be adding in these new drugs and breaking it out by the five… the serotonins and then the neurokinins. So in terms of our current utilization the top two products, the ondansetron and the granisetron are the two preferred products currently and you can see in terms of the users and paid amount pretty much everyone is just going for the ondansetron and then below we have the apipritant, which was not included on the PDL and so it did not require stepping through or using any of the preferred products and you can see the number of users and the amount spent is relatively small compared to ondansetron. So our current limitations for this class for ondansetron we have a dose limit of 24 mg per day. We have an EA required for the oral solution formulations for patients with the inability to swallow oral tablets or capsules when patients are 18 and older and we have that patients must step through all preferred drugs with the same indication before a non-preferred drug would be authorized. Our recommendation was to continue all the current limitations but I wasn't sure that since we're breaking it out between the serotonin and the neurokinins if there would be anything new that you would want to add since we currently didn't have any of those on the preferred drug list.

Amber Figueroa: Are you able to pull or somebody to read the final since we don't have it here of what the motion…

Susan Flatebo: It looks like we need to break this up into the 5HT3 antagonists and the NK1 antagonists and then I'm not sure where we would put the doxylamine. That would be separate if that would be, you know, pregnancy induced nausea. Not sure how to…

It currently looks like ondansetron is preferred and maybe that could be broken down for the 5HT3 class.

Ryan Pistoresi: For the current limitations we require that they step through all preferred drugs with the same indication and we want to carry that down. So they must step through all preferred drugs within the same mechanism of action?

Susan Flatebo: Yes.

Ryan Pistoresi: That's easier to copy.

Susan Flatebo: Do we want to choose an NK1 preferred?

Ryan Pistoresi: We won't at this time. So that is done after… during our cost analysis. So today we're just saying which drugs are eligible to be preferred, which ones aren't and then we'll do our internal cost analysis and then pick the preferred products.

Jordan Storhaug: I guess I kind of want clarification in the case of pregnancy, as well. I think right now it looks like ondansetron is the preferred agent in the cause of nausea in pregnancy and I kind of question if that is really the way that we would like it to be.

Ryan Pistoresi: Do you have any recommendations for how you would want to have the DUR board recommend pregnancy be handled as maybe a separate limitation?

Jordan Storhaug: For my practice, you know, doing obstetrics and delivery, Diclegis really is the first… the recommended first agent for… in the case of pregnancy mostly due to its low side effect profile and data there and then moving on to other drugs after that point. I guess I would move that it would be the preferred agent in the case of nausea and vomiting in pregnancy.

April Phillips: We currently have an EA set up for that so if they have the indication that the pharmacy can put in the EA and they can get it.

Ryan Pistoresi: Okay. Any other discussion? So I'm going to copy this. Let me zoom in.

Susan Flatebo: If there's no other comments I will make a motion. I move the Medicaid Fee-for-Service program implement the limitations for the antiemetic drug class listed on slide 17 as amended to include to continue all current limitations with the exception must step through all preferred drugs with same mechanism of action and indication before a non-preferred drug will be authorized and an EA for the doxylamine/pyridoxine for use in pregnancy induced through pregnancy and nausea in pregnancy.

Catherine Brown: I second.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? All right.

Ryan Pistoresi: So next up we have the anticoagulants and their current PDL status as of today we have the apixaban and dabigatran as our preferred options. In terms of our utilization you can see that in 2015 we had the most utilizers and spend in rivaroxaban but it is no longer preferred and our new preferred products are apixaban and dabigatran. So you can see that the utilization has changed from 2015 to 2016 and now most of our utilization in terms of the users and spend is with the apixaban and dabigatran.

So our current limitations are that patients must try all preferred drugs with the same indication before a non-preferred drug would be allowed unless not clinically appropriate or contraindicated and per the 2016 motion there was no therapeutic interchange, but based on the P&T motion that just carried the therapeutic interchange will apply to the apixaban, rivaroxaban and edoxaban. So we will go ahead and make that change.

On the next slide…

Amber Figueroa: You don't have any stakeholders for this group.

Ryan Pistoresi: Any discussion?

Diane Schwilke: If there's no discussion then I move the Medicaid Fee-for-Service program implement the limitations for the anticoagulant drug class listed on slide 21 as amended to include continue all current limitations except therapeutic interchange will apply to apixaban, edoxaban and rivaroxaban.

Nancy Lee: I second that motion.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? All right. Very good.

Ryan Pistoresi: All right. Our next drug class is the multiple sclerosis products and this page shows how they are on the PDL as of last year. In terms of our utilization and spend you can see that it has changed over some time. For some reason it has gone down since 2015 across a number of drugs; although I don't know why. I'm trying to think if there is any good rationale for that. No, I don't know why, but it looks like a number of drugs have gone down in terms of their utilization and spend from 2015 to 2016 and I'm sorry I don't have a good explanation for that. But this is what the current landscape looks like for our population.

For Tysabri we do have additional criteria for it. In addition to being on the preferred drug list, it does require that the prescriber and client must be enrolled with the Touch prescribing program. That it be prescribed a neurologist or an ARNP or PA working with a neurologist. That they have relapsing, remitting multiple sclerosis. That they've had the MRI prior to treatment. That they have tried and failed the other preferred MS treatments… or it doesn't

necessarily need to be preferred MS treatments if they have come into our population having tried another population without trying a preferred as long as they've had that preferred. As long as they have had the other MS treatment they would be eligible to meet that criteria. That they must not be amino compromised. Must be using it as monotherapy and that the dose limit is 300 mg every four weeks.

So our current limitations on the class is that we will allow the continuation of therapy of a non-preferred product to be allowed with the exception of the following which is Rebif and Extavia and that's because they do have alternatives that are preferred on our drug for the interferon beta 1A and interferon beta 1B. That there is no therapeutic interchange. That we do have the PA criteria for Tysabri which we just reviewed on the previous page and that they must step through a preferred product of each active ingredient with the same indication before a non-preferred drug would be allowed.

I don't think that that runs counter to the P&T motion that we just had. Never mind. We didn't have the like ingredients, no. We took that out. So then this should be fine as it is. So our recommendation was to continue all the current limitations. Do we have stakeholders?

Amber, do we have any stakeholders?

Amber Figueroa: We do, but I have a question first though. So for P&T Committee… well, here also no therapeutic… I guess… can you clarify the difference between no therapeutic interchange, but then these… we can't do continuation of therapy with the Rebif and the Extavia because there's a preferred similar. Is that just a different form of… route of administration or there's a different…?

Ryan Pistoresi: To understand your question – so the therapeutic interchange is when a new prescription comes to a pharmacy. So if someone was on a non-preferred product; I believe Aubagio is a non-preferred product on our PDL. And so if a patient came with that there wouldn't be eligibility to interchange it at the point of sale to another preferred MS product. So that way patients that were on a non-preferred product could continue on that without having that

interchange or if there was a new patient starting a product that the therapeutic interchange wouldn't apply to them.

Jordan Storhaug: Correct me if I'm wrong, but what I'm understanding this to mean is that there is no interchange between different ingredients, but that the preferred status may force someone to a specific label within that ingredient?

Ryan Pistoresi: Let me just read this. I believe that the way it is written, that they must step through a preferred product of each active ingredient with the same indication before a non-preferred drug would be approved, means that they would have to step through an Avonex before a Rebif would be approved. But if they wanted to start with another like an oral medication they wouldn't necessarily have to worry about that. I believe the active ingredients are just limited to the interferon beta 1A and interferon beta 1B at this point.

Amber Figueroa: Any questions at this point? Okay. We have some stakeholders. Let's go ahead and call them up. Dr. Margaret Olmon and then Lynda Finch is on the list but spoke earlier so I'm not sure she's going to speak again.

Ryan Pistoresi: I think she signed up on the DUR but meant to speak at the P&T. So I don't know if she still wants to.

Margaret Olmon: Thank you very much. My name again is Margaret Olmon and I'm from the medical affairs at Abbvie and I wanted to have an opportunity to talk to you a little bit about our mechanism of action because I think it's important that you consider having a product of each mechanism of action available for patients as part of the preferred list of drugs that you have available. Zinbryta is a new form of humanized monoclonal antibody that directly blocks activation of autoreactive T-cells, a major contributor to active acute and chronic inflammation in the nervous system of patients with MS. This targeted mechanism of action differentiates it from currently approved products for this treatment. Zinbryta also indirectly leads to an increase in CD56 bright natural kill cells. These are important cells that help regulate the immune system. This effect is thought to

further reduce the number of activated autoreactive T-cells that contribute to the nerve injury that is caused by MS. Zinbryta has a targeted mechanism of action that does not cause broad immune cell depletion and is reversible within six months. As you know, the activation of the JC virus is most likely happening in patients that have a weakened immune system so it is important that this drug does not cause broad immune cell depletion. From our PI it states that during Zinbryta treatment mean cell counts for the major immune cell subsets remained within normal ranges. Total lymphocyte TMV cell counts decreased less than 10% from baseline during the first year of treatment. Total lymphocyte counts returned to baseline levels approximately 8 to 12 weeks after the last dose of Zinbryta. I'm happy to answer any questions you might have about our mechanism of action or anything else with regard to this product. Thank you very much for your time.

Lynda Finch: Hi. Lynda Finch again from Biogen. I'm going to limit my comments just to Tysabri for the DUR. So there's a requirement for failure of other therapies prior to the use of Tysabri and this is something I think is important for you to realize that there are a subset of patients that have a highly aggressive early presentation of MS for which Tysabri's first line of therapy is perfectly appropriate and essential that they have access to it early on. Forcing these patients to try a less effective therapy before they can access the therapy that they need is like asking a cancer patient to try a less effective chemotherapy and then waiting until the cancer has metastasized before you allow them to get the more effective chemo.

MS therapy is really moving toward using more highly effective therapies earlier in disease to get good control of the disease. It's well accepted that higher frequency of MS attacks early in the disease is predictive of long-term disability. So there are some guidelines by experts in this field that American Academy of Neurology does allow for and recommend that Tysabri be used in patients who have an aggressive disease course and there's a consensus paper from the MS consortium that suggests that the use of Tysabri as an initial therapy for people with early aggressive disease and that is characterized by early frequent attacks and in complete recovery of those attacks and

accumulation of MRI lesions. So I ask you to reconsider your criteria here for requiring failure of other therapies prior to the use of Tysabri; particularly for these patients with early aggressive disease. Thank you.

Tammy Towers Parry: Thank you again. My name is Tammy Towers Parry and I wasn't planning to speak during this portion, but when I saw that sentence about trying and failing something else I really felt like it was my time.

So my goal now is to encourage you to please reconsider that statement and that portion about having to try and fail another medication before starting Tysabri. This leads back to where I got cut off earlier and I would refer you to consider reviewing the MS consensus statement which says that Tysabri should be considered as the initial agent of choice if there is early and aggressive evidence of disease especially with cognition and that brings us back to that primping that I was telling you about. It's really, really important in my case. Dr. John Hansen ordered Tysabri for me because, as we agreed on earlier, hands down this needs to be looked at individualistically. Time is of the essence and we're dealing with cognition and in my case the massive intellectual decline. Swedish Health & Services declined to authorize it. Of course we were stunned. We appealed. Appeals take time and the ERO overturned the denial and the reason they overturned it was because Tysabri should be considered first line for patients with early and aggressive disease especially if there is cognitive deficits and that is critical so that people can go on leading productive lives.

In my case it was too little too late. Time is of the essence. Ninety-three days is too long. The damage was done and so now that decision impacted 1,721 other people, my patients who no longer get to call me their primary care provider and more importantly I no longer get to call them my patients. So I really encourage you to take a look at that line item and reconsider it because asking a patient to try and fail another option is basically an invitation to ask them to try and fail and invite permanent brain damage which can permanently alter their lives and the lives of others. Thank you.

Amber Figueroa: All right. That's it for stakeholders. Any discussion?

Susan Flatebo: I agree. I think that that should be taken out, unless have tried and failed other MS treatments for the criteria for Tysabri. If you look at the product packaging it does not say they need to fail other treatments. It can be used as initial therapy.

Woman: The PA criteria is based on the REMS Program for Tysabri. So that's where it originally came from.

Ryan Pistoresi: So we do review each individual case that comes to us for Tysabri and although it is one of the criteria, you know, trial and fail. So if they have that, you know, it goes through that step, but if they haven't we can review medical circumstances. Have a one-on-one with the physician and talk about individual patient-specific criteria for that patient. So it's really, you know, having us make sure that they are enrolled in the REMS Program and that they are going through these criteria. So even though it says they must have tried and failed we do allow, you know, for additional circumstances when we do our clinical review, but we do want to have this in place so that it does come to our pharmacist for our review to make sure that they do meet these criteria.

Amber Figueroa: How long does that review take?

Ryan Pistoresi: I will allow April, our pharmacist who reviews these to comment.

April Phillips: It's actually reviewed by our physician consultants and it doesn't take that long. Once we get all the information back from the prescriber it is a matter of days.

Amber Figueroa: Is that driven by cost? Side effect profile? What drives that? Because I'm still concerned that it stays in there. Because if I'm a prescriber and I see must have tried and failed I'm not going to try because it's a waste of my time if it says in there must have tried and failed another one. So I don't want to waste my time filling out forms or talking on the phone if I think it's going to be denied.

Ryan Pistoresi: Okay.

Amber Figueroa: Just wondering what drives… what's driving this statement here?

April Phillips: It's part of the REMS Program that the… the Touch Program for Tysabri. It's also considered a second line agent.

Amber Figueroa: Can you clarify what REMS is?

Ryan Pistoresi: Risk Evaluation and Mitigation Strategies. So the FDA has special safety programs for certain medications where they feel that there needs to be additional programs in addition to the labeling for safe and efficacious use of medication.

We have another stakeholder. Lynda, we will need to have you speak into the microphone so that way it gets recorded in the transcription. Sorry.

Lynda Finch: I just want to ask that you take another looks at the REMS Program. There's no requirement in there for try and fail other therapies. Previously in the label for Tysabri, when it first came out on the market, it required… it basically said generally try after failure of another therapy, but that has been changed and there is no longer any label language regarding trying and failing other therapies and of course finally there's no language in the REMS Program or Touch Program regarding trying and failing other therapies. It does ask what other therapies you've been on and what you're currently on as part of that program though. So just take another look at that and make sure that that is correct if that is what you're basing it on.

Ryan Pistoresi: And Lynda, do you mind just staying your name and affiliation?

Lynda Finch: Sorry, Lynda Finch, Biogen.

Ryan Pistoresi: Great. Thank you.

Amber Figueroa: I feel at this point maybe we should… is it possible to table this so that we can put some more information together before we make a decision on this?

Ryan Pistoresi: Certainly. So what our recommendation is, is that we will revisit this with more information at our next DUR Board meeting for the Tysabri criteria. Would you like to do it for the full class or just the Tysabri?

Amber Figueroa: What do you guys think?

Susan Flatebo: I am curious about the ocrelizumab. Is there going to be limitations? Should we be setting limitations for the prescribing of that as well? I mean…

Ryan Pistoresi: So we didn't bring any ocrelizumab criteria to you because it wasn't part of our previous motion, but if you would like to add any type of limitations or any type of considerations for it we can go ahead and add that into the motion and then bring back the Tysabri for our next DUR.

Nancy Lee: I second that motion to re-evaluate… further re-evaluate the REMS Program criteria for Tysabri and also include additional information regarding ocrelizumab and then also if we could look into Tysabri… I think a stakeholder mentioned about early aggressive disease and look at whether or not there is information about that as well.

Man: [not at the microphone] Just to clarify, there is no REMS Program for [inaudible]. Ocrelizumab is [inaudible] question or concern.

Ryan Pistoresi: So there's a statement from the audience that ocrelizumab does not have a REMS Program, but I believe the REMS Program we were just looking for Tysabri and then for the ocrelizumab to…

Woman: Just to evaluate if there needs to be like prior authorization criteria…

Ryan Pistoresi: Or any other limitations to have it be different then…

Woman: Yeah.

Ryan Pistoresi: Okay. I just tried to summarize what we just discussed and I put it up in the motion to see if this is similar to what you intended or if there are any other considerations that we should add at this time?

Margaret Olmon: I just want to make sure I understand the current limitations for treatment based on the conversation you just had about Tysabri. Again, Maggie Olmon with Abbvie and I have a question about the current limitations with regard to treatment. It says here that the patient must step through a preferred drug in each active… of each active ingredient with the same indication before a non-preferred drug would be authorized. You had some concerns about a few of the non-preferred drugs that are currently listed as non-preferred. One of those is Tysabri. Another of those is Zinbryta and with those being non-preferred agents you have to step through four different other products in order to make sure that you've gone through each active ingredient that's on the preferred list. So although you're considering taking that language out of the PA criteria for Tysabri it would still stand as part of the general limitations. Is that the way I understand it to be?

Ryan Pistoresi: This is just for each active ingredient. So coming back to the list on the screen behind you that would really only apply to the glatiramer, the interferon beta 1A and the interferon beta 1B which do have multiple ingredients.

Margaret Olmon: So there's four products that would need to be tried… four kinds of products that would need to be tried before any of the non-preferred agents are used, which would include anything that's non-preferred on the list that you just had up. One of those is Tysabri. One of those is Zinbryta.

Ryan Pistoresi: As it currently is, until we do the cost analysis. So after this then we will re-determine which ones are preferred. So currently, yes, they would have to step through these preferred products for each ingredient.

Margaret Olmon: Okay. Just wanted to make sure I understood how the process currently works so that I'll understand it better later too, as well. Thank you very much.

Ryan Pistoresi: Yes. So Zinbryta didn't have the opportunity at the last one since it wasn't FDA approved, but now that it is, and now that it is eligible to be preferred, it may be one of the preferred products.

Margaret Olmon: Thank you.

Ryan Pistoresi: So here's the revised motion.

Jordan Storhaug: I move the Medicaid Fee-for-Service Program return to the next DUR Board meeting with information regarding the review of the Tysabri REMS Program and a prior authorization criteria and a review of ocrelizumab for coverage considerations.

Susan Flatebo: I second the motion.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed?

Ryan Pistoresi: So that is it. On to the next section. So these are the unique DUR only topics that are not related to the PDL. So the first one is a presentation on the FDA warnings on codeine and tramadol in pediatrics.

On April 20, so the day after our last P&T DUR session the FDA came out and issued a safety communication about the risks of using codeine and tramadol in pediatrics and they have also updated the labels of these products to include this information. So the result of this is from an evidence review by the FDA and the evidence review that they conducted did find serious risks in these populations that were associated with these medications. They also note that all

single ingredient codeine products and all tramadol products are FDA approved for use in adults only.

And in the FDA communication here's a list of the drugs that they included as part of that review, as well as what are FDA approved products.

So the label changes as of the 20th is that they added a contraindication for codeine to be used to treat pain or cough in children younger than 12 years of age and this is similar to a 2013 label update in which there was a contraindication to codeine to treat pain after surgery to remove the tonsils and/or adenoids in children younger than 18 years of age. There's now a contraindication for tramadol to be used to treat pain in children younger than 12 years of age and to be used to treat pain after surgery to remove the tonsils and/or adenoids in children younger than 18 years of age. So those two contraindications are the same between codeine and tramadol now. There's also a new warning against the use of codeine and tramadol in adolescents between 12 and 18 years of age who are obese or who have conditions such as obstructive sleep apnea or severe lung disease which may put them at greater risk for adverse events. They also strengthened the warning against mothers' breast feeding while taking codeine or tramadol due to the risk that it can be passed into their breast-fed infants.

In part of the communication they did note how many patients were potentially impacted by this and nearly 1.9 million patients age 18 and younger did receive a prescription for codeine with 1.4 as a pain product and then 483,000 as cough and cold products and in that same year, 2014, about 167,000 patients age 18 and younger received a prescription for tramadol.

Our utilization for these two products… this is the entire population. So it's not that high for just the kids. This was just what we see in our overall population. But going specific to the kids, you know, here is what we see in terms of codeine and tramadol and it's broken out by the 0 to 11, which is the contraindicative population and the 12 to the 17, which is the new strength and warning population. So you can

see most of the codeine utilization is in the 0 to 11 whereas you see higher use of tramadol in the 12 to 17. And then for this one the green means 2016 and the blue means 2015. I think that may have been flipped from the… So based on the review of the FDA communication and on the label changes and on the Washington Fee-for-Service utilization we are recommending that codeine and tramadol be placed on prior authorization for patients age 17 and younger and that the prior authorization would just seek a valid medical reason as to why non-pharmacologic, non-opioid pharmaceuticals cannot be or should not be used. So that is our recommendation. Were there any stakeholders?

Amber Figueroa: No stakeholders. I think we can see in the utilization that tramadol has decreased if I'm looking at it correctly overall and Tylenol with codeine has increased. I think that's probably in response to the opioid epidemic and trying to push people lower or what we would consider lower on the spectrum of strength as far as opiates. My concern… I mean I realize that we don't necessarily want to step outside of this FDA label change, but my concern is if we put a prior auth on codeine and tramadol thinking specifically of like dental pain and things like that then they are automatically going to give them Vicodin which I don't… in my mind doesn't sound any better. Again, I don't know that we can really address that here since the FDA didn't address it and we're responding to the FDA's comments. But my concern would be that it would push to prescribe more hydrocodone products.

Ryan Pistoresi: I did additional research in addition to just the FDA label change just to see what some of the other states were doing and some of the other states are also looking at doing prior authorization and they are also trying to figure out what to do in terms of dental pain for this population. I do know that the New Hampshire Board of Dentistry has put out recommendations for using NSAIDS and Tylenol in combination with each other for postoperative dental pain, but I'm not sure if we would be able to put that in as, you know, a step, especially since a lot of these prescribers, especially for the codeine are dentists.

Emily Transue: Just to clarify these concerns were around specific breathing problems in children from these medications so it wasn't a general opioid concern. I think this is specific to side effects of these drugs in that age group, just to clarify if that wasn't clear.

Jordan Storhaug: My understanding of this data is really that the understanding that codeine and tramadol being safer medications really has… the evidence has not bared that out and really that these should be treated more like a hydrocodone and I definitely suspect that… I definitely support this motion, but I suspect that it will lead to more hydrocodone being prescribed, but then avoiding opioids entirely for some patients, as well.

Nancy Lee: I had a question. A couple of meetings ago didn't we also have a discussion about opiates in general in pediatric patient population? And how does this kind of go hand-in-hand with that one?

Ryan Pistoresi: So that's a great question. So we are still evaluating how we are going to implement that policy that we presented back in December and in January and in February. So we're looking at ways to operationalize. So right now we are still looking at having a limit of 18 pills or dosage units, depending on what form is used for a pediatric patient, but we're still looking at how we're going to implement that across all of our programs. So we're still moving in that direction. There's new details that we're still working out, but so far it is not in place yet. In the case of this PA criteria and in terms of what our recommendations are for, a prescription for codeine, you know, would reject and say, you know, it needs prior authorization to determine medical necessity for these FDA contraindicated or FDA warning products and if they switch to a prescription like a hydrocodone like a Vicodin it would be limited to 18 pills or less depending on what… or how the prescription was written. That's kind of how the two come together although the other one has not been put in place yet.

Amber Figueroa: I'm still having trouble with this. Thinking about working in the walk-in and having, you know, kids who can't sleep because of their cough. You know, it's not common and I don't know if I would switch from

codeine to hydrocodone cough syrup, but I know a lot of people would if they would have to… not have to field the call or not have to fill out more paperwork just to know that the patient would get their prescription filled. Again, I don't think that's the intent of this, but I also don't think that swinging the pendulum to the entire other side that says any opioid prescription under age 18 has to have some kind of prior authorization is correct either. Think of all the appies(?), you know, the surgical things. This doesn't sit well with me. Anybody else have any other comments?

Susan Flatebo: I think just because of the FDA warnings and the respiratory risks to these children we at least need to, I think, need to have a prior authorization in place and since we've already approved the limitations on the opiates anyway, I think, you know, they're still not going to be able to write for a… there's going to be a specific at number 18 tablets. I think this would at least stop it and it's not going to say you can't write it, it just means that they are going to want another, you know, medical reason why.

Catherine Brown: I agree with Susan's statement.

Diane Schwilke: I was just going to give a little bit of, maybe, from the dispensing side I hear what you're saying, Amber about, you know, stepping it up, but I feel like that requires a lot more work on the part of the prescriber to, you know, in our setting we're in the same clinic and so it's fairly easy to provide a hard copy to follow-up with that, but in most pharmacies that's not going to be an easy process for the prescriber to make that change to go to a hydrocodone product because it's going to require a hard copy and there's all these rules around that anyway. So I don't know that in the broader sense that that is going to push a lot more hydrocodone. And I don't see a lot of these prescribed, at least in our setting. I think we do a good job of not prescribing a lot of these in general to kids. I don't know. I feel like there is going to be a lot of hoops anyway. So I don't know if it's going to be a huge issue and I also know that it does create a loophole that if it is not covered a lot of times parents are going to pay for it anyway for their kids. So I don't know.

Ryan Pistoresi: So this is our utilization again and so we are looking at about less than… a little over 200 from the 0 to 11 and a little over 150 for the… so we're talking, you know, a couple hundred in our population that are being affected, potentially being affected by this. Now we don't know what the current utilization is in 2017, especially with all the attention on opioids going on, but I'm just mentioning that it is not a big population that is being effected. If there needs to be pain management there are alternatives.

Dale Sanderson: So I'm just trying to make sense of this. If the codeine is the significant risk it seems like, you know, hydrocodone and oxycodone would be worse. Are we… help me with this.

Ryan Pistoresi: I do know other states that are looking at the hydrocodone, the oxycodone, some of the other ones, but as of today the FDA review was only on the codeine and the tramadol and I think that… it was because there has been some publications about some deaths in pediatrics. I know when speaking to a colleague in Tennessee there was a pediatric patient that had a breathing difficulty and actually died as a result of getting a codeine prescription from a dentist and so there was some movement out there in Tennessee which may have precipitated this as an FDA review.

Catherine Brown: I think it has to do with how the codeine is metabolized.

Ryan Pistoresi: Yes. Codeine does depend on the metabolism. So some people are ultra-rapid metabolizers and will metabolize the codeine into a morphine and have a much steeper curve in terms of the effect and can easily face the adverse events.

Man: Rather than oxycodone and hydrocodone?

Ryan Pistoresi: Yes. So the other opioid products do have slightly different metabolism and don't necessarily have the same variation as they do with the SIPS, the different ultra-rapid metabolizers.

Amber Figueroa: I move that the Medicaid Fee-for-Service Program implement the limitations for codeine products and tramadol products listed on slide 8 as recommended.

Catherine Brown: I second.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? Okay.

Ryan Pistoresi: Our last topic of today is the bisphosphonates. Let's go ahead and get into that presentation. The bisphosphonates, just a quick run through of our little order that we have. So we're going to go over some of the guidelines and evidence review and then we'll take a look at our utilization and spend and then move on into our recommendations.

So the bisphosphonates were first approved in the mid-1990s and are the most widely used drugs to treat osteoporosis. The way that these medications work is that they inhibit the bone resorption activity by the osteoclasts. This improves the… leads to an increase in the bone mineral density, which then improves the bone structure and then has a reduced risk of fracture. So currently there are four FDA approved bisphosphonates – alendronate, ibandronate, risedronate and zoledronic acid. In that list below I have what the approved usages are for either prevention or treatment, whether they are an intravenous injection or whether they are an oral tablet and then what the dosing schedules are so they can be done either daily or weekly or in some even up to once every two years. So quite a varied way to dose these medications.

In terms of their FDA approved use I've summarized the different indications in this table and you'll see that the alendronate, risedronate and zoledronic acid all have all five, where the ibandronate is only used for the treatment and prevention of osteoporosis in post-menopausal women.

In terms of the guidelines we've had two recent guidelines be updated in the last year with recommendations for osteoporosis. So the American College of Physicians recommends that alendronate, risedronate, zoledronic acid or denosumab to be used first line to reduce hip and vertebral fractures in women with known osteoporosis and for the bisphosphonates to be used to reduce vertebral fracture in men who have clinically recognized osteoporosis. The other guidelines are from the American Association of Clinical Endocrinologists and this one recommends alendronate, risedronate, zoledronic acid or denosumab for patients with no prior fragility fractures or are at moderate fracture risk. And they do note that although there are no head-to-head trials with clinical outcomes the current evidence suggests that these four therapies offer broad spectrum anti-fracture efficacy.

To summarize that here's a table from the American College of Physicians. It's not the same as the one that I just presented although it looks the same. It's just showing that the effect on fracture risk between the four bisphosphonates and pretty much the alendronate, risedronate and zoledronic acid are all high quality and show improvement. Then to the far right column are the adverse events associated with each.

In terms of the evidence review I did find an AHRQ-funded systematic review of 315 studies and this one did note that the number needed to treat for bisphosphonate to prevent one vertebral fracture over one to three years is about 60 to 89. So that 60 to 267 person years. The number needed to treat for 1 non-vertebral fracture is 50 to 60. So that's 50 to 180 person years. And there's an estimate of 72 to 956 events of mild upper gastrointestinal symptoms that will occur per 1,000 people treated with the bisphosphonates. And I will note that this unit is not per person so it's not saying that 956 people will have those events. It's just that some people may have multiple events over the course of treatment, which is I believe up to five years before they are on a drug holiday. Cochrane review of the bisphosphonates found that alendronate offers a clinically important benefit in secondary prevention of vertebral, non-vertebral hip and wrist fractures. But for primary prevention only the vertebral

fractures had a clinically important reduction. For the risedronate the Cochrane review found that it had clinically important benefits for the secondary prevention of vertebral, non-vertebral and hip, but not risk. And that there was no statistically significant reductions for primary prevention. So it did not show that for the vertebral or non-vertebral fractures.

In terms of our utilization pretty much all our users are using the alendronate. We do have some patients that are using the zoledronic acid and the risedronate. In terms of the amount spend it's a lot more even. Maybe not even, but a lot more pronounced with the risedronate, zoledronic acid and the ibandronate taking up a much higher proportion of the costs compared to alendronate versus the utilization. It presented in another way. This way you can kind of see going back and forth what the changes between the utilization and spend relative to the alendronate. And then when you remove the alendronate our utilization is significantly higher for the ibandronate than the risedronate although you see that for 2016 it has been increasing for the risedronate where it has been increasing for the ibandronate. In terms of the spend similar look at how it has changed relative.

So our recommendations based on the review of the practice guidelines, clinical evidence, and current costs and utilization we are recommending that alendronate be the preferred bisphosphonate for Medicaid Fee-for-Service. That risedronate be the second option based off of the guidelines of clinical evidence after trial and failure of alendronate. That all other bisphosphonates be the third option after trial and failure of both alendronate and risedronate and that zoledronic acid be available to patients demonstrating a contraindication to oral bisphosphonate therapy. So if they are unable to take any of the oral bisphosphonates they can move to the zoledronic acid as their bisphosphonate.

Any stakeholders for the bisphosphonates? Okay. So I've prepared a motion for you on the slide although I will open it up for discussion about this.

Dale Sanderson: Is there a definition of the trial? Is it a length of trial? Parameters to judge failure? How long do you allow for… say this is a failed trial?

Ryan Pistoresi: For this definition our trial would just be one fill. So if they've had a fill for the alendronate; they take it once and have a very severe GI reaction that would be considered a trial and failure or they can try it for a number of years and see, well it's not efficacious. That would be considered a failure and that would also be a trial. So as long as they've had it for at least one administration that would be considered a trial.

Amber Figueroa: I think the recommendations are appropriate. Does anybody else have any discussion about it?

Jordan Storhaug: I move the Medicaid Fee-for-Service Program implement the limitations for the bisphosphonates listed on slide 13 as recommended.

Diane Schwilke: I second that.

Amber Figueroa: All in favor?

Group: Aye.

Amber Figueroa: Opposed? Okay. Great.

Ryan Pistoresi: So that's everything we had prepared for you today.

Amber Figueroa: I apologize for running over, guys, but it was a good meeting. Lots of good discussions. The meeting stands adjourned. Thank you.