Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
P&T Meeting Notes
December 18, 2019

Lisa Chew: Okay. Good morning, everyone. This is Lisa Chew. We're going to convene the Washington State P&T Committee. I want to remind everyone that this is a recorded meeting. So, please be sure to state your name before making your comment. Let's start off with introductions. We'll start at this end of the table.

Petra Eichelsdoerfer: Petra Eichelsdoerfer, United Healthcare.

David Johnson: David Johnson, United Healthcare.

Jaymie Mai: Jaymie Mai, Labor and Industries.

Luke Dearden: Luke Dearden, pharmacist employees and retiree benefits at Health Care Authority.

Susan Flatebo: Susan Flatebo, committee member.

Jordan Storhaug: Jordan Storhaug, committee member.

Catherine Brown: Catherine Brown, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Lisa Chew: Lisa Chew, committee member.

Virginia Buccola: Virginia Buccola, committee member.

Alexander Park: Alexander Park, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Umang Patel: Umang Patel, Magellan Medicaid.

Marissa Tabile: Marissa Tabile, Health Care Authority.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

Ryan Taketomo: Ryan Taketomo, Health Care Authority.

Jose Zarate: Jose Zarate, Health Care Authority.

Amy Irwin: Amy Irwin, Health Care Authority.

Lisa Chew: Thanks. So, we have a few announcements, the most important one is that there are cookies up at the front. So, please help yourself. I spent all night baking.

Donna Sullivan: Today is Lisa Chew's last P&T Committee meeting with us. So, Lisa, I just wanted to thank you for your service, being here I think it's six years now, for all your... two years as Chair. Thank you for all your leadership and support in these meetings. It's been wonderful working with you. I also wanted to introduce Luke, or let you know that we do have new pharmacists with us, so Luke Deardon and Ryan Taketomo. They are two new pharmacists that are with the Health Care Authority. Luke is working with the employees and retiree benefits. So, the public employees, school employee, uniform medical plans. Then, Ryan is our clinical strategy pharmacist. They'll be probably attending the meetings on and off in the future. So, I just wanted to let you know who they are. I also needed to make an announcement, more for the audience and the stakeholders. I just wanted to remind manufacturers that it is inappropriate for you to be contacting committee members outside of the meeting and trying to discuss topics of the PDL or the P&T Committee meeting with them in their clinic. So, please do not contact them personally or through your professional channels outside of the P&T Committee. So, there have been a couple of contacts that have been reported, since the last meeting. So, I just wanted to remind the audience that that's inappropriate for you to do that. I think that's it. Now, we'll do the vote on the new Chair to replace Lisa.

Lisa Chew: Okay. So, we need to find a new Chair for the P&T Committee, and we have some volunteers or nominations?

Leta Evaskus: So, Ginny is the Vice Chair right now, and traditionally, Vice Chairs have been nominated up to Chair. So, if you do want to nominate Ginny.

Lisa Chew: I think that would be great if she's willing. Was that a nomination?

Female: Yes. It was.

Lisa Chew: Any seconds?

Alexander Park: I second that.

Lisa Chew: Okay. All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Congratulations, Ginny. You're now the new Chair.

Leta Evaskus: This is Ginny's first meeting as Vice Chair. Was. So, she'll start as Chair in 2020. So, you now need to vote on a new Vice Chair. Ginny, you might want to nominate somebody.

Susan Flatebo: I nominate Jordan Storhaug for Vice Chair.

Lisa Chew: Any seconds?

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. Congratulations, Jordan. Alright. I just want to say, it's been an honor to actually serve on this committee for the last six years, and I want to thank the support from the Health Care Authority. I've learned a lot just being on the committee for six years, in particular, I

want to thank Donna, Leta, and Ryan for just their support and guidance through the process.

Alright. So, now we're going to move onto our first agenda item is the atypical antipsychotics. Do we have Brittany on the phone?

Brittany Lazur: Hi. This is she.

Lisa Chew: Okay, Brittany. Your slides are up.

Brittany Lazur: Great. Thanks, so much. So, as you mentioned, I will be presenting the findings of a most recent surveillance report on second generation antipsychotics.

So, this presentation will take a form that you're probably very familiar with by now. So, we'll first start with a little bit of topic history. We'll go into our inclusion criteria, key questions and methods for the surveillance, and we'll spend most of our time on findings and summary.

So, slide two here, to provide a little bit of topic history, this topic has been reviewed multiple times throughout the history of the Drug Effectiveness Review Project. The most recent time being update number five, which was published in October of 2016. Since then, there have been two scans of the literature and FDA actions, the first being on April, 2017. The second being in November of 2018. Again, this is the most recent surveillance, the findings that I'll be presenting to you today.

So, in terms of the populations that were included in the surveillance, we were really looking at a comprehensive list. These were really from the last report. These include adults and adolescents with schizophrenia or related disorders; adults, adolescents, and children with bipolar disorder; adults with major depressive disorder; children and adolescents with autism spectrum disorder; and children and adolescents with disruptive impulse control or conduct disorders.

So, in terms of the interventions, we were really looking at a comprehensive list of the second generation antipsychotics and the comprehensive [inaudible] would still be here on this slide. We included

both oral and injectable formulations that have been approved by the FDA. I'd like to refer you to table 2 in the surveillance report, which shows a really comprehensive table of these second-generation antipsychotics, their formulations, and their indicated populations.

So, in terms of comparators, we were really looking at head-to-head evidence. So, evidence of one 2nd generation antipsychotic compared to another. We were looking at this for all populations. For populations for which we did not find sufficient evidence, or there was a lack of evidence for head-to-head, we also included placebo-controlled trials. So, these populations included children and adolescents with bipolar disorder, autism spectrum, or the conduct disorders. We also included placebo controlled evidence for adults with major depressive disorder.

In terms of the outcomes, we looked at quality of life, functional capacity, hospitalization, persistence, mortality, symptom response, and then various adverse events. For the surveillance, we were really focused on looking for randomized control trials.

Our key questions here, there are quite a few. This is really evidence of how large this topic is and how large the prior reports on this topic have been. So, really, our key questions boil down to comparative benefits and harms in the individual populations that we just discussed here. So, key questions one, two, and three really deal with adults and adolescents with schizophrenia or other psychotic disorders, major depressive disorder, or bipolar disorder. Key question four, five, and six focus on comparative benefits and harms in children and adolescents with bipolar disorder, autism, and then those conduct disorders. Finally, for key question seven, we were looking for any differences in the comparative benefits and harms of these 2nd generation antipsychotics in subgroups of these populations.

So, we're on slide eight here, and just to touch on our methods for the surveillance report, we first do a comprehensive search for clinical trials in these two registries that we have listed here on this slide. So, clinicaltrials.gov, and the ISRCTN Registry. We then take trials that we've identified that are relevant, and we use the trial number and plug them into OVID Medline to identify if there are any published systematic

reviews or published interventional studies related to these trials. We also do comprehensive searches of the FDA website and comprehensive Google searches for any FDA actions. I just want to note that all those searches for literature spanned the entirety of the period of time, since the last report. So, January, 2015, to September of this year, but then FDA actions really focus in on the time period since the last surveillance. So, that would be of 2018.

So, moving onto our findings for new drug formulations and indications. These are since 2018.

So, on slide 10, for this surveillance period, we did not identify any newly approved drugs or formulations; however, we did identify a new expanded indication for cariprazine. It is now indicated for treatment of depressive episodes in adults with bipolar one disorder. This expanded indication came in May of this year.

So, moving onto new serious harms or warnings, again, since the last surveillance topic in 2018.

So, as you can see here on slide 12, we have identified a number of new serious harms and warnings for 2nd generation antipsychotics. This is kind of a busy slide here. So, it's oriented to the information in this table. In the first column, we have the generic name, uh, of the drug for which the serious harm and warning was issued. The second column is the brand name or sometimes you'll see multiple brand names to indicate different formulations for which the serious harm or warning is indicated. A third column, you'll see the date for which the harm or warning was issued. Then, finally in the last column, we have a summary of the harm or warning. I just wanted to bring a couple to your attention, as there are quite a few here. So, I wanted to note the harm and warning for aripiprazole lauroxil, or Aristada, this is an increased risk of death for elderly patients with dementia related psychosis. Another that I'd like to bring to your attention is cariprazine, or Vraylar. In 2019, a warning was issued for increased risk of suicidal thoughts or behaviors in children, adolescents, and young adults. Then, finally, I'd like to bring your attention to the warning for ziprasidone. In 2018, there was a warning issued for increased risk of cerebrovascular event, or adverse reactions,

such as stroke and death in elderly patients with dementia related psychosis.

So, moving onto studies that identified... again, these are comprehensive, since the last report on this topic in 2016.

Here on slide 14, here is the summary of the new studies identified, since the last report. We have found a total of 14 new studies, since that last update report in 2016. We have identified seven new head-to-head studies, six pertaining to adolescents and adults with schizophrenia and one pertaining to children with comorbid autism spectrum disorder and ADHD. We have also identified seven new placebo-controlled trials, three in children and adolescents with bipolar disorder, two for adjunct treatment in adults with major depressive disorder, one in children and adolescents with autism spectrum disorder, and then finally one in children with comorbid oppositional defiant disorder and ADHD.

So, this slide and subsequent slide will have an overview... kind of more of a granular look at the individual studies that we have identified in our surveillance searches. This, again, is kind of a busy slide. So, I'll just walk you through how it's laid out. So, the first column here will have the author and year of the publication and the trial number from the registry, if available. Second, we have the sample size, the duration of the study, and the population that was studied. Then, in the third column, we have listed the interventions and the comparisons in each of these studies. And then, finally, in the last column, we have the outcomes that we're focused on in these studies. So, here on this slide, we have the studies that we've identified specifically for patients with schizophrenia. A couple that I want to note to you here of interest, one is Cuomo, 2018. This is a comparison of aripiprazole injectable to paliperidone palmitate injectable, so a head-to-head injectable trial. Then, the other study that I'd like to bring to your attention is the Huang, 2018. This is a comparison of olanzapine oral to paliperidone palmitate injection. So, an oral versus injection study. Just as a high-level overview, these studies really range in terms of sample size from pretty small, 57, to quite large at 461 participants. Most of these studies focus on changes in symptom severity.

So, we're on slide 16. This slide illustrates the study that we've identified for patients with bipolar disorder and also major depressive disorder. So, first starting with bipolar disorder, we've identified three placebo-controlled trials that you see here on this slide. They range from 59 participants to quite large to 347 participants. Two of them were quite short, 6 to 12 weeks, but one did have longterm outcomes that were identified. So, the study was 50 week in duration. Moving onto studies of major depressive disorder, we did identify those two placebo-controlled trials. Again, in these studies, 2nd generation antipsychotics were used as adjunct treatment to antidepressants. So, you see here aripiprazole and brexpiprazole and cariprazine. These studies were relatively short in duration, six to eight weeks. It had 394 and 812 participants respectively. Again, as you can see on the slide, these studies did focus on changes in symptom severity.

So, finally, we have the studies that we've identified for autism spectrum disorder and oppositional defiant disorder. So, we've identified two studies for autism spectrum disorder. One is a placebo control trial, you see here in the first line. The second is a head-to-head study comparing aripiprazole and risperidone. You can see they are really different in terms of the length of studies. One is quite short, eight weeks. The second one is 24 weeks. Finally, we did identify that one oppositional defiant disorder study is eight weeks in duration, and it's a comparison of risperidone and methylphenidate with methylphenidate and placebo.

So, let's move onto identified ongoing studies that we found in a 30-month period.

So, we're on slide 19 now, and we have identified a total of 16 ongoing studies in the surveillance period. Of note, more than half of them, or 10, are focused on adults with schizophrenia. In addition, four studies focused on adults with major depressive disorder. One study is on children and adolescents with autism spectrum disorder. There is one study that we identified in adolescents and adults with substance use disorder and psychosis. Based on the information that we've identified in the child registry, we estimate that eight of these studies may be published within the next year.

So, let's wrap up with some summary and put this into context with what we've identified cumulatively since the last report.

Since the completion of the most recent updated DERP systematic review in October of 2016, we have identified a total of 14 new randomized control trials. Six of those were identified in this surveillance period, and we've identified a quite even split in the randomized control trials. So, seven head-to-head studies and seven placebo control trials. We've also identified 16 ongoing studies, all of which were found in the surveillance period. These include 12 head-to-head studies and four placebo control trials. We have also identified three new indications, one of which we discussed today that was identified in the surveillance period. We found seven new serious harms or warnings for second generation antipsychotics, and they were all identified in this surveillance period. Finally, since the last report, we have identified three new formulations; however, none of these were identified in this surveillance period. They were all identified in prior scans. So, I'd be happy to take any questions that you have at this time. Thank you.

Lisa Chew: This is Lisa Chew. Thank you, Brittany. Any questions from committee members? Brittany, there doesn't seem to be any questions. So, should we move onto the Magellan presentation?

Leta Evaskus: Technical difficulties. I don't know why it just went out. Hang on.

Umang Patel: While Leta is pulling up the slides, I just wanted to inform the committee that for this P&T, the structure of the presentation is a little bit differently. There is a lot of therapeutic classes in here. So, out of respect for time, a lot of the dosing and availabilities are put in the appendices for the committee's leisure. Most of the indications are presented. I will not be going over them in granular detail. The majority of the focus will be on guidelines and newer medications, as well.

So, first, we have antipsychotics for 2nd generation. Giving a quick overview of the different disease states that fall under this umbrella, first thing, autism. Autism spectrum disorder is one of the most common developmental disabilities in children in the U.S. Overall estimates of prevalence vary widely, but most recently was approximated at roughly

16.8 per 1000 children aged 8 years. The CDC reported a recent rise in autism over the past few decades. Two key criteria for the diagnosis of autistic disorder, uh, per the DSM-5 are impairments in social communication, both verbal and nonverbal, and social interaction, along with a restrictive repetitive range of interests, activities, and behavior. Now, regarding the guidelines for autism, according to the American Academy of Child 2014 and the Adolescent Psychiatry, and American Academy of Pediatrics in 2016, many medications that have been used for the treatment of autism are not indicated for the disorder. However, oral formulations of Abilify and Risperdal are FDA approved for the treatment of irritability associated with autism in children. The AACAP recommends pharmacotherapy only when there is a specific symptom targeted, but they do not specify the use of one antipsychotic agent over another. Similarly, guidelines, according to the AAP have been published and do not specify the use of one agent over another, and the AAP states that given the risk and benefits of atypical antipsychotics, these agents should only be used to treat severe irritability and problem behavior in ASD only in the following situations: 1. Where safety is an issue. 2. The behaviors interfere severely currently with current functioning, such as a change in school or residential placement would be necessary otherwise. 3. Other interventions have failed or resulted in incomplete improvement. 4. Behaviors unrelated to psychosocial stressors, communication difficulties, underlying medical or psychiatric conditions, or environmental factors. 5. Lastly, lower risk intervention cannot be implemented.

Continuing on to bipolar disorder here, lifelong prevalence estimates bipolar disorder ranges from 0.9 to 2% of the population, characterized by episodes of mania, depression, or mixed state. Criterion used to diagnose bipolar 1 disorder is the presence of a manic episode, such as persistent elevate, expansive, or irritable mood for at least one week with increased energy or activity, or mixed features specifier, rapidly alternating polarity of moods, sadness, irritability, and mania for at least one week, and three or more other characteristic symptoms. These other symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation. Excessive involvement in

risky, pleasurable activities. According to the APA in 2002, there is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity, mortality. Firstline treatment for more severe manic or mixed episodes require the initiation of lithium or valproate plus an antipsychotic agent. Second generations are preferred over first, due to their more tolerable adverse event profile. For bipolar manic episodes with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of standard antidepressants as monotherapy can precipitate a manic episode in bipolar patients. During maintenance treatment, recommendations suggest to first optimize the medication dose in patients with bipolar disorder, especially in patients experiencing a breakthrough manic episode and then consider adding another firstline agent. Lastly, a guideline watch supplement was published in 2005 and included additional data on the use of second generations as monotherapy or adjunctive therapy in an extended release formulation of carbamazepine for the acute treatment of manic or mixed episodes and stated that these provide clinicians with additional treatment options.

Moving over to depression, national epidemiological data among adults reported that prevalence of 12 month and lifetime major depressive disorder, MDD, based on DSM-5 criteria, is approximately 17.3 million American adults, or 7% of the U.S. population. The U.S. Preventative Services Taskforce recommends screening for MDD in adolescent ages 12 years and older and in adults. This should be supplemented with precautions to ensure accurate diagnosis, as well as appropriate treatment and followup. The evidence of screening in patients younger than 12 years is inefficient to make a recommendation at this time. According to the APA in 2010, for patients who exhibit psychotic symptoms during an episode of MDD treatment should include a combination of an antipsychotic and antidepressant medication, or ECT, electroconvulsive therapy. Second generation medications may increase the rate of response or remission of depressive symptoms in patients who typically have not responded to more than two antidepressants, even when psychotic symptoms are not present. Lower doses are used for antidepressant augmentation than for treatment of psychosis. Lastly, the APA does not consider these guidelines current, based on the publication date, but new updates or revisions have now been published.

According to the ACP in 2016, after review of literature, they found that a cognitive behavioral therapy in second generation antidepressants are similarly effective and have similar discontinuation rates. ACP recommends treatment with either CBT or second generation antidepressants for MDD after discussing treatment effects, adverse effects, preferences, and accessibility with the patient, and no clinical conclusions were made regarding the efficacy of second generation antipsychotics.

There is an estimated 1 million with Parkinson's in the U.S. with about 60,000 new cases each year. It is a progressive neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. Roughly 20 to 30% of patients with Parkinson's experience hallucinations, and up to 8% experience delusions in advanced stages. Atypical antipsychotics have been used to treat hallucination and illusions associated with Parkinson's psychosis; however, in patients with only mild hallucinations, antipsychotic treatment may not be necessary. Per the American Academy of Neurology in 2006, their guidelines recommend that clinicians consider clozapine for patients who have Parkinson's and psychosis. The absolute neutrophil count must be monitored, since clozapine can cause fatal agranulocytosis. Also, quetiapine does not exacerbate motor symptoms of Parkinson's and may be considered for patients with Parkinson's and psychosis. Due to a better side effect profile, many clinicians may consider quetiapine as a first choice. Lastly, olanzapine and risperidone should not be used, due to potential for worsening motor function. Nuplazid was not approved at the time of guideline development, but it is the only FDA approved medication for the treatment of Parkinson's psychosis.

Continuing on. Still in Parkinson's, the APA published practice guidelines on the use of antipsychotics to treat agitation or psychosis in dementia, in patients with dementia, these guidelines do not specify the role of Nuplazid, but they do note that extrapyramidal side effects of other antipsychotic medications and the potential of cognitive worsening may be greater in patients with Parkinson's disease dementia compared to other types of dementia. According to the Movement Disorders Society in 2019, they found that Nuplazid was efficacious and to have an acceptable risk without requiring specialized monitoring. Thus, the

researchers concluded that its use for psychosis and Parkinson's is clinically useful, but they also state there is a lack of safety data regarding durability beyond six weeks. Notably, they also weigh in on other agents in this class that are not indicated for PD psychosis, stating that olanzapine is not clinically useful, quetiapine is possibly useful, and clozapine is also useful but requires specialized monitoring. They also emphasize that all antipsychotics should be used with great caution in demented patients with psychosis, due to the risk of adverse effects, such as falls, impaired cognition, pneumonia, etc.

Moving on to schizophrenia here. The most common psychotic illness is schizophrenia, which effects 1% of the population. Between 25 to 50% of schizophrenia patients attempt suicide, and 10% of patients succeed. Symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, negative symptoms, and at least one of these should be delusions, hallucinations, or disorganized speech. Per the APA in 2004, goals of treatment are to stabilize the patient and reduce or eliminate the symptoms, improve quality of life and adaptive functioning, and reduce the likelihood of relapse. Antipsychotics are the standard drugs used in patients with schizophrenia to achieve these goals. The guideline recommends a second generation as a firstline therapy, due to its decreased risk of EPS, extrapyramidal symptoms, and tardive dyskinesia with first generation antipsychotics, suggested as appropriate firstline options for some patients. 2009 guideline watch from the APA modifies the recommendation to state that first generations may be equally effective as second generations. The statement is based on studies that have been published, since 2002. Notably, as these guidelines are more than five years old, the APA does not consider them current; however, they have again, not published or updated any revisions. Per the AACAP in 2013, they recommend antipsychotic medications as primary treatment for schizophrenia, spectrum disorders in children and in adolescents. They recommend against the use of clozapine, as firstline. They state that ziprasidone has not demonstrated efficacy in this population, and it is not FDA indicated for this population and caution on its use with olanzapine due to weight gain. Ultimately, they state that the choice of which agent is based on FDA approval, adverse effect profile, patient family preferences, provider comfort, and familiarity along with cost. Again, as this practice

parameter is over five years old, it is considered a historical practice parameter. Again, newer guidelines are not yet available.

The final disease state that is under this umbrella is Tourette's Disorder. The prevalence of Tourette's is unknown, but observational studies have suggested a prevalence of roughly 1% in school-aged children. Tourette's is a genetic tic disorder characterized by motor and vocal tics. Generally, individuals have repetitive stereotype movements of vocalization, such as sniffing, muscle tension, and blinking. DSM-5 criteria for Tourette's Disorder state multiple motor and at least one vocal tic are present during the illness, not necessarily simultaneously and have been present for one year or greater, although they may wax and wane in frequency. Onset of these symptoms may occur prior to 18 years of age to be considered Tourette's Disorder. Peak tic severity typically occurs between the ages of 10 and 12 years. Tics usually improve during adolescence with 18% of those older than 16 experiencing no tics, and 60% having minimal or mild tics six years after initial examination. Per the American Academy of Neurology, this in 2019, no evidence exists demonstrating that that treatment is more effective than the earlier it is started, and watchful waiting is reasonable, especially in those without tic-related functional impairment. Comprehensive behavioral intervention for tics, CBIT, may be considered as initial therapy in patients who are motivated to attempt treatment. Patients should be assessed for comorbid conditions, such as ADHD, OCD, anxiety disorder, oppositional defiant disorder, and mood disorders. Alpha-2 adrenergic agonist may reduce tic severity, particularly in patients with ADHD. Regarding other specific pharmacologic agents, haloperidol, risperidone, aripiprazole, and botox, are probably more likely than placebo to reduce tic severity. Pimozide, ziprasidone, topiramate, and metoclopramide are possibly more likely than placebo to reduce tic severity. Overall, there is insufficient evidence to determine their relative efficacy of these drugs. Notably, a higher risk of drug-induced motor movement disorders is associated with haloperidol, pimozide, and risperidone, and with longterm use of metoclopramide. Lastly, patients with severe Tourette's syndrome resistant to medical and behavioral therapy may benefit from deep brain stimulation, or DECIBELS.

Now, those are all the background and the guidelines for the disease states that fall into this category. On the next few slides, you will see the medications that fall into the second generation antipsychotics, whether or not they are available generic, other indications, along with schizophrenia, bipolar, which is broken down into acute manic episodes, depressive episodes, acute mixed, and maintenance. As I stated earlier, I'm not gonna go into all of these in great depth, since there are a lot more therapeutic classes, but I will give the committee just a few minutes to look over these indications on the next few slides.

After the indications, we do have just two medications that I did want to just highlight, per recommendations from the Health Care Authority. The first is Nuplazid. This is the medication I alluded to earlier. It's indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Some warnings and precautions: QT interval prolongation can occur. Avoid use with drugs that increase QT interval and in patients with risk factors for prolonged QT interval. It is noted that it can increase mortality in elderly patients with demented related psychosis. It is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. The dosage is 34 mg taken orally once daily and can be taken with or without food. The availability are both capsules and tables.

On the next slide here, we do have Vraylar or cariprazine. It's an atypical antipsychotic medication indicated for three-fold, the treatment of schizophrenia in adults, acute treatment of manic or mixed episodes associated with bipolar 1 disorder in adults, and treatment of depressive episodes associated with bipolar 1 disorder in adults. In terms of warnings and precautions, elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. Not approved for the treatment of patients with dementia related psychosis. Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Lastly, closely monitor all antidepressant treated patients for clinical worsening and emergence of suicidal thoughts and behavior. Again, the dosing is stratified by indication, and the availabilities are found as capsules.

And the last slide for this therapeutic class, the black box warning. So, all antipsychotics, including Nuplazid, have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia related psychosis. Abilify, Abilify Mycite, Latuda, Symbyax, Seroquel, Seroquel XR, have the same boxed warning as the antidepressants in regards to an increased risk of suicide in children, adults, and young adults. Clozapine has severe additional boxed warnings due to a significant risk of severe neutropenia, which is defined as a neutrophil count less than 500 per/mL, which may increase the risk of serious and potentially fatal infections. Clozapine is only available through a clozapine risk evaluation and mitigation strategy program. Seizures are associated with the use of clozapine. This is a dose-related effect. Caution must be used when administering clozapine to patients with a history of seizures or predisposition to seizures. Patients must also be warned to avoid engaging in activities where loss of consciousness may cause harm to themselves or others. Myocarditis occurs with clozapine at a rate of five cases per 100,000. Over half of these cases were fatal. Clozapine also carries warning for cardiomyopathy and mitral valve incompetence. Orthostatic hypotension with rare collapse, one case per 3,000 patients, and respiratory and/or cardiac arrest, occur at a higher rate in patients receiving clozapine, especially during dose escalation in the initial titration phase. Moving onto loxapine inhalation powder, it has a boxed warning cautioning of bronchospasms that can potentially lead to respiratory distress and respiratory arrest. Healthcare facilities administering this medication must have access to short-acting bronchodilators for immediate treatment of bronchospasms. Zyprexa Relprevv has a boxed warning stating that patients are at risk of postinjection delirium sedation syndrome. This may result in severe sedation, including coma and/or delirium after each injection.

Lisa Chew: Thank you, Umang. Any questions? Okay. We have five stakeholders. Dr. Nik Seifter, Dr. Michael Moore, Dr. Valerie Ng, Dr. Paul Thompson, and Dr. Mae Kwong. If the stakeholders could come up to the podium. Please state your name and who you represent. You will have three minutes for your comments. I will let you know when your time is up.

Nik Seifter: Thank you, everyone. My name is Nik Seifter. I am a pharmacist and director of health economic and outcome research for Sunovion

Pharmaceuticals. I appreciate the opportunity to provide some information in support of retaining Latuda on the Washington Medicaid PDL. Briefly, I'll start with the indication. Latuda is indicated for the treatment of schizophrenia in adults and adolescents 13 to 17 years of age. Lurasidone is also the only agent in its class with an indication as both monotherapy and adjunctive therapy with lithium and valproate for the treatment of major depressive episodes associated with bipolar 1, or bipolar depression. This is in adults. Additionally, Lurasidone is the only agent in its class with an indication for treatment of pediatric patients 10 to 17 years of age with bipolar depression, as a monotherapy. I refer you to the prescribing information for a full list of warnings, precautions, and adverse events. Evidence based guidelines intended for physicians globally recommend Lurasidone as a firstline therapy for acute bipolar depression. This is the 2018 CANMAT and ISBD guidelines, which is Canadian Network for Mood and Anxiety Treatments, and International Society for Bipolar Disorders. Hey recommend Lurasidone among firstline therapies, as monotherapy or adjunctive therapy with lithium and valproate for acute bipolar depression in adults. Lurasidone is also the only firstline agent recommended in children and adolescents with acute bipolar depression. Turning to outcomes data, a recent independent network metaanalysis included 20 randomized control trials for antipsychotic drugs with multiple efficacy and tolerability outcomes in children and adolescents with schizophrenia. Regarding weight gain, Lurasidone was similar to placebo and significantly better than risperidone, paliperidone, clozapine, quetiapine, and olanzapine. Regarding prolactin increase, Lurasidone was similar to placebo and superior to paliperidone, olanzapine, haloperidol, and risperidone. I will close with a brief highlight of two longterm safety studies in youth populations. So, the first is 305 children or adolescent patients aged 10 to 17 years of age with bipolar depression entered into longterm open label extension study for up to two years with treatment of Lurasidone. Lurasidone was flexibly dosed, 20 to 80 mg daily, continued improvement in depressive symptoms was observed during longterm treatment, and longterm treatment with Lurasidone was associated with minimal effects on weight, lipids, prolactin, and measures of glycemic control. In the second study, 271 adolescents, 13 and 17 years of age with schizophrenia, entered in a longterm open label extension study with up to two years of treatment with Lurasidone. This study was also flexibly

dosed 20 to 80 mg daily. Long term treatment with Lurasidone showed continued improvements with schizophrenia symptoms, as measured by PANS total score, and continued improvements in measures of functioning and quality of life. Lurasidone was generally well tolerated with minimal changes in weight, metabolic parameters, and prolactin. So, I appreciate your time, and I again respectfully request Lurasidone is retained on the PDL for Medicaid beneficiaries of Washington. If you have any questions, I'll be happy to answer them.

Lisa Chew: Thank you, Dr. Seifter. Any questions? Okay. Next doctor, Dr. Michael Moore.

Michael Moore: Hi. My name is Dr. Michael Moore. I'm a neuroscience medical science liaison with Otsuka Pharmaceutical Development and Commercialization Inc. I want to thank the Washington State P&T Committee for this opportunity to share information on Ability Mycite, the world's first ever fully integrated digital medicine to objectively track drug ingestion. Now, I only have two minutes and 40 seconds left. So, I will be concise. We have a giant problem in medicine. People living with chronic lifelong illnesses struggle with taking daily medication. In fact, the adherence rate in major depressive disorder, bipolar 1 disorder, and schizophrenia hovers at around 50%, meaning that essentially it's a coin toss whether a patient suffering from serious mental illness is actually taking their medication, as prescribed. So, if the patient isn't taking their medication, and if the provider doesn't know if the patient is taking their medication, that's a serious fundamental flaw that needs addressed in treatment. Enter Abilify Mycite, the first of its kind drug device combination product approved by the FDA in November of 2017. Abilify Mycite is an aripiprazole tablet embedded with an ingestible event marker sensor that's intended to track drug ingestion and is indicated for use in adults with schizophrenia, bipolar 1 disorder, and as an adjunctive treatment for major depressive disorder. Now, the Abilify Mycite system is comprised of other components, like, the Mycite patch, which is a wearable sensor that records the date and time of drug ingestion, along with the patient's rest and activity levels. There is the Mycite app, which is accessed on a smartphone and allows the patient to review and enter their behavioral health data, like, daily moods, rest quality, and reasons for a missed dose. Lastly is the Mycite dashboard, which is accessed by healthcare providers

and family and caregivers of the patient who have been invited and approved by the patient themselves. Now, we currently anticipate that the Abilify Mycite system is to be used in a short-term manner that is for two to three months. It's also important to note, we are not stating, nor claiming, that Abilify Mycite will improve patient compliance. In addition, Abilify Mycite should not be used in realtime during emergencies, or in modifying the aripiprazole dosage, and in fair balance, I call your attention to the two box warnings for Abilify Mycite. First, an antipsychotic class one for increased mortality in elderly patients with dementia related psychosis. The second an antidepressant class warning for suicidal thoughts and behaviors in pediatric and young adult patients. So, for additional safety information, please refer to the full prescribing information for Abilify Mycite. So, for all these reasons, we request that Abilify Mycite be placed in an optimal formulary position, and as Otsuka's neuroscience medical science liaison, I'd be happy to share information that the committee requests. With that, I'd like to thank you all, and have a happy holidays.

Lisa Chew: Thank you, Dr. Moore. Any questions? Thank you. Dr. Valerie Ng.

Valerie Ng: Esteemed members of the P&T Committee, good morning. My name is Valerie Ng. I am a pharmacist. I am with Indivior's managed care medical science team. Thank you for giving us your time today and for allowing me to share with you information on Perseris, which is an extended release formulation of risperidone. Perseris is indicated for the treatment of schizophrenia in adults. It is the first and only second generation antipsychotic injected subcutaneously once a month in the abdominal area. For patients who have never take risperidone before, tolerability should first be established with an oral risperidone prior to starting Perseris. Perseris is initiated at a dose of 90 mg or 120 mg, and the prescriber should not administer more than one dose per month. Based on average plasma concentrations of risperidone and its total active [inaudible], 90 mg of Perseris corresponds to 3 mg of oral risperidone per day, while 120 mg of Perseris corresponds to 4 mg per day of oral risperidone. Neither a loading dose, nor any supplemental oral risperidone is recommended. The most common adverse reactions observed during the clinical trials were increased weight, sedation somnolence, and musculoskeletal pain. For complete safety data, please

refer to the full prescribing information of Perseris. The FDA approval of Perseris was based on a phase-3 study assessing the safety and efficacy of Perseris in adults with a diagnosis of schizophrenia under the DSM-4 TR criteria, who exhibited an acute episode within eight weeks of screening of the study. The phase-3 study was a randomized double-blind placebo controlled eight-week study of 337 patients receiving 90 mg, or 120 mg of Perseris or placebo. The efficacy of Perseris was demonstrated by statistically significant improvements in the primary and secondary clinical endpoints, which were the positive and negative syndrome scale scores and the clinical global impression severity of illness scores respectively. The improvement at each timepoint from baseline was also statistically significant versus placebo. Furthermore, there was a 12-month phase-3 open label longterm safety and tolerability study conducted on Perseris. In closing, we request the Committee to consider the coverage of Perseris, as a preferred treatment option for patients who are suffering from schizophrenia. At this time, I would be happy to take any questions you may have.

Lisa Chew: Thank you, Dr. Ng. Any questions? Alright. Thank you. Alright. Next is Dr. Paul Thompson.

Paul Thompson: Hi. Good morning. My name is Paul Thompson. I'm a psychiatric pharmacist and medical science director with Alkermes. I appreciate the time to come up here and provide testimony on Aristada Initio. The committee is already familiar with Aristada, as it's been on the PDL for a number of years. I'm here today to talk about our new product Aristada Initio that was approved in June, 2018. Aristada Initio in combination with oral aripiprazole is indicated for the initiation of Aristada when used in treating schizophrenia in adults. It contains a black box warning, which you spoke to earlier with increased mortality in patients with mets related psychosis. The only hypersensitivity is those hypersensitive to aripiprazole. Aristada Initio comes in one strength, 675 mg. It does have different pharmacokinetic profiles. It is aripiprazole lauroxil, as well as Aristada is aripiprazole lauroxil, but due to the larger crystals in Aristada Initio, its dilution is much quicker. Therefore, they are not interchangeable, and it is only to be used as an initiation regimen. It can be used with a 30 mg oral dose of oral aripiprazole, and then any of the Aristada current formulations, the monthly, every six week, or two month

doses can be administered either the same day or up to ten days after the one day initiation regimen. It can be administered in the deltoid or gluteal muscle. The most common adverse event with Aristada was akathisia followed by a headache, insomnia, injection site reactions, the most common being pain, but others, induration, swelling, or redness that occur in less than 1%. Then, pharmacokinetic studies are Aristada Initio, the safety was generally consistent with what was observed in Aristada trials. So, in closing, Aristada is the first longacting injectable antipsychotic with once monthly, every six week, and every two month dosing options. Aristada Initio is a one day initiate in conjunction with the 30 mg oral tablets. It is a one-day initiation regimen option opposed to the 21 days of oral therapy patients would have had to take prior to its approval. I wanted to respectfully request the committee considers and adds Aristada Initio to the state formulary and PDL. I appreciate and thank you for the time today to provide this information. I can answer any questions if you have any.

Lisa Chew: Thank you, Dr. Thompson. Any questions? Okay. Thank you. The next one is Dr. Mae Kwong.

Mae Kwong: Good morning. My name is Mae Kwong. I am a pharmacist with Janssen Scientific Affairs. I am here today to thank you for making Invega Sustenna and Invega Trinza available to Washington Medicaid adult schizophrenia patients. Both are longacting and injectable atypical antipsychotics containing paliperidone palmitate. Invega Sustenna is a once monthly intramuscular injection, and Trinza is the only longacting injectable delivered every three months after adequate treatment with Invega Sustenna for four months. Invega Sustenna is the only longacting injectable antipsychotic that has shown superiority versus oral antipsychotics. The PRIDE study, which is now the Invega Sustenna label showed a delay in relapse by six months, which is 416 days versus 226 days for Invega Sustenna versus oral antipsychotics in a randomized comparative study conducted in real world patients with schizophrenia and a history of incarceration. These are patients typically not included in clinical trials. An overall 32% reduction in relapses and 35% reduction in hospitalizations, arrest, or incarceration was observed. Multiple studies have demonstrated improvements in adherence, persistence, and healthcare resource utilization outcomes for Sustenna, as well as other

longacting injectable antipsychotics. These positive outcomes lower medical costs, which offset the pharmacy costs associated with these longacting injectable antipsychotics. The burden of schizophrenia remains substantial in the United States. Oral antipsychotic adherence rates are low at about 32% depending on what studies we're looking at. And relapse is common and costly. Clinical guidelines recommend longacting injectable antipsychotic use in situations beyond just antipsychotic nonadherence. Invega Sustenna is the only longacting injectable to show superiority to a group of oral antipsychotics in delaying treatment failure among adults with schizophrenia. The longterm economic impact, the patients treated with Invega Sustenna have shown a reduction in reincarceration, healthcare resource utilization, and cost. In patients who are appropriately transitioned to Invega Trinza from Invega Sustenna demonstrate high adherence, high persistence, and economic benefit or neutrality. For these reasons, I thank the committee for continuing to keep Invega Sustenna and Invega Trinza on the Washington Medicaid formulary and available to adults schizophrenia patients in Washington. Thank you.

Lisa Chew: Thank you, Dr. Kwong. Any questions? Alright. Thank you. So, we're going to move onto the motion. There are actually three motions, I think, we need to make for this class. The first one is surveillance report, and we need to make a motion of whether the committee accepts the report as adequate, or we want to request a more thorough review. Because this is a surveillance report, new drugs are not eligible for inclusion on the PDL.

Ryan Pistoresi: So, just to update you on that. So, these surveillance documents are what we, as states, review to understand if we want to move forward with a new report through the Drug Effectiveness Review Project. So, as you can see from this surveillance document, we saw that there were a lot of new studies. We did work with the other states and vote to commission a new report. So, we will have that ready for you at one of the future P&T meetings, likely this time again next year, so the December 2021. So, some of the drugs that were not eligible to be included today should be able to be reviewed then when we get the big updated report with all those studies that were mentioned earlier today.

Susan Flatebo: I move that we accept the scan as adequate.

Alexander Park: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Now, we move on to making two motions, I believe that we need to separate out oral drugs and injectable drugs here. So, the first motion would be around the oral drugs.

Ryan Pistoresi: So, yes, previously when we've done the antipsychotics class, we've had it all as one motion, but as there have been more and more injectable versions, we decided to split them out. That way, it helps us when we're making these recommendations and building the Washington PDL to have these drugs kind of more similar and split out like we have some of the other drug classes, like, the estrogens where we have multiple dosage forms. One of the other reasons that we wanted to split it out is that when talking with L&I, we found out that they participate for the oral medications but not the injectable ones. So, this helps you kind of understand when you're making the motion for the orals, it will apply to UMP and L&I, and for the injectables, primarily to UMP. So, that way, it just gives you a little bit more visibility in what motions you're making and how these motions would impact the Washington PDL, and thus the programs participating in the Washington PDL.

Alexander Park: Question for the oral drugs motion, do we need to add the Nuplazid as a separate indication for Parkinson's psychosis?

Ryan Pistoresi: You can make that as the motion, since it is one of the newer indications that wasn't, I guess, previously covered in the original motion.

Donna Sullivan: I believe we had previously decided that Nuplazid was not considered to be in this particular class, because it's indication is for Parkinson's disease related dementia or psychosis, not schizophrenia. So, it's not part of the class.

Alexander Park: What class then does it fall in?

Donna Sullivan: We have it in... it's not on the Washington PDL. So, it's handled through the... whichever agency is using the Washington PDL through their typical business management, how they manage their PDL outside those classes.

Alexander Park: Okay. In that case, looking at the oral drugs motion, I could make a motion. I would just ask the verbiage be changed where it says removing all roots of the administration. I guess we need to take that out, since we're doing an oral only motion. Then, another for injectable so we can say remove that. Then, make it all the drugs.

I guess I have to read all that, huh? Okay. After considering the evidence of safety, efficacy, and special populations for the treatment of schizophrenia and bipolar disorder in adults and children, major depressive disorder in adults and children and adolescents with autism spectrum disorder, or other disruptive behavior disorders, I move that aripiprazole, asenapine, brexpriprazole, cariprazine, clozapine, iloperidone, Lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone are efficacious for their approved FDA indications and should be preferred on the Washington Preferred Drug List. Second generation antipsychotics cannot be a subject to therapeutic interchange in the Washington Preferred Drug List. The Preferred Drug List should include at least one medication that is considered safe in pregnancy.

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Now onto injectable drugs, the motion for that.

Virginia Buccola: So, can we copy the text and stop at the list of oral medications? Then, cut and paste the list of injectables? Or, I don't know if we need to... never mind. Go ahead. What I was going to say before is, I didn't know if

we needed to specify the brand name of the specific injectable. Do we need to list that on the injectable next to the drug name?

Ryan Pistoresi: So, the reason that we broke that out is because we had previous versions of aripiprazole that were considered reviewed because they were in previous reports, but like the Abilify Mycite was approved after the last time we had an updated report. So, it was considered not reviewed. So, we've done that in the past where we've kind of said, you know? For most of the aripiprazole, they have been reviewed, but for some that are unique or specific, they have not yet been reviewed. When we go through the cost analysis, that other forms of aripiprazole may be eligible to be preferred, but for example, the Aristada Initio has not been reviewed by this committee yet. So, to answer that question a little bit further, it does need to be in the motion.

Virginia Buccola: So, whatever preferred forms of the listed drugs...

Ryan Pistoresi: Would be considered in the motion. Yes.

Virginia Buccola: ...we don't need to detail them. Okay.

Leta Evaskus: I just added the last part of the oral drugs motion. So, let me know if you want to change that.

Lisa Chew: Virginia, do you want to read the?

Virginia Buccola: Sure. After considering the evidence of safety, efficacy, and special populations for the treatment of schizophrenia and bipolar disorder in adults and children, major depressive disorder in adults and children and adolescents with autism spectrum disorder, or other disruptive behavior disorders, I move that aripiprazole, olanzapine, paliperidone, risperidone, and ziprasidone are efficacious for their approved FDA indications and should be preferred on the Washington Preferred Drug List. Second generation antipsychotics cannot be subject to therapeutic interchange in the Washington Preferred Drug List. The Preferred Drug List should include at least one medication that is considered safe in pregnancy.

Catherine Brown: I second.

Lisa Chew: All those in favor say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Alright. Let's move onto the CGRP, the surveillance report. Curtis, are you on the phone?

Curtis Harrod: Yes, I am.

Lisa Chew: Hang on just a moment. We're putting the slides up.

Curtis Harrod: Yep.

Leta Evaskus: Your slides are up.

Curtis Harrod: Alright. Thank you, very much. So, my name is Curtis Harrod. I'm at the Center for Evidence Based Policy representing the Drug Effectiveness Review Project. I'll be presenting on a surveillance document around calcitonin gene related peptide inhibitors for migraine prophylaxis, also known as CGRP inhibitors. On the next slide, slide number one is just an overview of the presentation today. It will follow the same structure as Brittany's earlier.

So, moving onto slide number two, we have our topic history. So, in 2008, specifically October of 2008, we completed an original systematic review on this topic. Subsequently a surveillance document was completed in March of 2019. This is our second one of those. So, continuing on from that October, 2018, review will give you an idea of the body of literature and FDA actions that have come out.

On slide number three is our background. So, for CGRP inhibitors, they are used to prevent migraines, specifically chronic and episodic migraines, although that is evolving, and I will cover that under the FDA action section. The chronic migraine is described as at least 15 headache days in a month, where episodic is roughly described as less than 15, though there are some different definitions used for episodic migraines. Three CGRP inhibitors specifically galcanezumab, fremanezumab, and

erenumab are FDA approved, and those were all approved in 2018, where eptinezumab was expected to be approved multiple times at this point, as of late in 2019, unfortunately, that still has not been approved, although it is included in our scope for the report.

Moving onto slide number four, we will begin with our PICO, our population, intervention, comparators, and outcomes. For population, we're focusing on adults with episodic and chronic migraines. This includes individuals with no previous treatment history, as well as those who are unresponsive to other migraine prophylaxis. As I mentioned before, CGRP inhibitors that we're covering within this scope are erenumab, fremanezumab, galcanezumab, and eptinezumab. Nothing that three are subcutaneous injections. Only eptinezumab is an IV infusion.

Moving onto slide number five, our comparators. We have multiple of them. We look for studies that compared one CGRP inhibitor to another. We also looked at the comparator for migraine prophylaxis, such as selected antidepressant, anticonvulsion, betablockers, onabotulinumtoxinA, and sham or placebo controlled trials were also included in the scope.

So, moving onto slide number six, we have our laundry list of outcomes here. So, there's a suite of outcomes that are used to measure migraines, and those are all included within the scope, such as frequency, intensity, and duration of those events; pain, including intensity in duration. Moving onto more functional outcomes, quality of life, and then some other types of outcomes, such as employment related outcomes. Are individuals able to return to work and function, as if they did not have migraines, for instance? Use of rescue therapies, and we get into tolerability and adverse events to wrap up our list of outcomes.

So, on slide number seven, our key questions are the focus here. There are four of them. The first one is addressing the efficacy and effectiveness of CGRP inhibitors to prevent episodic and chronic migraines. The second focuses on adverse events or harms with CGRP inhibitors for preventing migraines. The third is around subgroups, so different classes, such as gender, if there's a comorbidity present. We

look for all types of subgroups here. Our fourth key question is looking at the pipeline of studies on ongoing studies for CGRP inhibitors.

So, moving onto slide number eight, covering our methods. Brittany did a great job of covering this slide previously. So, I'll just touch on it real quick again here. We searched for registered trials, and looked for those identifiers within databases for new randomized control trials on this topic. We also searched the FDA website, Interwatch, Google, etc. to identify FDA actions, such as newly approved drugs, formulations, indications, or identify serious harms or warnings.

So, now, we'll move onto slide nine, which is the transition slide to our findings for this surveillance period. On slide number ten is the one randomized control trial that we identified during this period. That's the Dodick et al. 2019 study. There are 665 patients in this randomized trial, all of whom had chronic migraines. There are four different groups. Eptinezumab was given in four different groups, and we are comparing those to a placebo. Our outcomes consist of migraine responders, as well as adverse events. We did identify a secondary analysis, actually multiple secondary analyses, with regards to the REGAIN study. The REGAIN was identified in the previous surveillance document. It was built on that. That was focusing on galcanezumab for chronic migraines.

So, moving onto slide number 11, the focus is on ongoing studies. We have identified 20 ongoing studies, two of which are head-to-head. That specifically is erenumab versus another drug, and not a CGRP inhibitor, however; 18 placebo control trial, and you can see the breakdown there. Two in eptinezumab, seven in erenumab, six in fremanezumab, and three in galcanezumab. Then, we have two placebo control trials within those 18 that are focused on the pediatric population, just noting that that's not included in the DERP scope. I just wanted to point that out. These are both erenumab one in episodic migraine, as well as chronic migraine.

So, now we'll move onto slide number 12 focusing on new indications and harms identified during this surveillance period. The FDA gave a new indication in June of 2019 for galcanezumab to treat episodic cluster headache in adults. So, cluster headaches are defined as those that occur in periods lasting from seven days all the way to one year. These are

separated by pain-free periods lasting up to or more than three months. Cluster periods generally last between two weeks and three months. Personally speaking, these sound absolutely terrible. This is approved for galcanezumab now. We are aware that other CGRP inhibitors are being evaluated for this indication, too. Cluster headache was not a part of the DERP systematic review in the initial scope, although there are studies that were used for FDA approval. I have listed one specifically here on this screen. In March of 2019, the FDA added a new warning concerning erenumab, and this is for hypersensitivity reactions. This is consistent with other CGRP inhibitors. So, erenumab was late to the game with giving this warning; however, it is consistent now with the other two that are approved by the FDA that is.

So, we're on slide 12, and we'll move onto slide number 13 now. So, we have our new drugs or formulation slide. There were no new drugs or formulations for CGRP inhibitors. I mention that eptinezumab still has not been approved by the FDA, though they have submitted. We just do not know when that is going to occur.

So, moving onto slide number 14, covering the summary of our surveillance document here today. We'll move onto slide 15. So, we have three placebo control trials that have been identified, since the original systematic review on CGRP inhibitors, and one specifically during surveillance period. So, those three consist of galcanezumab for chronic migraine, erenumab for episodic migraine, and one on eptinezumab in chronic migraine. That was the one for this surveillance period. We have 20 ongoing studies, two of which are head-to-head, 18 that are placebo control trials, so a large body of evidence forthcoming. One new indication identified from this period on galcanezumab in cluster headaches in adults. Then, the one warning that I mentioned on hypersensitivity reactions for erenumab. Then, I also noted that there are no new drugs or formulations identified during this surveillance period. So, I would be happy to take any questions that you have on this topic.

Lisa Chew: Thank you, Curtis. Any questions from the committee members? So, Umang, will you be doing your presentation here? Or is that saved later for under the DUR? Here? Okay. So, Umang, the CGRP agents.

Umang Patel: Perfect. Thank you. Moving over to just a little bit of background. I know Dr. Harrod alluded to some background here. There will be overlap. Migraines account for 10 to 20% of all headaches in adults and affect over 39 million men, women, and children in the U.S. Headache is one of the most common complaints by patients when presenting to a physician; 64% of physician diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bedrest due to their migraine symptoms. In addition, 18% of women, 6% of men, and 10% of children experience migraine and epidemiologic profile that has remained stable over many years. Roughly 85% of patients with migraine headaches suffer less than three to four attacks per month. The median frequency of migraine attacks among migraine sufferers is 1.5 per month. A migraine headache must be differentiated from a tension type headache. The key criteria for the diagnosis of migraine headache includes an episodic headache lasting from 4 to 72 hours with at least two of the following symptoms: Unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity. During the headache, at least one of the following are present, nausea and/or vomiting, photophobia and phonophobia.

Continuing on with migraines, again, it is a complex neurological condition that can involve debilitating headache and sensory changes. A migraine attack, the neurologic changes occur in the cortex, brainstem, hypothalamus, thalamus, as well as peripheral and central portions of the trigeminal vascular system. The attacks are usually episodic, occurring less than 15 days per month, but some migraine sufferers experience chronic, daily headaches defined as 15 or more days per month. Again, the key features that I mentioned, I'm not going to repeat them, are listed here.

Moving onto the next slide, we'll pivot over to cluster headaches. It is a severe primary headache disorder characterized by extreme pain on one side of the head and autonomic symptoms, such as nasal congestion or lacrimation. These CH periods can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration. The estimated lifetime prevalence of cluster headaches is more than one in

1000. And they can either be episodic or chronic in nature with episodic being the predominant form. Individuals with episodic cluster headaches experience periods of attack followed by periods of remission, whereas individuals with chronic cluster headaches have minimal to no periods of remission between headache attacks.

On the next slide here, you'll see the three medications that fall under the CGRP class. We have Aimovig, Ajovy, and Emgality. You can see all three are indicated for the preventative treatment of migraine in adults, where Emgality has an additional indication for the treatment of episodic cluster headaches in adults. Below, we have the indications, dosage, and availability, which I will not be going over, but it is there for the committee's leisure.

Moving on to the guidelines, in 2018, the FDA approved the first CGRP inhibitors, Aimovig, Ajovy, and Emgality, for preventative treatment of migraines in adults. According to the American Headache Society in 2019, they released a position statement on integrating new migraine treatments into clinical practice. Unlike oral prophylaxis agents, the CGRP inhibitors do not require slow dose escalation, have a faster onset of therapeutic benefit, and have favorable tolerability profiles. The committee also recommends initiating CGRP inhibitors for migraine prophylaxis in patients 18 years of age or older with the following: Diagnosis of migraine with or without aura, experiencing four to seven monthly headache days with moderate disability and inability to tolerate, or inadequate response to a six-week trial of at least two oral prophylactic agents. Diagnosis of migraine, again, with or without aura, experiencing 8 to 14 monthly headache days, and inability to tolerate or inadequate response to a six-week trial of at least two oral prophylactic agents. Lastly, diagnosis of chronic migraine and either inability to tolerate or inadequate response to a six-week trial of at least two oral prophylactic agents, or at least six months of onabotulinumtoxinA treatment. According to the guidelines, a response to CGRP inhibitors therapy should be assessed after three months for monthly injections or six months for quarterly injections. Therapy should be continued if clinically meaningful treatment benefit can be documented. The statement also addressed nonpharmacologic therapy, including neuromodulation and biobehavioral therapy.

Continuing on with the guidelines, the American Headache Society in 2016 recommend sumatriptan subcutaneous at a dose of 6 mg, zolmitriptan nasal spray at a dose of 5 or 10 mg, and 100% oxygen at 6 to 12 liters per minute for the acute treatment off episodic or chronic cluster headaches. Pharmacological therapies considered to be probably effective for episodic and chronic cluster headaches include sumatriptan nasal spray 20 mg, as well as zolmitriptan oral at a 5 to 10 mg dose. Sphenpalatine ganglion stimulation is a potential nonpharmacologic treatment option for patients with chronic cluster headaches who are not satisfied with current therapy; however, it is not routinely available in the U.S. Octreotide 100 mcg subcutaneous, as well as lidocaine 10% nasal spray are considered to be possibly effective for both episodic, as well as chronic cluster headaches. As of the date of guideline publication, insufficient evidence existed to support the use of dihydroergotamine nasal spray, somatostatin, or prednisone. In general, the strength of the recommendation for the treatment modality should be considered in conjunction with the potential safety profile prescriber experience, patient specific factors, and cost. Emgality is the first FDA approved treatment for episodic cluster headache that decreases the frequency of acute attacks, but it was not available at the time of these guideline developments.

Moving over to the American Academy of Neurology and the American Headache Society in 2015, nonopioid analgesia with NSAIDs or combinations, such as aspirin, acetaminophen, plus caffeine are recommended as firstline therapy for patients with mild to moderate migraine pain. Due to well established efficacy, the triptans have become the drug of choice for treating migraine attacks. The response rate to triptans is about 60%. Studies suggest that 38 to 50% of patients with migraines are candidates for preventative therapy. Indications for preventative therapy include four or more migraine attacks per month, or eight or more migraine days per month, acute medication overuse, and debilitating migraine. They do advise that antiepileptic medications, such as divalproex sodium, sodium valproate, or topiramate and beta-blockers, such as metoprolol, propranolol, and timolol are established as effective in migraine prevention. Naratriptan, zolmitriptan, antidepressants are probably effective in migraine prevention, but no

triptan is approved for the prevention of migraines at this time. All available triptans are effective treatments. Dihydroergotamine, acetaminophen NSAIDs, select opioids, sumatriptan, naproxen combo, and acetaminophen aspirin caffeine combination were also rated as effective. No recommendation was offered regarding an advantage of one triptan over another, and the update to this guideline is still in progress. Our last guideline here, the American Academy of Neurology and American Headache Society in 2019 issued new guidelines on the pharmacologic treatment for pediatric migraine prevention. The key recommendations include counseling patients and caregivers on lifestyle modifications, such as sleep habits and tobacco use. Advise patients and caregivers that most trials of preventative medications have failed to show any benefit over placebo in children, except for propranolol, which may 'possibly' result in a 50% reduction in headache frequency. They recommend to counsel patients and caregivers to treat an attack early for most benefit, firstline ibuprofen oral solution 10 mg/kg in children and adolescents, and counseled patients and caregivers about medication overuse. Sumatriptan, naproxen combination tablets and zolmitriptan nasal spray are options in adolescents. They recommend to offer antiemetics to treat substantial nausea and vomiting.

Lisa Chew: Thank you, Umang. Any questions? Okay. We have two stakeholders. We have Dr. Karen Campbell and Mr. Anthony Wheeler. We also have a couple of emails in your packet. Please come up to the podium, state your name, who you represent, and you will have three minutes for comments.

Karen Campbell: Good morning. My name is Karen Campbell. I'm a pharmacist with Amgen Medical Affairs. I appreciate the opportunity to provide the committee with an update on Aimovig, erenumab. Of the three CGRP products, even with the soon to be approved fourth product, Aimovig is the only CGRP antagonist that specifically targets the CGRP receptor. Its mechanism of action is unique, in that it inhibits the receptor function but does not interfere with the CGRP ligand interactions at the other receptor site in the body. Aimovig recently released its four-year longterm data demonstrating clinically meaningful and sustained efficacy, as well as safety, which is important for a chronic condition. Results of the two open label extension studies evaluating the longterm use of

Aimovig in episodic and chronic migraine populations were presented at the American Headache Society meeting in Philadelphia in July of this year. At the four-year interim analysis of the ongoing five year episodic migraine study, three-quarters of the patients achieved 50% reduction in monthly migraine days, along with a reduction in pain intensity. Half achieved 75% reduction, and one-third reported being migraine free during the last month of treatment. The safety profile is similar to or less events than those observed in the double blind treatment phase. There were no safety signals. At the one year of the chronic migraine open label extension study, two-thirds of the chronic migraine patients converged to episodic. The rates of adverse events were consistent with those observed in the short-term placebo control trial with injection site reactions and constipation being the most commonly reported adverse events occurring at equal to or less than 3%. Aimovig had a label change recently in the warning and precaution section, which states, constipation with serious complications has been reported following the use of Aimovig in the postmarket setting. Migraine pathophysiology is multifactorial and complex. It is a very heterogenic disorder. No two patients' migraine experience is exactly the same, nor the response to therapy. As observed with the triptans. We respectfully ask the committee to ensure providers have therapeutic options so that there are no delays for patients to receive the most effective treatment to reduce their migraine days, duration, severity, and disability. I thank you, and are there any questions?

Lisa Chew: Thank you, Dr. Campbell. Any questions? Thanks. Mr. Wheeler?

Anthony Wheeler: Alright. I'm Anthony Wheeler. I'm an employee of Eli Lilly and Company, which manufactures galcanezumab. This is marketed as Emgality. It's part of the CGRP inhibitor class of drugs. This was originally approved last year for the preventive treatment of migraine. You've reviewed this drug before. So, I just wanted to provide a short update, which is that earlier this year, Emgality was approved for the treatment of episodic cluster headache. This is a much less common headache disease than migraine, but it is very debilitating, and there are very few FDA approved treatments for it. The dosing and administration for cluster headache is a little bit different than migraine. It's three 100 mg prefilled syringes every month, during a cluster period. Whereas, in migraine it's a single

dose auto-injector device once a month. That's 120 mg. In a phase-3 randomized control trial, Emgality reduced the frequency of weekly cluster headache attacks compared to placebo. Those were the registration data that formed this indication. So, I'm happy to try to answer any questions that you have. Thanks, as always, for letting me provide an update.

Lisa Chew: Any questions? Thanks, Mr. Wheeler. We do have a third stakeholder, Dr. Maria Agapova. Please state your name, who you represent, and you will have three minutes.

Maria Agapova: Good day. My name is Maria Agapova. I'm a senior medical outcomes liaison at Teva Pharmaceuticals. Thank you very much for having me here. I am here to provide additional information that may have not yet been reviewed about Ajovy, fremanezumab, injection. Just a note that to date, in postmarketing setting, the safety of Ajovy has not yet warranted updates to label warnings and precautions. Also, an ongoing trial has been completed and is now in the peer review domain. That's the FOCUS study. It's very important to the setting of the AHS position paper, because it's studied 838 episodic and chronic migraine patients who had inadequate response to two, three, or four classes of standard of care preventives. In that study, patients treated with fremanezumab or Ajovy, experienced statistically significant reductions in monthly average number of migraine days. These were 4.1 for the monthly and 3.7 for the quarterly groups compared to just 0.6 day reductions in the placebo group across the 12-week assessment period. Within the FOCUS trial, adverse events of greater than 5% incidence were injection site erythema. That's 6% all fremanezumab groups versus 5% placebo. Injection site duration was equal across all groups at 4%. Nasopharyngitis 4% of fremanezumab groups versus 4% placebo. Serious adverse events were rare and did not defer between treatment and placebo groups. In terms of what's coming in 2020, there is, in development, in addition to the prefilled syringe, an auto-injector. Fremanezumab is also being investigated in posttraumatic headache in a phase-2 randomized clinical trial. In terms of how Ajovy differentiates from standard of care, I just wanted to highlight that there is demonstrated efficacy across multiple dimensions of migraines. So, that includes frequency, intensity, duration, quality of life, symptoms, such as nausea and photophobia, and even

reductions in rescue medication utilization and medication overuse. Improved tolerability and low discontinuation rates with this drug compared to standard of care. Then, there's also multiple options for dosing and administration, including monthly and quarterly dosing, dose administration by physician, caretaker, or self, and we see rapid onset of effect with the differences, as early as one day or one week, and long-lasting action, because it is a monoclonal with a 32-day half-life. So, we ask the committee, based on this evidence, to continue to grant access to Ajovy for patients in the State of Washington. I thank you for your time, and I will take any questions.

Lisa Chew: Any questions? Alright. Thank you, very much. Okay. Let's move on to the motion. I think the first motion is for the surveillance report, whether we want to move this as adequate? Or do we want to request a more thorough review?

Ryan Pistoresi: So, to update you on that, we are commissioning a new review from the Drug Effectiveness Review Project that will be available later in 2020, but since we are trying to move toward a kind of more consistent cycle for reviewing these drugs and drug classes, it will likely be rereviewed here again next December.

Jordan Storhaug: I move that we accept the scan as adequate.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Now, the second motion is whether we want to reiterate the prior motion or make modifications to that.

Catherine Brown: I move to reiterate the prior motion.

Jordan Storhaug: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: And any opposed? The motion carries. Okay. I think we are adjourning the P&T Committee. We have a ten minute break. So, 10:41 and 47 seconds.

Ryan Pistoresi: As Leta brings up the slide deck, just to remind the committee, since antipsychotics, at least the second generation, was reviewed in the beginning, I won't be going over background and guidelines, since they are similar and, again, out of respect for time.

Okay. Alright, moving on. Again, there is no background and guidelines here. So, we'll move right over to the indications. Again, dosing and availability is in the appendices. For the first generation antipsychotics, we have them stratified based on oral, I believe, injection, and inhaled. So, on the first slide here, further stratified by medications that are available in generic form, additional indications, and whether or not they are indicated for schizophrenia, psychotic disorder, and bipolar disorder. While the committee kind of just looks at this, just to give a little bit of background. For first generation antipsychotics, all first generation and second generation antipsychotics do have a warning regarding neuroleptic malignant syndrome, characterized by rigidity, hypothermia, and autonomic instability. It is rare, occurs within the first week of treatment, and dose increase. All antipsychotics may reduce the body's ability to regulate core body temperature. Caution should be used in patients who will be experiencing conditions contributing to an increased core body temperature. In addition, significant neurotoxicity, including rigidity and inability to speak may occur in patients using an antipsychotic who also have thyrotoxicosis. The last is the all antipsychotics, except loxapine inhalation, share a warning that tardive dyskinesia may develop in patients treated with these drugs.

You can see the oral medications are continued, along with inhaled and short-acting injectables. This is a short therapeutic class, because, like I said previously, all of the disease and background and guidelines were

reviewed previously. On the last slide here, we have the longacting injectables for first generation. Any questions?

Lisa Chew: Any questions for Umang. There are no stakeholders for this class.

Leta Evaskus: I just want to point out that we're going to have you do the motions in this PowerPoint, so that I can type into it. So, the page numbers listed apply to this PowerPoint presentation, not in your folder. It's gonna look like I'm talking about Umang's presentations when I mix them in. You'll see.

Lisa Chew: There are no stakeholders. Should we move to the motion?

Donna Sullivan: Marissa, are you going to walk through? Gotcha. So, we're gonna make motions now for the Apple Health PDL. So, I just want to clarify that the motions that were made for the Pharmacy and Therapeutics Committee, those apply to the Washington PDL. The Apple Health PDL is a different preferred drug list managed by Medicaid. We do follow your recommends from the P&T committee portion of the meeting, but we also need you to make motions that guide the Apple Health PDL selection. Then, for the drug classes that are not on the Washington PDL. So, we're going to make motions now that will be specific to the first generation and second generation antipsychotics, the combination products that were included in those classes. Then, the miscellaneous antipsychotics. So, that's Nuplazid and several others. So, we're recommending that all products in the drug class listed on slide two are considered safe and efficacious and eligible to be preferred and allow grandfathering at the discretion of the Health Care Authority. All nonpreferred products require a trial of three preferred products, one of which must be a preferred generic before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred. So, I want to give a little background on the second bullet. The previous motion that you made from the last meeting said that they would be required to try one generic and two preferred products. So, I just reworded that second bullet to be three, one of which must be a generic. I have put up a proposed motion, if you would like to edit it, please let us know and Leta will make any changes you find necessary. If you would like to see what the PDL currently looks like, we

can pull it up and look at it online, if you'd like to take a look at these classes.

Jordan Storhaug: I guess my concern is really on slide two, we've only listed four categories of medicine. It would be helpful for me if we actually had the individual products listed for making this motion.

Donna Sullivan: So, let's...

Leta Evaskus: Donna is going to bring up the website, and we'll switch to hers.

Donna Sullivan: ...Okay. Okay. I probably need to make that bigger. So, for the first generation antipsychotics, chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, trifluoperazine, and that was it on the preferred products. So, essentially, in this particular class, all the generics are preferred. Most of the branded products are off patent. So, they are multisource. So, they are nonpreferred. They require prior authorization to make sure that they use the generics. Any questions about those drugs? Okay. And then the second generation antipsychotics, it's the aripiprazole, all the different formulations, clozapine, the I don't know that we have... I'm just going to say the generic names, olanzapine, paliperidone, quetiapine, and the quetiapine XR, and ziprasidone. Then, again, most of these are preferred, unless they are branded. If they are multisource brand, they are nonpreferred. I do want to point out that Abilify Mycite is nonpreferred, as well as the Aristada Initio. I think those are the only two brands that are not available generically. Those are the only two brands that are not preferred. Any questions about the second generation antipsychotics? The combination products, there's an olanzapine fluoxetine product, the generic for Symbyax. It's nonpreferred. It's less costly to actually take the two different products separately. Then, the miscellaneous products are the [inaudible], Nuplazid, and Vraylar.

Alexander Park: So, when we say in the motion all products in the drug classes listed on slide two, we're talking about first-second generation combos and miscellaneous. Those are the four classes?

Donna Sullivan: Correct.

Alexander Park: Okay.

Donna Sullivan: And the motion will be for each individual drug class. So, as far as the interchange, the preferred status. So, we'll treat each drug class individually, but instead of having to say the same motion over four times, I'm just rolling them all up into one statement.

Leta Evaskus: Should I bring the motion back up? Okay.

Lisa Chew: Question for Donna. So, let's say you tried a second generation three of the preferred products, can you move to a combination then nonpreferred?

Donna Sullivan: No. That would...

Lisa Chew: Stay within that class.

Donna Sullivan: ...you would have to, it would stay within that class.

Susan Flatebo: What were the miscellaneous agents again?

Donna Sullivan: Equetro, Nuplazid, and Vraylar. They should be in the appendix that Umang provided in the second generation antipsychotic presentation.

Alexander Park: Since we're combining this, which I appreciate by the way. Thank you. Do we need to clarify, when we say the nonpreferred products require a trilogy of preferred products? Do we need to say that within the respective class?

Donna Sullivan: You could. If you prefer to make it more clear.

Alexander Park: Okay. That might be more clear. I would appreciate that.

Donna Sullivan: Okay. Then I have a point of order question. So, when we do the P&T motion, it reads somewhat similar to this, but we say they are safe and efficacious for their approved indications when we do the P&T motion, but I notice we don't say that for the DUR motions. Is there...

Donna Sullivan: That's probably just that I didn't happen to remember to do that. So, we can insert that, as well.

Alexander Park: Yeah. I like that wording.

Donna Sullivan: I would put medically accepted indications, because Medicaid does have a slightly different nuance from an FDA approved indication. There is also medically accepted indications that include off-label use that is supported in the compendia.

Virginia Buccola: I will go ahead and make the motion. So, I move that all products in the antipsychotic drug classes listed on slide two are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the Health Care Authority. All nonpreferred products require a trial of three preferred products within the same subclass, one of which must be a preferred generic before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Alexander Park: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. Let's move onto the antimanic agents.

Umang Patel: Moving forward to the antimanic agents, some of this, again, has been reviewed in the atypical antipsychotics in the first half. So moving to bipolar disorder, lifelong prevalence estimates bipolar ranges from 0.9 to 2% of the population characterized by episodes of mania, depression, or mixed state. Criterion used to diagnose bipolar 1 disorder is the presence of a manic episode persistent, elevated, expansive, or irritable mood for at least one week with increased energy and activity, or a mixed features specifier, defined as rapidly alternating polarity of moods, sadness,

irritability, and mania for at least one week, and three or more other characteristic symptoms. These are defined as inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual, or pressured speech, flights of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky pleasurable activities. The criterion for diagnosing bipolar 2 disorder includes one or more depressive episodes nearly every day during the same two-week period with at least one hypomanic episode lasting at least four days. The depressive episodes are marked by the appearance of five or more depressed symptoms, which include a depressed mood, most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation, or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness, or inability to concentrate, and recurrent thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated expansive or irritable mood with increased energy and activity, and three or more other symptoms. These include inflated self-esteem, I mentioned these just earlier, so I'm not going to repeat these here.

Moving to the guidelines again, I apologize, because there was so much on the antipsychotics, I wanted to unpack this again. The APA in 2002 stated there is no cure for bipolar disorder, but the appropriate pharmacologic treatment can decrease morbidity, mortality. Firstline pharmacologic treatment for more severe manic or mixed episodes require the initiation of lithium or valproate plus an antipsychotic agent. Second generations are preferred over first, due to their tolerable adverse event profile. For bipolar manic episodes with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of antidepressants in bipolar patients, misdiagnosis having nonbipolar depression can precipitation the first manic episode. The firstline therapy treatment for a bipolar depressive disorder includes treatment initiation with lithium or lamotrigine. Antidepressant monotherapy is not recommended. An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. If an acute depressive episode does not respond to optimal dose of firstline medication treatment, then the addition of lamotrigine, bupropion, or paroxetine is recommended. Patients with

bipolar depression experiencing psychotic features usually require adjunctive treatment with an antipsychotic, and a 2005 guideline Watch states that olanzapine, fluoxetine combo, or Symbyax and quetiapine may also be effective for depressive episodes. During the maintenance treatment, recommendations suggest to first optimize the medication dose in patients with bipolar disorder, especially in patients experiencing a breakthrough manic episode. Then, consider adding another firstline agent if dose optimization of the initial agent does not lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patients for a response. A guideline Watch supplement was published in 2005 and included additional data on the use of second generation antipsychotics as monotherapy or adjunctive therapy. Extended release formulation of carbamazepine for the acute treatment of manic or mixed episodes and stated that these provide clinicians with additional treatment options.

Moving forward to the APA, in 2002, following remission of acute episode, patients may remain at particularly high risk of relapse for a period of up to six months. This phase of treatment is considered in the APA guideline as part of the maintenance phase. The medications with the best empirical evidence to support that their use in maintenance treatment include lithium and valproic. Possible alternatives include lamotrigine, carbamazepine, and oxcarbazepine. If one of these medications was used to achieve remission from the most recent depressive or manic episodes, it generally should be continued. For patients treated with an antipsychotic medication during preceding acute episode, the need for ongoing antipsychotic treatment should be assessed, and varying level of evidence exist for maintenance treatment of bipolar disorder. Again, these guidelines are well over five years old. So, the APA does not consider them current. However, no published updates or revisions have been made. Here, you can see we have a current product listing of all lithium medications. This is a lithium agent clinical review, but because it's under an antimanic agent, the background was more encompassing. In the indications here, you can see for all lithium, I guess, varying doses and availability, as well.

The final slide for this, we do have a new medication, and it is not a lithium medication, but because it is an antimanic, I felt remiss if I didn't

put it in here. Equetro is a new medication that is indicated now as a mood stabilizer, indicated for the treatment of acute manic or mixed episodes associated with bipolar 1 disorder. If you can see that there is some text that is not bolded. That is if it was not new or updated or related to the antimanic agent, I did not bold it on this slide. There are some black box warnings associated with Equetro. Serious dermatologic reactions, serious and sometimes fatal reactions include TEN, toxic epidermal necrolysis, and Steven Johnson Syndrome have occurred. Patients of Asian ancestry have a ten-fold greater risk of said TEN and SJS compared to other populations. If this does occur, discontinue Equetro immediately. Aplastic anemia and agranulocytosis have occurred with this medication. There is a warning for this, aplastic anemia, agranulocytosis have occurred and obtain a complete pretreatment hematologic testing prior to starting. Consider discontinuing if significant bone marrow depression does develop. For dosages, there is a long list of dosage. That is in the TCR on the web portal for the committee, and the availability are extended release capsules here. Any questions?

Lisa Chew: Thank you, Umang. Any questions? There are no stakeholders for this class. So, let's move to the motion. Would it be helpful to pull up the specific drugs under this class, like we did with the last one?

Donna Sullivan: Yes. We can do that. And I just want to also point out, while I am making this conversion, you might have noticed that we have Equetro in the antipsychotic miscellaneous class. We use Medispan's categorization of the drugs to determine which drug classes they go in. I'm verifying that Medispan actually calls this a miscellaneous antipsychotic. So, that's why it's included in that class. So, for us, for the Apple Health PDL, the antimanic class is just the lithium products, all of them with the exception of Lithobid, which is a multisource brand, are preferred. Any questions? Okay. I'm going to give it back to Leta.

Leta Evaskus: I am just going to copy further medically accepted medications, if you want to add that in to this.

Alexander Park: I move that all products in the antimanic agents drug class are considered safe and efficacious for their medically accepted indications, and are eligible for their preferred status and grandfathering at the discretion of

the Health Care Authority. All nonpreferred products require a trial of two preferred products before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Jordan Storhaug: I second.

Lisa Chew: All those in favor say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Let's move on to migraine agents.

Umang Patel: Moving onto antimigraine agents. This covers triptans and others. Again, the background and the guidelines were reviewed in the CGRP class. So, I will focus more on the triptans and others kind of to help differentiate special populations and things like that. So, on this slide here, you can see the indications for the triptans. Primarily, all have indications for acute treatments for migraine attacks, with or without aura in adults. A few to note, for pediatrics, you have almotriptan, Maxalt, and Treximet with the respective pediatric indicated agents. Sumavel and Imitrex also have an indication for acute treatment of cluster headache episodes in adults, as well.

Continuing on with indications, again dosing and availability are in the appendices. While you're, I guess, looking over this, just to give you a little bit of special populations for the triptans and others, for patients who are pregnant, please note that Cafergot dihydroergotamine mesylate, ergomar, Migergot, and Migranal are category X. So, they are not recommended in patients who are pregnant, as it can cause fetal harm. Cambia is pregnancy category C, as in Charlie prior to 30 weeks of gestation, and then it is category D, as in delta afterwards. Midrin is category C, as in Charlie and Aimovig does not have adequate data on developmental risk associated with pregnant women.

Continuing on with this, just to give you a background, there are two black box warnings, specifically ones that do contain NSAIDs. They can cause an increased risk of cardiovascular thrombotic events, including

myocardial infarctions and stroke. It is contraindicated in the setting of coronary bypass graft surgery, as well.

Moving onto the next slide, just to give a new medication here to touch base on it, we have Reyvow, which is lasmiditan. On October 2019, the FDA approved this medication, which is a serotonin 5HT1F receptor agonist indicated for the acute treatment of migraines with or without aura in adults. The limitations of use, it is not indicated for the preventative treatment of migraines. It does contain a controlled substance, lasmiditan. The controlled substance schedule for it is to be determine after the DEA reviews it. So, we do not know what control substance category it is yet. Warnings and precautions, driving impairment may occur. Advise patients not to drive or operate machinery until at least eight hours after taking each dose. It may cause CNS depression and should be used with caution if patients are using it with alcohol or other CNS depressants. Reactions consistent with serotonin syndrome were reported in patients taking this medication and discontinue if serotonin syndrome does occur. The dosing is recommended as 50 mg, 100, or 200 taken orally, as needed, and no more than one dose in 24 hours. The availability are tablets, as well. Just for special populations for this medication, safety and efficacy have not been established in pediatric patients. For hepatic impairment, no dosage adjustment is needed for patients with mild or moderate hepatic impairment, which is Child Pugh A or B, but it has not been studied in severe hepatic, which is child Pugh C. Any questions?

Lisa Chew: Any questions? Hang on a minute. I didn't get the stakeholder. There are no stakeholders for this. Okay.

Donna Sullivan: So, we're gonna switch over to look at the PDL online. Down at the bottom of the screen, you'll see that Aimovig, and Ajovy are nonpreferred and Emgality is our preferred agent. Currently, they all require prior authorization that they have to try and fail two of the traditional prevention agents before they can get one of these. Then, with the, I think it's Emgality that has the cluster headache indication, it would be allowed for that particular indication. Any questions about the PDL? Okay.

Leta Evaskus: It's a little awkward, but we're saving paper, right?

Diane Schwilke: I move that all products in the migraine agents CGRP drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All drugs within this class may require prior authorization for medical necessity. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorization, unless contraindicated, not clinically appropriate, or only one product is preferred.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Alright, and the motion carries.

Donna Sullivan: I'm going to... for the... did we go over the statins and everything yet? Okay. Never mind, but we are going to combine the motions for the other the others and the triptans. I just forgot to do that previously, but the motions are almost identical. So, I think we can edit those. Not triptans, I'm sorry. My brain is not functioning today. I'm getting a cold. So, we're going to combine the triptans, the other, and the ergomar-derivatives. So, I apologize for misspeaking there.

Alexander Park: Since we're doing that mashing up again of the multiple classes, can we add the verbiage about within each respective class?

Donna Sullivan: Then add triptans up there. I would just delete ergo derivatives and migraine agents. In their respective classes.

Alexander Park: I'm sorry. I think that would be added after the verbiage about the trial of two preferred products. So, this new drug, the lasmiditan, this falls under the other class?

Donna Sullivan: So, we have the triptans. I don't know if we have captured it yet. It's not on the market? Or it's not in the Medispan? It's not... it hasn't come into our drug reference table yet. So, at this point in time, there is not an NDC that is available for us to claim, but it will probably be in its own class. So, right now, we're not making it a motion on it. The other class is Cambia is the only drug in that class right now. I can pull up those drug classes. Cambia is a diclofenac 50 mg powder. It's just an NSAID. So, here you can see the migraine agents other. Then, well I'll go up and the triptans, essentially, most of the generics are preferred. So, we have sumatriptan, rizatriptan, are preferred, and naratriptan. Then, zolmitriptan is not preferred. When you see PA required, that's generally either on the dosage forms or the combinations require prior authorization. Or it's a brand name that has a generic available. Any questions?

Lisa Chew: In terms of motive administration, there are enough preferred, like, subcutaneous injections. For the preferred, sumatriptan, like the injectable is a preferred?

Donna Sullivan: Yeah. So, we have all of the formulations of sumatriptan are preferred. The generic formulations, as well as the rizatriptan tablets and the dispersible tablets are preferred. Yeah. So, we have injectable sumatriptan, nasal sumatriptan, and the oral.

Leta Evaskus: Do you want the committee to first make this motion? Or is this considered...

Donna Sullivan: It's going to be one motion, just that one slide we just edited.

Leta Evaskus: Okay.

Jordan Storhaug: All products in the migraine agent classes are considered safe and efficacious for the medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the Health Care Authority. All nonpreferred products require a trial of two preferred products in their respective classes before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only product is preferred.

Alexander Park: I second.

Lisa Chew: All those in favor say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. So, let's move onto antihypertensives.

Umang Patel: Thank you. So, this class has got classes within itself. So, we will go over angiotensin modulators, which include ARBs and ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics. As the members of the committee can imagine, most of these medications, there's not too many updates and changes. So, indications, dosing, and availabilities are in the appendices. I will try to go over their respective background and guidelines if it's relevant for each subgroup in here.

So, moving forward, hypertension, approximately 116 million or roughly almost half of the adults in the United States have hypertension. The highest age-related prevalence is among African-American men and women at 58.6 and 56% respectively. It is estimated that hypertension is controlled in only 54% of patients with the condition. It is an independent risk factor for cardiovascular disease and can lead to heart failure and stroke if uncontrolled for a prolonged period. Angiotensin receptor blockers, or ARBs, are indicated for the treatment of hypertension, either alone or in combination with the antihypertensive medications. In terms of nephropathy, since this does fall under the ARBs and ACE inhibitors umbrella, approximately 25% of patients with diabetes with develop microalbuminuria during the ten years after diagnosis in 25 to 40% will develop diabetic nephropathy over 20 to 25 years after diabetes onset. Diabetic nephropathy is the most common cause of endstage renal disease in the U.S., accounting for 40% of all patients with endstage renal disease who are on dialysis. Types 1 and 2 diabetes increase the risk of nephropathy and follow the same progression to renal insufficiency and failure. Guidelines by the ADA in 2019, the AACE in 2015 and updated in 2019, the AHA and ASA in 2014, and JNC-8 suggest that all patients with diabetes should receive an ACE inhibitor or

an ARB for the treatment of hypertension to reduce the risk of stroke, and to delay the progression of diabetic nephropathy.

Pivoting over to the guidelines, JNC-8 recommended to start antihypertensive therapy in patients at least 60 years of age when a systolic blood pressure is 150 mg/Hg or greater, or a diastolic blood pressure is 90 mm/Hg or greater with a goal of systolic blood pressure less than 150 and diastolic less than 90. For patients younger than 60, and in adults with CKD therapy should be initiated when systolic is 140 or greater, and diastolic is 90 or greater, and target blood pressure is less than 140/90. In non-African-American population, initial treatment should include a thiazide type diuretic, calcium channel blocker, or an angiotensin converting enzyme, ACE inhibitor, or ARB. For African-Americans, initial treatment should include a thiazide type diuretic, or a calcium channel blocker. In patients with CKD treatment, treatment should include an ACE inhibitor or ARB to improve kidney function, regardless of race or diabetes status. If blood pressure goal is not reached within one month of starting treatment, the dose should be increased, or a second drug from another class should be added, and a third drug can be added if needed.

According to the American College of Cardiology and the American Heart Association, joint guidelines in 2017, the guideline revised the classification system for blood pressure. The initiation of drug therapy should be based on a combination of average blood pressure, atherosclerotic cardiovascular disease, or CVD risk, and comorbid conditions. For high risk, which is preexisting CVD or estimated ten-year risk of greater than 10%, adults with stage 1 hypertension defined as average systolic blood pressure of 130 to 139 mm/Hg or diastolic of 80 to 89 mm/Hg. Treatment should be initiated in a patient with blood pressure of greater than or equal to 130/80. For low-risk adults, they specify the threshold for drug treatment is if it's greater than or equal to 140/90. Regardless of risk, the goal blood pressure after initiating treatment is less than 130/80. Firstline therapy recommendations in these guidelines include thiazide diuretics, CCBs, ACE inhibitors, or ARBs. Patients in stage 2 hypertension, defined as systolic greater than or equal to 140 or diastolic greater than or equal to 90, they should be initiated with two firstline treatment agents with differing mechanisms of action.

For hypertension in adults, these guidelines note that is simultaneous use of an ACE inhibitor and ARB and/or renin inhibitor is potentially harmful and not recommended. For resistant hypertension, the AHA provides additional guidance with an initial focus on optimizing firstline therapies, including ARBs.

The AHA in 2018 defines resistant hypertension as above goal elevated blood pressure despite concurrent use of three antihypertensive drug classes at maximally tolerated doses, or blood pressure that requires four or more medications to achieve a target level. Hypertension is typically treated with a diuretic, a longacting calcium channel blocker, and a renin-angiotensin system blocker. That's defined as an ACE inhibitor or an ARB. Similar to the 2017 ACC, AHA blood pressure target of less than or equal to 130/80 mm/Hg in patients on antihypertensive therapy, diagnosis of resistant hypertension should be made based on a 24-hour ambulatory blood pressure measured after medication adherence has been confirmed. Resistant hypertension assessment should consider lifestyle, drug-drug interaction, secondary hypertension, and presence of end organ damage. Recommend treatment for confirmed resistant hypertension include optimization of lifestyle interventions, use of a longacting thiazide-like diuretic, such as chlorthalidone or indapamide, and addition of a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone. If blood pressure remains above target levels, addition of agents with different mechanism and possible referral to a hypertension specialist are advised.

I apologize, this is a duplicate slide from what I just said, so moving right along. According to the ACP and the AAFP in 2017, they recommend initiating antihypertensive therapy in adults 60 years of age or older with a systolic blood pressure of 150 or greater and a target of less than 150 to reduce the risk of mortality, stroke, and cardiac events. A stricter goal of systolic less than 140 may be considered in older patients with a history of stroke or TIA to reduce the risk of recurrent stroke, or in older adults with high cardiovascular risk to reduce the risk of stroke or cardiac events. The clinician and patients should discuss the risk versus benefit when determining the most appropriate blood pressure goal. These guidelines also state that providers should consider treatment with nonpharmacologic options, such as weight loss, diet, exercise, as well as

pharmacologic treatment. Treatment burden, such as total number of medications prescribed, drug interactions, and adverse events, given the potential for other comorbid conditions, should also be taken into consideration. If pharmacologic therapy is chosen, generic formulations should be prescribed when available to reduce the cost and thereby aid treatment adherence.

In terms of pediatric hypertension, it is estimated that 3.5% of children and adolescents have hypertension. According to the American Academy of Pediatrics in 2017, the published guidelines on diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, the goal of treatment is to achieve a blood pressure that decreases the risk of organ damage in youth and decreases the risk of hypertension in adults. For children and adolescents on treatment for hypertension, the blood pressure goal is less than 90th percentile, and less than 130/80 mm/Hg. Lifestyle modification, such as diet and physical exercise, are recommended for potential benefit to reduce blood pressure. Firstline therapy options include an ACE inhibitor or an ARB, longacting calcium channel blocker or thiazide diuretic. Treatment should begin at a low dosage and titrate as needed, and a second agent may be added if needed. Beta-blockers are not recommended as initial pharmacologic treatment in children, due to the side effect profile and to follow the therapy recommendations of beta-blockers in adults. In longterm studies on the safety of antihypertensive medications in children and their impact on future cardiovascular disease are limited.

The last disease state that is encompassed here are MIs, myocardial infarctions. Since many of these medications have dual indications, in the setting of an acute MI, ACE inhibitors have been shown to reduce mortality rates, even in those with normal left ventricular function. ACE inhibitors should be started and continued indefinitely in all patients recovering from STEMI, unstable angina, or NSTEMI with left ventricular ejection fraction of 40% or less, and for those with hypertension, diabetes, or CKD, unless otherwise contraindicated. ACE inhibitors are also considered a reasonable option in patients who are at lower risk, and ARBs are recommended in place of ACE inhibitors in those who are intolerant of ACE inhibitors. According to the Agency for Healthcare Research and Quality in 2011, they published a comparative effectiveness

report for the ACE inhibitors, ARBs, and aliskiren. The ACE inhibitors and ARBs appear to have similar longterm effects on blood pressure among individuals with essential hypertension. It is possible that aliskiren may be more effective than ACE inhibitors, but no differences were found in studies when compared to ARBs. For mortality and major cardiovascular events, there is insufficient evidence to determine if there are any different effects of ACE inhibitors versus ARBs on those serious outcomes. ACE inhibitors have been shown to have a greater risk of cough than ARBs, and the direct renin inhibitor.

The final guideline here, the ACC and the AHA in 2017 for the management of heart failure recommended routine combined use of an ACE inhibitor or angiotensin receptor blocker with a beta-blocker is recommended in all patients with a reduced ejection fraction heart failure, unless contraindicated. Drugs with an indication for heart failure include many ACE inhibitors and beta-blockers, ARBs that are indicated for heart failure when a patient is intolerant to an ACE inhibitor include candesartan and valsartan. In addition, for patients with reduced ejection fraction heart failure, diuretics are recommended, if fluid retention is present. Aldosterone antagonists, such as spironolactone and eplerenone are recommended in patients who also have adequate renal function, and digoxin can be beneficial to decrease hospitalizations due to heart failure. The combination of hydralazine and isosorbide dinitrate is recommended in African-Americans with reduced ejection fraction heart failure who are persistently symptomatic with the use of an ACE inhibitor and beta-blocker. These guidelines recommend the use of ARBs in patients unable to tolerate an ACE inhibitor and in patients with heart failure following an NSTEMI or STEMI.

So, moving along to the angiotensin modulator and combinations. So, here, you have the ARBs, and you'll have the combinations, as well. There is a large amount of slides here, in terms of the medications, whether or not they are available in generic formulation, and indication. So, here we have the single agents for angiotensin for ARBs. While you look over these, just to give you kind of a background on the mechanism of action for these, the ACE inhibitors are competitive inhibitors for the ACE enzyme, the angiotensin converting enzyme, which converts angiotensin 1 to angiotensin 2, a potent vasoconstrictor, and angiotensin

2 causes vasoconstriction, release of aldosterone, and antidiuretic hormones, sympathetic activation, and constriction of the efferent arterials of the glomerulus and the kidneys. In terms of angiotensin receptor, ARNIs, they increase the natriuretic peptides that are degraded by metabolism through initiation of neprilysin and simultaneously inhibit the effect of angiotensin 2. Thiazide diuretics, such as hydrochlorothiazide, its pharmacologic effects by blocking the reabsorption of sodium.

Moving on here, on the next slide, we do have the combination products. You'll see the combination, at least here, are ARBs and thiazide diuretics. Again, while you're looking here, for pediatric patients, Cozaar, Benicar, and Diovan are indicated for treatment of hypertension in children age 6 to 16 years. Atacand is indicated for the treatment of hypertension in children 1 to 17 years of age. Safety and efficacy in the pediatric population have not been established in other ARBs. It is important to note, in terms of pregnancy, all products in this class carry a box warning for fetal toxicity. They are Category X.

Moving onward here, we have all of the ACE Inhibitors. I did mention the mechanism of action earlier. Several ACE inhibitors here, including benazepril, enalapril, fosinopril, and lisinopril have been shown to be safe and effective in children age 6 to 16 years. Enalapril can be used in children as young as 1 month. Ramipril was studied in pediatric patients with elevated or high blood pressure and chronic renal failure and found effective in reducing blood pressure.

Pivoting over the beta-blockers. First, we have the combinations here. So, beta-blockers are approved for a variety of conditions. This review will focus on the following cardiovascular uses of beta-blocker, such as hypertension, heart failure, angina, myocardial infarction, and cardiac arrhythmia. For pediatrics, safety and efficacy of beta-blockers in children has not been established, except for metoprolol ER. So, Toprol-XR and propranolol. Safety and efficacy for propranolol, for infantile hemangioma, has not been established in pediatric patients greater than 1 year of age. For pregnancy, acebutolol, pindolol, and sotalol are pregnancy Category B. Atenolol is Category D. All others are Category C.

We do have single agents continued along with other combinations with diuretics.

The final two under this umbrella. We have the calcium channel blockers here. Again, calcium channel blockers inhibit the calcium ions that move across the cell membranes. This essentially leads to a decrease in the contraction in the myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance.

This is stratified by dihydropyridines. On the next slide, we have non-dihydropyridines. In terms of pregnancy for this class, all products in this class are pregnancy Category C, as in Charlie. For pediatrics, the effective antihypertensive oral dose of amlodipine in pediatric patients, age 6 to 17 years is 2.5 mg to 5 mg. So, it is indicated. Safety and efficacy for all other calcium channel blockers have not been established for pediatric patients.

On the last slide here, I did not include... so the diuretics are in your appendices. The reason I did not make a screenshot here was, it would just be slides and slides long. So, if you would like to see the list of diuretics, their indications, dosing, and availability, I direct you to look in the appendix. Any questions?

Lisa Chew: Any questions for Umang? So, just a question on the slide, slide 55 should be titled calcium channel blockers, right? It says beta-blockers.

Umang Patel: Yes. It should. That should say calcium...

Lisa Chew: I just wanted to make sure we're...

Umang Patel: Yeah.

Lisa Chew: There are no stakeholders for this class.

Leta Evaskus: Are the appendices in the online? Okay.

Umang Patel: Yes. So, the appendices are printed in the binders. They are available in the web portal and the specific therapeutic class reviews are also on the web portal, as well.

Leta Evaskus: I don't think they're printed. Did you see them?

Umang Patel: It is slide 140 and 141. And just for the, for the committee's knowledge, Magellan, for some of these classes that are retired, we say, because no updates have happened, there are not regular therapeutic class review updates. We have these current product listings. So, if you may be wondering well, why does this look different than say, my other slides? That is why.

Donna Sullivan: This is Donna. Were there stakeholders? I'm sorry. I didn't quite hear you.

Lisa Chew: No stakeholders.

Donna Sullivan: Okay. So, we're going to switch over and look at the classes. The PDL, the way that they list out on the PDL are in a different order. The ACE inhibitor combinations, you can see that we have mostly the generic combinations preferred with some of the more expensive generic combinations will be nonpreferred. The single products, again, the generics are essentially all preferred, except for quinapril is not preferred. Then, when we have the ACE inhibitor combinations. Most of these combinations, it's cheaper to take the individual product. So, they are nonpreferred. They require prior authorization because there's only the one preferred product in this particular class. The reason why they're on PA is to basically let the provider know to prescribe the individual components. Here is more of the combination products. The angiotensin receptor blocker, ARB, the single components we have the irbesartan, losartan preferred, as well as valsartan. Telmisartan is not preferred. The combination product, Tekturna, which is aliskiren plus hydrochlorothiazide is nonpreferred. We prefer that they take the two individual generic products. You can also see that Tekturna and aliskiren are also nonpreferred. These are on PA that we actually ask that they try an ACE inhibitor combination first. Then, we'll approve if those are not effective. Entresto is preferred. It's on prior authorization for medical

necessity. Try and fail of ACE inhibitors plus other products. Then, we're moving into the other... did we go over the alpha blockers? Okay. I'll skip the alpha blockers through those. So, then we have the beta-blocker combination products. Again, mostly generics preferred. More of the single beta-blocker products, again, mostly generics preferred. As you can see, it's a long list. Calcium channel blockers same, generics preferred. We didn't go over the hydralazines. I think those are next, right? The nitros?

Umang Patel: Yep.

Donna Sullivan: Okay. I think that's the end of the classes that are included in what Umang just presented. Any questions?

Lisa Chew: Quick question. So, the combination products are a separate class than the individual agents. So, you would have to try, you can't do two preferred of a single agent, and then jump to a nonpreferred combination. You'd have to do...

Donna Sullivan: If you tried, like, an ACE inhibitor, two preferred ACE inhibitors with hydrochlorothiazide combination, or the two products, we would likely allow the combination product to be approved. Most of the ones where we have the combinations, the combinations, they're generic, and their components are generic. The combination product prices are significantly higher. So, what we're really asking you to do is take the individual generic components. If there was a medical reason why the patient just couldn't manage taking two pills versus one pill, then we would take that into consideration.

Lisa Chew: Any questions? Should we move to the motion?

Susan Flatebo: I move that all products in the antihypertensive drug classes listed on slide 13 are considered safe and efficacious for their medically accepted indication and are eligible for preferred status and grandfathering at the discretion of healthcare. Neprilysin inhibitor, angiotensin 2 receptor antagonist combinations may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products with the same indication within their respective drug

class before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Diane Schwilke: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries.

Donna Sullivan: We're scheduled for lunch break right now, but we're a little bit ahead of time. Lunches won't be delivered until 12:00. So, we have about 15 more minutes. So, I'm suggesting maybe we move onto the next presentation.

Lisa Chew: Okay. Cardiovascular agents.

Umang Patel: For cardiovascular agents, this will encompass coronary vasodilators that Donna mentioned a second ago, sinus node inhibitors, and pulmonary hypertension agents.

Coronary vasodilators, angina pectoris is a clinical syndrome of coronary artery disease. It is caused by decreased oxygen delivery to myocardial tissues. It presents as chest discomfort, including burning, heaviness, or sensation of choking, or pain in the jaw, neck, ear, and shoulder. Symptoms may also include nausea, shortness of breath, or sweating. It is associated with an increased risk of cardiac death and MI. Nitrates, such as nitroglycerin and isosorbide are approved to treat or prevent angina pectoris caused by coronary artery disease include immediate release and extended release oral tablets, translingual spray, sublingual tablets, and transdermal ointment and patches. Lingual formulations of nitroglycerine are used to relieve the symptoms of an acute attack, as firstline therapy. They can also be taken prior to engaging in activities that may precipitate an acute attack. These nitrates relax vascular, smooth muscle causing venous and arterial dilation. The vasodilation leads to a pooling of venous blood and decreased venous return to the

heart, which is defined as preload, reduction in systemic and pulmonary arterial pressure, defined as afterload, and reduced cardiac output overall. By decreasing the preload and overall, myocardial tissue oxygen demand is reduced, and pain of angina pectoris is improved. This medication is poorly absorbed in the GI tract. However, it has good absorption via transmucosal and transdermal routes. In general, nitroglycerine has a faster onset and shorter duration of action compared to isosorbide formulations. Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate. Unlike dinitrate, it is nearly completely bioavailable and has no active metabolites.

Here, we have the medications, indications, dosing, and availability for the committee's viewing. We are looking at nitroglycerine, just the different, essentially, formulations and precursory and metabolite of said nitroglycerine.

Moving over to the next slide, we have Nitro-Bid, GoNitro, Nitrostat, and Nitro-Dur. For the guidelines here, the American College of Physicians, the American college of Cardiology Foundation, the American Heart Associated, the American Associated of Thoracic Surgery, the Preventative Cardiovascular Nurse's Association, and the Society of Thoracic Surgeons in 2012 stated relief of symptoms in patients with stable IHD recommend beta-blocker should be prescribed as initial therapy. Calcium channel blockers for longacting nitrate should be prescribed when beta-blockers are contraindicated or cause unacceptable side effects. Calcium channel blockers or longacting nitrates in combination with beta-blocker should be prescribed during initial treatment with beta-blocker is unsuccessful. The organizations recommend that sublingual nitroglycerine or nitroglycerine spray should be used for immediate relief of angina. Sublingual nitroglycerine tablets, or translingual spray, are drugs of choice to abort acute anginal attacks and prophylactically to prevent angina due to activity. Alright.

So, moving over to sinus node inhibitors. So, disease state background, heart failure is a progressive syndrome caused by a change in cardiac structure or cardiac function resulting in a failure of the heart to deliver an adequate supply of oxygenated blood to the tissues. CAD, or coronary artery disease, is the cause of heart failure in about 75% of

cases. The incidence of heart failure in the U.S. exceeds 5 million, and many of these patients are over the age of 70 years of age. Typical symptoms include dyspnea, fatigue, and fluid retention. In a response to a decrease in cardiac output, a number of compensatory mechanisms occur, such as activation of the sympathetic nervous system, and the renin angiotensin aldosterone system. Goals of treatment include improving patient symptoms, slowing disease progression, and prolonging survival. Overall, five year survival is approximately 50% for all patients with a heart failure diagnosis with survival declining with increased disease symptoms and severity. Mortality rates have declined over the last few decades, due to improved pharmacotherapy, including the use of agents to antagonize the sympathetic nervous system and the RAAS system. Effects, such as beta-blockers, ACE inhibitors, and ARBs. Corlanor inhibits the diastolic inotrope current in the sinoatrial node resulting in a dose-dependent reduction in heart rate. Unlike beta-blockers, Corlanor has no negative inotropic effects.

The one medication that kind of falls under this is Corlanor. Since it is one medication, I'll go over it specifically here. It is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable symptomatic, chronic heart failure with left ventricular ejection fraction less than or equal to 35% who are in sinus rhythm with a resting heart rate of 70 beats per minute or greater, either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker. The treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients greater than or equal to six months of age is also a second indication. Dosing and availability is there. In terms of pregnancy, this medication may cause fetal toxicity when administered to pregnant women, based on animal findings. In terms of hepatic impairment, no dose adjustment for this medication is required in patients with mild or moderate hepatic impairment, but it is contraindicated in severe hepatic impairment. For renal impairment, there is no dose adjustment for creatinine clearance 15 to 60 mL/minute, but there is no data available for patients with creatinine clearance less than 15.

Moving over to the guidelines here. The ACC, the AHA, and the Heart Failure Society of America in 2017 stated it can be beneficial to reduce

heart failure, hospitalization, in patients with symptomatic, defined as NYHA class 2 and 3 stable, chronic heart failure, defined as a left ventricular ejection fraction of less than or equal to 35% who are receiving guideline directed evaluation and management including a beta-blocker at a maximum tolerate dose, and with a heart rate of greater than or equal to 70 beats per minute at rest and who are in sinus rhythm.

Moving over to pulmonary hypertension, pulmonary hypertension, the prevalence varies substantially depending on the type, etiology, and underlying condition, but it is estimated to be roughly 15 per million people. It is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined as a resting mean pulmonary arterial pressure or MPAP of greater than or equal to 25 mm/Hg. Symptoms include dyspnea, dizziness, syncope, fatigue, peripheral edema, anginal palpitations, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension does not have a cure, and if left untreated is a life-threatening disease with poor prognosis. Management should be limited to specialized centers where the clinicians are experienced in the evaluation and treatment of patients with pulmonary hypertension. Although the number of approved therapies for pulmonary arterial hypertension have grown in the past years, the prognosis is still poor with approximately 50% mortality within the first five years of diagnosis.

Continuing on with the background, there are many causes of pulmonary arterial hypertension, including idiopathic or underlying disease and hereditary causes. Cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone, morphogenetic protein receptor type 2 gene plays a key role in the pathogenesis of heritable pulmonary arterial hypertension. Other etiologies include drug and toxins, collagen vascular resistance, HIV, portal hypertension, chronic thromboembolism, and congenital heart disease. The World Health Organization classifies patients into five groups based on their etiology. Group I is referred now to pulmonary arterial hypertension. Group II refers to pulmonary hypertension due to left heart disease. Group III refers to pulmonary hypertension due to lung disease. Group IV refers to pulmonary hypertension due to blood clots in the lungs. Group V refers

to pulmonary hypertension due to blood and other rare disorders. In 2013, clinical classifications were updated to provide the same pulmonary hypertension classifications for adults and pediatric patients. In addition, the individual categorization of the persistent pulmonary hypertension of neonates was included.

On the next two slides, you'll see the medications with the respective indications. It is stratified by oral agents, which includes Letairis, Tracleer, Opsumit, Adempas, Uptravi, Revatio, Adcirca, and Orenitram. We have inhalation agents here, Ventavis and Tyvaso, as well.

In terms of special populations for pediatrics, safety and efficacy of Letairis, Opsumit, Adempas, Uptravi, Revatio, Adcirca, Ventavis, and Tyvaso have not been established in pediatric pulmonary hypertension patients. The safety and efficacy of Tracleer has been established in patients 3 years of age and older with idiopathic or congenital pulmonary arterial hypertension to improve pulmonary vascular resistance, which is expected to result in an improvement in exercise ability. In terms of pregnancy, previously categorized as pregnancy category X, Letairis, Tracleer, Opsumit, and Adempas are in that category. Adcirca is Category B. Ventavis, Orenitram are categorized as Category C and B respectively. An interesting subgroup to note, patients who are smokers, so plasma concentrations of Adempas are reduced by 50 to 60% in patients who smoke, and higher doses may be considered in this population. There is a REMS program. So, for Letairis, Tracleer, there are REMS program, which include elements to ensure safe use. Opsumit, Letairis and Adempas, again, require all female patients that are enrolled in their respective REMS program to essentially, it includes a medication guide, monthly pregnancy testing, and patient counseling for pregnancy planning and requirement for contraception, as well.

On the last indication slide here, we have prostanoids, and we have PD-5 inhibitors. So, we have Flolan, Veletri, and Remodulin for the prostanoids. We have Revatio, as well, for the PD-5 inhibitors.

Moving forward to the guidelines. So, the treatment guidelines by the European Society of Cardiology and the European Respiratory Society, in February of 2016, stated at the time of diagnosis of pulmonary arterial

hypertension, they said the suggested initial approach is the adoption of general measures, such as exercise training, psychosocial support, rehabilitation, and the initiation of supportive therapy, such as oral anticoagulation, diuretics, digoxin, and longterm oxygen therapy if needed. Patients who are at low or intermediate risk for one year mortality can be treated with either initial monotherapy or initial oral combination therapy. If initial monotherapy is chosen, no evidence based firstline monotherapy can be proposed, because there are no head-to-head comparisons. If initial combination therapy is chosen, ambrisentan plus tadalafil has been given a higher grade recommendation because of the combination has been proven to be superior to initial ambrisentan or tadalafil monotherapy into delaying clinical failure.

Essentially, the treatment guidelines are stratified, as I mentioned earlier, by initial monotherapy and initial combination therapy. You can see, it is stratified by which type of pulmonary hypertension classification they have, and the strength of recommendation on the far right column.

Moving forward, the American College of Chest Physicians in 2014, which had an update in 2018, recommended at the time of diagnosis of pulmonary arterial hypertension, they suggest the initial approach is treatment of contributing causes of pulmonary arterial hypertension, such as sleep apnea or systemic hypertension. The adoption of general measures, supervised exercise activity, influenza pneumonia vaccinations, and avoidance of pregnancy, high altitude, and nonessential surgery is recommended. The initiation of supportive therapies, such as oxygen therapy if needed to maintain oxygen saturations greater than 91%, and lastly palliative care. Unless there is a contraindication, acute vasal reactivity testing should be performed at a facility with experience in performing and interpreting the test. A trial of high dose oral calcium channel blocker, such as amlodipine, diltiazem, and nifedipine, is recommended in patients with a positive acute vasal reactive test. Furthermore, CCB should not be used empirically to treat pulmonary arterial hypertension in the absence of demonstrated acute vasal reactivity. Patients should be followed closely for response and side effects of therapy. Alternative or additional pulmonary arterial

hypertension therapy should be initiated, if improvement to WHO-FC I or II are not seen after the trial of a CCB.

Continuing on with the chest guidelines, in treatment naïve patients who are not candidates for, or who have failed CCB therapy, treatment is based on WHO functional class. In treatment naïve patients with WHO-FC 1, continued monitoring for disease progression is advised. In treatment naïve patients with WHO-FC II, initial combination therapy with ambrisentan and tadalafil to improve six minute walk distance is suggested. In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, sildenafil, bosentan, macitentan, tadalafil, and riociguat is recommended. In treatment naïve patients with WHO-FC III without rapid disease progression or poor prognosis, initial combination therapy with ambrisentan and tadalafil to improve that six-minute walk distance was suggested. If patients are unwilling to take or cannot tolerate combination therapy, then, monotherapy with ambrisentan, bosentan, sildenafil, low or moderate quality to improve six minute walk for all three products, macitentan, tadalafil, or riociguat is recommended. Lastly, treatment naïve patients in WHO-FC IV initial therapy with a parenteral prostanoid agent is recommended. If a patient cannot comply with the parenteral administration, inhaled prostanoid is in combination with an oral endothelin receptor antagonist, or an oral PD-5 inhibitor are alternatives. As I mentioned before, the reason some of the text in this is bolded is, those are reflective of the 2018 update. Any questions?

Lisa Chew: Thank you, Umang. Any questions for Umang. So, we have one stakeholder, Ms. Christine Hui. Please come up to the podium. Please state your name, who you represent, and you'll have three minutes for comments.

Christine Hui: My name is Dr. Christine Hui, Pharm.D., and I am representing United Therapeutics Corporation. United Therapeutics Corporation was started by our founders after their daughter was diagnosed with pulmonary arterial hypertension, or PAH, and they realized how few treatment options were available. Our first PAH medication [inaudible] for injection was improved in 2002, and we continue to develop and commercialize new therapies, including Tyvaso inhalation solution and [inaudible] while

we continue our pursuit to find a cure for PAH and endstage lung disease. Today, I am going to introduce the latest clinical updates, as they relate to United Therapeutics medication Orenitram. Orenitram was FDA approved in December of 2013, and it is indicated to improve exercise capacity in patients with PAH. The study that established effectiveness included predominantly patients with WHO functional class II to III symptoms and etiologies of idiopathic or [inaudible] PH or PH associated with connective tissue disease. We continued to build upon the efficacy and safety data at post approval. My update today pertains to the results of the Freedom EV Clinical Trial with Orenitram. Based on the results of Freedom EV, United Therapeutics has received an Orenitram label amendment from the FDA with additional indication of delaying disease progression in patients with PAH. The data has also been presented at multiple leading scientific conferences to date. Freedom EV was a global event driven study with 690 patients randomized 1:1 to either Orenitram or placebo. At randomization, all participants were taking a phosphodiesterase type 5 inhibitor, soluble guanylate cyclase stimulator, or an ERA, for endothelin receptor antagonist as background therapy. The primary objective was to determine the effect of Orenitram on time to first adjudicated clinical worsening event. Clinical worsening events were defined as death, hospitalization due to worsening PAH, initiation of inhaled or infused prostacyclin, disease progression, or unsatisfactory longterm clinical response. Participants were predominantly female and less than 65 years old with idiopathic or heritable PH. Median time on approved therapy at randomization was six months. At baseline, the majority of participants had functional class II symptoms and median six-minute walk distance was 405 meters. Orenitram significantly reduced the risk of clinical worsening event by 26% when compared to placebo, which was driven by a 61% reduction in the risk of disease progression. Orenitram also demonstrated statistically significant improvements in key secondary endpoints. Median six-minute walk distance improved with Orenitram at week 36 and week 48, and trended toward improvement at week 24 without reaching statistical significance. [inaudible] score and functional class were significantly improved with Orenitram at week 24 compared to placebo. Orenitram participants shifted to lower risk criteria compared to placebo from week 12 through week 16. Prostacyclin adverse events were more common with Orenitram and

18.9% of Orenitram participants' permanent discontinued treatment for adverse events compared to 4.1% of patients receiving placebo.

Lisa Chew: Please wrap up your comments. Thank you.

Christine Hui: Given the findings of Freedom EV Study, we ask the committee move Orenitram to preferred on the Washington State Medicaid PDL for PAH patients who rely on your organization to provide access to the medications. Thank you for your attention, and I'm happy to take any questions.

Lisa Chew: Thank you. Any questions? Okay. Thanks, very much.

Donna Sullivan: Do you want to take a look at the drug classes online first? Okay. So, we'll start with the nitrates. So, mostly, again, preferred products are... generic products are preferred. We do have the nitroglycerine ointment patches, sublingual tablets all have a preferred product. The only nitroglycerine formulation that is not preferred right now is the sublingual spray. So, then, we skipped to the pulmonary arterial hypertension drugs. So, Letairis and Tracleer are preferred. This says continued. Then, we also have the ambrisentan, bosentan are also preferred. The phosphodiesterase inhibitors, Adcirca and sildenafil generic tablets are preferred. [inaudible] receptor antagonist Uptravi is preferred. The prostaglandin vasodilators. We have Tyvaso and Ventavis as our preferred products. For the SGC stimulator, Adempas is preferred. Then, the sinus node inhibitor [inaudible] is preferred. I believe that's it. Any questions? We are going to do three motions. So, we'll do the nitrates. Then, we'll do the sinus node inhibitors. Then, we'll lump all the pulmonary hypertension subclasses into one motion.

Catherine Brown: I move that all products in the cardiovascular agents, nitrates drug class, are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is police report.

Donna Sullivan: Before we get a second, did you mean to leave out for their medically accepted indications?

Catherine Brown: No.

Donna Sullivan: Okay. So, can we insert that into the motion?

Alexander Park: I'll move to insert that. I will also second the motion made by Catherine.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. The motion carries.

Donna Sullivan: So, with the sinus node inhibitors, it's on prior authorization for medical necessity. There is only the one drug in there. So, really the third bullet is only there in case there should be another product that comes to market, but right now, there's only one drug, and it is preferred.

Susan Flatebo: I move that all products in the cardiovascular agent sinus node inhibitor drug class are considered safe and efficacious for their medically accepted indication and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. Sinus node inhibitors may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorization, unless contraindicated, not clinically appropriate, or only one product is preferred.

Diane Schwilke: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries.

Donna Sullivan: So, we have the five different pulmonary hypertension products or drug classes of the endothelia receptor antagonist, the phosphodiesterase inhibitors, prostacyclin receptor agonist, SGC stimulators, and the prostaglandin vasal dilators. So, we'll lump these all into one motion. We can go to the next one. They will all require prior authorization to determine their medical necessity. With the two preferred products, I don't think that this one is necessarily within their own class. As far as the prior authorization goes, we don't have the policy here for you to approve today, but we might require certain drug classes to be used in stepwise fashion before the other drug classes are used, but I don't have that policy completed to present today. I'm going to put Amy on the spot. Do we have these configured right now so that they are tried and failed, or tried two within their subclass? Do you know off the top of your head?

Amy Irwin? Nope. But I can find out for you.

Donna Sullivan: Actually, I think I misspoke earlier. I think they need to try two preferreds within the class before they can have the nonpreferred within their class. It's not... but they do also have stepwise criteria where we might require a phosphodiesterase inhibitor before we might allow one of the others that are to be used. Any questions? Okay.

Alexander Park: I just want to clarify. So, were you saying that we do require products to be used within each respective class, as far as preferred/nonpreferred, or were you saying that that policy is not prepared yet?

Donna Sullivan: I said a lot of stuff. So, what I said is, for the trial of the two preferred products, it is within the same class. However, the policy, and I'm looking to see if we do have it online. We didn't update it. So, that's why we didn't bring it back. I can just show it to you really quick. So, it went into effect August of 2018, and these are the drugs that are on the prior authorization. They have to have that diagnosis. What I was talking about was the history. They have to try generic sildenafil, or the products within the same preferred drug class before they can get a nonpreferred drug. Then, is that for pulmonary? Yeah. So, history of sildenafil and trial of one preferred product in that same drug class. Any questions before I give it back to Leta? Leta was just asking me if we should require

a trial of two preferred products within the same indication or change that to one.

Amy Irwin: I don't show that these have tried and fail. I show that they are PA required.

Donna Sullivan: Okay. So, that tells me that we handle the tried and failed, the tried two preferred within the policy. So, I think that we can just get rid of that statement that says all nonpreferred. Just get rid of that last statement. So, part of the medical necessity determination is that they have used other more cost-effective products first, so sildenafil plus one other preferred product.

Alexander Park: I move that all products in the drug class listed on slide 20 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. Pulmonary hypertension agents may require prior authorization to determine medical necessity.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. So, I think it's lunch time. Should we take a 30 minute break? Okay. So, we will come back at 12:47, 12:48. Thank you.

Lisa Chew: We are reconvening the DUR board. We are going to start off with a stakeholder for pulmonary hypertension. Please state your name, who you represent, and you'll have three minutes.

John Hartney: My name is John Hartney. I'm a medical science liaison with Actelion Pharmaceuticals. Thank you for this opportunity to speak with you today about Opsumit and Uptravi. Both were studied in longterm event driven trials and are indicated for the treatment of pulmonary arterial hypertension WHO group I, to reduce the risk of disease progression and

reduce the risks of hospitalization for PAH. Uptravi is an orally administered selective prostacyclin receptor agonist that has uniquely demonstrated a benefit to patients as monotherapy in combination with one or even two PAH agents. Opsumit is an endothelia receptor antagonist, or ERA, and its effectiveness was established in a longterm study in PAH patients with predominantly WHO functional class II and III symptoms treated for an average of two years. Opsumit reduced the risk of disease progression by 45% compared to placebo, as monotherapy, as well as in combination with either a PD-5 inhibitor or inhaled prostanoid. With regards to the safety profile for Opsumit, Opsumit, like all ERAs, has a box warning for embryo fetal toxicity, for which there is a REMS program for females. The ERAs have caused elevations of immuno transferase, liver failure, and decreases in hemoglobin concentrations. Obtain baseline liver enzyme and measure hemoglobin prior to initiation of Opsumit and repeat, as clinically indicated. So, in summary, Uptravi is a prostacyclin receptor agonist indicated to delay disease progression and reduce the risk of hospitalization for PAH. Opsumit in monotherapy or combination therapy with either a PD-5 inhibitor or inhaled prostanoids is indicated to delay disease progression and reduce hospitalization for PAH. Thank you for your time and consideration today.

Lisa Chew: Any questions? Thank you. I guess based on stakeholder input, do any of the committee members want to make any changes to the motion before the break? I see people shaking their heads, so no. Alright. So, we can move onto bone density regulators. I'll just say, I'm a little disappointed at how many cookies are left over. It's almost 1:00. So, I'm threatening to make a motion that everybody needs to take one. I'm not bringing them home.

Umang Patel: Thank you. You definitely made me a little nervous when you started off with, I'm disappointed. So, I thought, oh... that's great. Alright. So, for the next one, bone density regulators or bone resorption suppression and related agents. As always, a little bit of background. So, osteoporosis is characterized by the deterioration of bone tissue and low bone mass. Approximately 10 million Americans have the diagnosis of osteoporosis and additional 43 million have low bone mass, placing them at increased risk. As many as one in two women and one in five men are

at risk for osteoporosis related fractures during their lifetime. One in four men in the U.S. over the age of 50 will have an osteoporosis related fracture in his remaining lifetime. Osteoporosis is common in all racial groups, but it is the most common in Caucasians. There are three categories of osteoporosis, postmenopausal, which effects mainly trabecular bone in the decade after menopause, as estrogen deficiency increases bone resorption more than bone formation; age-related, which age-related osteoporosis results from increased bone resorption that begins shortly after peak bone mass is obtained. The cortical and trabecular bone are both effected. Lastly, secondary osteoporosis, which is caused by medication, such as glucocorticoids, excess thyroid replacement, some antiepileptic medications, and longterm heparin use, or other diseases, such as hyperthyroidism, or type 1 diabetes.

Moving onward here, we have the indication of the medications that fall into this class. As you can see, we have Binosto, Fosamax, we have Fosamax Plus D, etidronate, Boniva, Actonel, and Atelvia. These are all bisphosphonates here. We're not going to go onto the next slide yet, but there are calcitonins and others in here for bisphosphonates. The mechanism of action may adsorb to bone appetite and are permanently incorporated into the bone. Osteoclasts are unable to adhere to bone surfaces containing bisphosphonates and ultimately are not able to resorb and turn over bone. So, bisphosphonates, including alendronate, etidronate, ibandronate, and risedronate. The inclusion of vitamin D with alendronate promotes calcium absorption. In terms of pregnancy for special populations in this class, the majority of the products in this class are pregnancy Category C, with the exception of Prolia and Evista, which are pregnancy Category X. I'll go over those in the next slide. Tymlos is not indicated in pregnant women or in women of reproductive potential. Calcitonin-salmon nasal spray is Category C. Evenity is not indicated for use in women of reproductive potential. In terms of hepatic impairment, Evista should be used in caution with patients with hepatic impairment, as well.

Moving on to 'others' in this. These are medications, such as Tymlos, Prolia, Evista, Forteo, and Evenity. Again, the mechanism of action on these: Tymlos is a PTH receptor analog, which acts as an agonist to the PTH1 receptor. This results in an activation of the camp signaling

pathway and target cells, and it basically increases bone mineral content that is correlated with increase in bone strength at the vertebral and/or nonvertebral sites. We have Prolia, which is a RANK ligand. It's a transmembrane or soluble protein essential for the formation and function and survival of osteoclasts, the cells responsible for bone resorption. So, this medication binds to RANKL and prevents it from activating its receptor. Evista, largely mediated through estrogen receptor binding and binding results in activation of certain estrogenic pathways that act to decrease resorption of bone and reduce the biological markers of bone turnover. Lastly, Forteo, which contains recombinant human parathyroid hormone and stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity. Keep in mind, Evenity does carry a limitation for use, in that it should only be used for a maximum of 12 monthly doses, because of decreased efficacy after that time. If further treatment for osteoporosis is necessary, it is recommended to switch to another agent in this class.

Moving onto guidelines, the North American Menopause Society in 2010 recommend bisphosphonates as firstline drugs to treat postmenopausal women with osteoporosis. This is defined as having a T-score of less than or equal to -2.5. Calcitonin is not a firstline drug for postmenopausal osteoporosis treatment. However, it is an option for women with osteoporosis who are more than five years beyond menopause. Pharmacologic options approved for the treatment of postmenopausal osteoporosis included denosumab, teriparatide, and calcitonin. Pharmacologic options approved for the prevention and treatment of postmenopausal osteoporosis include bisphosphonates, and the estrogen agonist antagonist raloxifene. They note that there is controversy regarding the optimal duration of bisphosphonates therapy and the length of a 'drug holiday,' and state that these should be based on an individual assessment of risk and benefit. Tymlos was not available at the time of these publications in 2010.

Moving forward with the National Osteoporosis Foundation in 2014, they recognize all FDA approved medications for the prevention and/or treatment of osteoporosis, as all possible options. Treatment agent of choice should be based on available clinical information, in addition to

intervention thresholds. The duration of the pharmacologic therapy should be specific to each individual with the need for continuation of medications reviewed on an annual basis. The AACE and the ACE in 2016 recommend alendronate, risedronate, zoledronic acid, and denosumab as initial therapy for most patients at high risk of fracture. Teriparatide, denosumab, zoledronic acid should be considered for patients unable to use oral therapy, and as initial therapy for patients at especially high fracture risk. Raloxifene or ibandronate may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy. The guidelines also stated, few patients are using calcitonin as longterm treatment for osteoporosis, because more effective agents are available to increase bone density and reduce fracture risk. Again, Tymlos was not available at the time of these publications.

Moving over to the American College of Physicians in 2017, and this is an update to their 2008 guidelines. They recommend physicians offer pharmacologic treatments to reduce the risk for hip and vertebral fractures in women with known osteoporosis and treatment should occur for five years. However, the recommend against bone density monitoring during the five-year period. They recommend against using menopausal estrogen, or estrogen with progesterone or raloxifene for osteoporosis treatment in women. They further state that treatment decisions in older osteopenic women, defined as 65 years of age or greater who are at high risk of fracture, should be based on a discussion with the patient regarding her preference, fracture risk, and treatment benefits, harms, and cost. Regarding therapy in men, they recommend that clinicians offer treatment with bisphosphonates to reduce the risk of vertebral fractures, and those with clinical osteoporosis. These guidelines are based on a systematic review of literature and evidence for specific pharmacotherapy treatments, which are detailed in the publication. Again, Tymlos was not available at time of these publications.

Final guidelines here, the Endocrine Society, this year in 2019, they recommend pharmacologic therapy for postmenopausal women at high risk of fracture, especially those with recent fractures. This population should be treated initially with a bisphosphonate or denosumab to reduce fracture risk. However, ibandronate is not recommended to

reduce the risk of nonvertebral or hip fracture. For postmenopausal women with a very high risk of fracture, the guidelines recommend starting with either teriparatide or abaloparatide for up to two years of treatment before switching to a bisphosphonate or denosumab to maintain bone density. Raloxifene, calcitonin, and a hormone replacement therapy are only recommended if patients are not appropriate candidates for treatment with bisphosphonates or denosumab and do not have any other contraindications to these therapies. Evenity was FDA approved in April 2019. Its use for the treatment of osteoporosis in postmenopausal women has not yet been addressed by any guideline at this time. Any questions?

Lisa Chew: Any questions for Umang? So, we have one stakeholder, Dr. Karen Campbell. Please come up to the podium. Please state your name, who you represent, and you will have three minutes.

Karen Campbell: Good afternoon. My name is Karen Campbell. I am a pharmacist with Amgen Medical Affairs. I appreciate the opportunity to address the committee on a new biologic Evenity for the treatment of osteoporosis in postmenopausal women at high risk for fracture. Evenity is a monoclonal antibody with a unique mechanism of action. It inhibits the activity of sclerostin, a negative regulator of bone mass, and an inhibitor of bone formation. Evenity's dual mechanism of action stimulate bone formation and, to a lesser extent, increase bone resorption resulting in rapid increases in trabecular and cortical bone mass, and improvement in bone structure and strength. Evenity's phase-3 program includes two large fracture trials with nearly 12,000 postmenopausal women with osteoporosis. First phase-3 study frame enrolled over 7000 postmenopausal women with low BMD. Evenity significantly reduced the incidence of new vertebral fracture through month 12 compared to placebo. Significant reduction of fracture risk persists in Evenity group, even after all the subjects were transitioned to Prolia for months 12 to 24. Second phase-3 study, ART, was a head-to-head study of over 4000 postmenopausal women at high risk for fracture. Those who received Evenity for 12 months prior to switching to alendronate had lower fracture rates than the patients on alendronate throughout the study. In addition, a phase-3 study called Structure evaluated the efficacy of Evenity compared to teriparatide in postmenopausal women at high risk

for fracture previously treated with bisphosphonates. Evenity carries a box warning, which states Evenity may increase the risk of myocardial infarction stroke, and CV death. Evenity should not be used or initiated in patients who have had an MI or stroke within the preceding year. Evenity builds bone rapidly over 12 months, reduces fracture risk, and demonstrates superiority over alendronate. I respectfully request the committee consider coverage for postmenopausal women with imminent fracture risk who require an alternative to the current treatment options. Thank you. Happy holidays and I'm happy to answer questions.

Lisa Chew: Thank you, Dr. Campbell. Any questions? Okay. Thanks.

Donna Sullivan: We have the bone density regulator class, alendronate is preferred. Etidronate is not preferred. We have ibandronate preferred, as well, for the bisphosphonate class, as well as the zoledronic acid. The generic calcitonin is preferred, as well as we do prefer the Miacalcin brand, as well. Forteo is also preferred, as well as Prolia. Xgeva is also preferred. So, we have the Evista, Osphena are not preferred. Then, generic raloxifene is preferred. Questions?

Alexander Park: Question similar to what we've been talking about in the morning when we group various pharmacologic categories together. When we say trial of two preferred products with the same indication, are we lumping all these together, bisphosphonates, calcitonins, [inaudible]?

Donna Sullivan: No. It's within their drug class.

Alexander Park: Thank you.

Susan Flatebo: I move that all products in the drug classes listed on slide 23 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering, at the discretion of Health Care Authority. Bone density regulators may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products with the same indication within their respective drug class before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one preferred product is preferred.

Alexander Park: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? This motion carries. So, let's move onto antiemetics and antivertigo agents.

Umang Patel: Moving forward with antiemetic, antivertigo. So, chemotherapy induced vomiting, or emesis, and nausea can significantly impact a patient's quality of life leading to poor compliance with future chemotherapy or radiation treatments. In addition, nausea and vomiting can lead to several adverse events, such as nutrient depletion, metabolic imbalances, erosion of self-care, anorexia, diminished performance and mental status, wound dehiscence, tears in the esophagus, and cessation of potentially useful or curative cancer treatment. Approximately 70 to 80% of all cancer patients receiving chemotherapy, experience nausea and/or vomiting, whereas 10 to 44% experience anticipatory nausea and/or vomiting. Furthermore, more than 90% of patients using highly emetogenic chemotherapeutic agents will experience acute emesis. However, only approximately 30% of these patients will experience a vomiting episode if they receive an antiemetic prior to their highly emetogenic chemotherapeutic treatment.

Motion sickness is a result of a conflict between the various senses, in regards to motion. The overall incidence of dizziness, vertigo, and imbalance is 5 to 10%. There are multiple causes of vertigo, such as head trauma, cerebellar lesions, vestibular disease, or a migraine. Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom. There are both nonpharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal. The medications typically cause drowsiness or similar adverse effects. Symptomatic treatment of motion sickness generally includes the use of antihistamines, benzos, and antiemetics. Vestibular rehabilitation in select patients may be used with a goal of treating the underlying cause. Nausea and vomiting of pregnancy, also known as

‘morning sickness,’ can occur at any time of day and can effect pregnant women with varying symptoms from nausea to severe vomiting. Lifestyle changes for women with nausea and vomiting of pregnancy include rest, avoiding nauseating stimuli, eating small, frequent, low-fat meals that are low in spices.

Moving forward to the medications in this subclass. They will be broken down by their specific subgroup. On the first slide here, we have anticholinergics, antihistamines, and phenothiazines. So, for anticholinergics, we have Transderm Scop. We have Dramamine, Benadryl, and we have Antivert, Bonine, Dramamine less Drowsy, all under antihistamines. For phenothiazines, we have Compazine, or Compro, and Phenergan. Again, to give a little bit of mechanism of action, for anticholinergics, it is suggested that Transderm Scop exerts its activity in the central nervous system by blocking activity to the vomiting center and the vestibular nuclei. For the antihistamines, the H1 antagonists act on the vomiting center and vestibular pathways making them effective in the prevention and treatment of motion sickness, induced nausea and vomiting. Lastly, the phenothiazines on this slide block postsynoptic dopaminergic receptors in the brain, and the mechanism contributes to the depression of the reticular activating system and effects the basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis.

Just to go back to this slide to touch on subpopulations for pediatrics, Dramamine and Benadryl have been used to prevent and treat nausea and vomiting associated with motion sickness in pediatric patients. Phenergan and prochlorperazine should not be used in pediatric patients less than 2 years of age. Safety and efficacy of Transderm Scop has not been established.

Moving forward with the medications in this class. We have NK1 receptor antagonists, which include Emend, Cinvanti, aprepitant suspension and then the capsules and suspension, as well. We have fosaprepitant, so Emend for injection and Varubi. So, aprepitant exerts its main antiemetic action by occupying the brain substance PNK1 receptors. This pathway regulated the behavioral responses to our noxious and stressful stimuli.

Moving onward, next we have 5HT3 antagonists. His consists of Anzemet. We have granisetron, Sustol, Sancuso, Zofran, Zuplenz, Aloxi, and palonosetron, as well. These selectively block the 5HT3 receptors while the mechanism of action of these is not fully elucidated. They are not D2 receptor antagonists.

On the last indication slide, we have some combination and other mechanisms. So, we have combinations of NK1 and 5HT3 receptor antagonists, which are Akynzeo. That's phosnetupitant and palonosetron injectable, along with netupitant and palonosetron. We have cannabinoids consisting of Marinol, Syndros, and Cesamet. Antidopaminergic agents consisting of metoclopramide oral disintegrating tablets and metoclopramide obviously not disintegrating tablets. Antihistamine combos, so we have Diclegis, Bonjesta, and others. So, Emetrol OTC and Tigan.

So, to pivot over to the guidelines, the ASCO, the American Society of Clinical Oncology antiemetic guidelines recommends the choice of antiemetic treatment should be based on the radiotherapy and chemotherapy agent with the greatest degree of emetic risk. Optimal treatment should be used with initial chemotherapy to limit anticipatory nausea and vomiting. In regards to chemotherapy, patients with minimal emesis risk should not be routinely offered antiemetic prophylaxis. For patients who are receiving low emetic risk chemotherapy, the guidelines recommend adults should be offered a single dose of a 5HT3 antagonist or a single 8 mm dose of dexamethasone prior to treatment. For patients receiving moderate emetogenic chemotherapy, the recommendations are treatment with a two-drug combination of a 5HT3 antagonist and dexamethasone on day one. In patients receiving high emetogenic chemotherapy, the recommendations are a four-drug combination of an NK1 receptor antagonist. Duration is based on the specific formulation. A 5HT3 receptor antagonist on day one, dexamethasone on day one through four, and olanzapine day one through four. Patients with breakthrough nausea and vomiting despite optimal prophylaxis, including olanzapine may be offered an additional drug from another class for subsequent treatments. Those who did not receive olanzapine should be offered olanzapine first. For multiday chemotherapy after assessing

emetic risk of the agents prescribed, patients should receive an agent of highest therapeutic index daily during chemotherapy and for two days thereafter.

In terms of radiation therapy, patients with select low emetogenic risk of radiation therapy should be offered dexamethasone with other alternatives considered for rescue therapy based on prior treatment and location of the specific radiation. Patients with moderate emetogenic radiation therapy should receive a 5HT3 receptor antagonist with or without dexamethasone prior to each fraction for the first five fractions of radiation, and patients with high emetogenic radiation therapy should receive a 5HT3 receptor antagonist and dexamethasone before each fraction, and on the day after each fraction, even if radiation therapy is not planned for that day. For pediatric patients, according to the ASCO, if they are receiving moderate emetogenic chemotherapy, the recommendation again is a 5HT3 antagonist and dexamethasone. If they are receiving high emetogenic chemotherapy, the recommendation is a 5HT3 receptor antagonist aprepitant if they're eligible, and dexamethasone noting the higher weight-based dosing may be necessary. In pediatric patients receiving high emetogenic chemotherapy who are unable to receive dexamethasone should receive palonosetron and aprepitant.

Moving over to the National Comprehensive Cancer Network in 2019, the choice of antiemetic agents should be based on emetic risk of chemotherapy prior experience with antiemetics and patient factors. It should be initiated prior to the start of chemotherapy to provide maximal protection against chemotherapy induced emesis. The antiemetic therapy should be continued for the same timeframe as the duration of the emetic activity of the chemotherapeutic agent being used. The guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk intravenous IV chemotherapy, oral chemotherapy, and radiation therapy, as well as breakthrough treatment. To prevent acute and delayed emesis in patients receiving IV high emetogenic chemotherapy, these guidelines recommend a three or four drug combination of an NK1 receptor antagonist, 5HT3 receptor antagonist on day one, and dexamethasone on days one through four

with or without olanzapine, days one through four. Or, they recommend a three drug regimen of olanzapine, palonosetron, and dexamethasone.

Continuing with the NCCN guidelines. In terms of preventing acute and delayed emesis in patients receiving IV moderate emetogenic chemotherapy, 5HT3 antagonist and dexamethasone as a three-day regimen is recommended. NK1 antagonist should be used for select patients with additional risk factors or previous treatment failures with a steroid, and a 5HT3 antagonist alone ranging from one to three days based on the treatment regimen selected. These guidelines do not specify a specific 5HT3 antagonist or NK1 antagonist over another. An equivalent alternative to this include three day olanzapine containing regimen, such as olanzapine, palonosetron and dexamethasone. For IV low emetogenic risk chemotherapy, dexamethasone, metoclopramide, prochlorperazine, or an oral 5HT3 antagonist may be used and repeated daily for multiday doses of chemotherapy. There is no routine prophylaxis for patients who receive minimal emetic IV chemotherapy. For breakthrough treatment of chemotherapy induced nausea and vomiting, the general principle is to add one agent from a different class, as needed, to the existing regimen. Lastly, for these guidelines, for radiation induced nausea and vomiting associated with upper abdomen or localized sites or total body irradiation, oral granisetron or ondansetron with or without oral dexamethasone, as pretreatment for each day of therapy, is recommended.

Pivoting over to the American Society of Anesthesiologists, the published recommendations on the prevention of postoperative nausea and vomiting within their guidelines on postanesthetic care. They recommend routine assessment and monitoring for nausea and vomiting. For prophylaxis, and treatment, they evaluated the following classes of medication and rated them based on the quality of evidence. This ranges from A to C from randomized control trials to informal opinions and determination of whether or not it is a B, as in beneficial, or E, as in equivocal. So, antihistamines received an A3-B evidence, 5HT3 receptor antagonist received an A1-B evidence as a class. Tranquilizers and neuroleptics, such as droperidol, received a category A1-B evidence. Haloperidol A2-B. Hydroxyzine A3-B. Perphenazine A3-B. Lastly, prochlorperazine A1-E evidence. For prophylaxis of postoperative nausea

and vomiting using multiple agents, they determined that multiple agents may be used when needed. This was a category A2-B. They further note that pharmacologic treatment of nausea and vomiting is recommended, as it improves patient satisfaction, comfort, and reduces time to discharge.

Lastly, according to the American College of Obstetricians and Gynecologists in 2018, prompt treatment of nausea and vomiting of pregnancy is important to prevent hyperemesis gravidarum. Firstline treatment consists of nonpharmacologic options, such as assessing supplementation change options, ginger capsules, or acupuncture. For persistent symptoms, pharmacologic treatment with vitamin B6 or B6 plus doxylamine including co-formulated products, such as Diclegis or Bonjesta, are recommended. If symptoms continue to persist, other medications can be considered for off label use, including dimenhydrinate, diphenhydramine, prochlorperazine, and promethazine. Should symptoms still continue to persist, treatment options are based on hydration status and include the previously mentioned off label options, as well as additional options of chlorpromazine, methylprednisolone, metoclopramide, ondansetron, and trimethobenzamide. No single method has demonstrated superiority over another. Treatment options within each step are presented alphabetically in the guidelines rather than any specific ranking or preference order. Diclegis, a fixed dose combination of the antihistamine doxylamine 10 mg plus pyridoxine 10 mg, is the first FDA approved pregnancy category A delayed release combination medication for the treatment of nausea and vomiting of pregnancy. Any questions?

Catherine Brown: I have one. For the NCCN guidelines, were there recommendations around oral chemotherapy?

Umang Patel: I believe it was primarily just IV, but I can look back and check, but I remember the crux of it was for IV. The ASCO were primarily oral chemotherapy recommendations.

Susan Flatebo: They actually have guidelines for oral, and they also have ranked them moderate, high, or low emetogenic risk. So, the same guidelines usually cover the oral, as far as, their recommendations are a little bit different,

because they're usually with oral agents, but they do have recommendations.

Umang Patel: And that's for the NCCN?

Susan Flatebo: Yeah.

Lisa Chew: any other questions? There were no stakeholders for this class.

Donna Sullivan: So, just to review, the antiemetic class, the 5HT3 receptor antagonists, we have granisetron, ondansetron, our preferred, both the oral solution, the tablets, and the ondansetron dispersible tablet. Going to the antiemetics, antivertigo other, so Bonjesta and Diclegis are nonpreferred, but we do have the doxylamine pyridoxine combination preferred on the PDL. Going down further, Akynzeo is nonpreferred. And it's on prior authorization for PA required. Aprepitant is preferred, as well. All of the others are on prior authorization. Any questions?

Susan Flatebo: For the aprepitant, is that both the injectable form? Or is that just the oral?

Donna Sullivan: At this point in time, we only have the oral formulation on the PDL. So, the injectable form we haven't put onto the PDL, but we can make that consideration if you want it to be available. This is mostly stuff that would be available from the retail pharmacy.

Lisa Chew: So, there would be two separate motions then, one for 5HT3? Okay.

Susan Flatebo: I move that all products in the antiemetic/antivertigo agents 5HT3 receptor antagonist drug class are considered safe and efficacious for their medically accepted indication and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products required a trial of two preferred products with the same indication before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Nancy Lee: I second that motion.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: And any opposed? This motion carries.

Leta Evaskus: We have the second motion.

Diane Schwilke: I move that all products in the drug classes listed on slide 28 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. Antiemetics, antivertigo agents may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products in their respective drug class before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. Now, let's move onto substance use disorder.

Umang Patel: The next will be substance use disorder or opiate dependence. Prescription and illicit opioid abuse and misuse has reached national interest and was declared a national public health emergency by DHHS Acting Secretary in 2017. The 2017 National Survey on drug use and health reported that there is an estimated 30.5 million Americans age 12 years of age and older who are currently the past month illicit drug users. There were approximately 11.4 million people age 12 years or older in the United States who misused opioids in the last year. Approximately 19.7 million people aged 12 years or older in 2016 were considered to have a substance use disorder in the past year, including 14.5 million

people with an alcohol use disorder, 7.5 million with an illicit drug use disorder, and 2.1 million with an opiate use disorder. The drug addiction treatment act of 2000, or DATA, in order to become a qualified practitioner, physicians must be licensed under state law to practice medicine, obtain a waiver from the U.S. Substance Abuse and Mental Health Services Administration, and notify the Secretary of Health and Human Services of their intention of prescribing or dispensing buprenorphine. Such practitioners hold a modified DEA registration, in which they are designated by a unique identifier and must include it on each prescription written. Prescribers are limited in the number of patients they may treat under a waive, but they may request approval to treat additional patients. Medication assisted treatment or MAT, the U.S. Substance Abuse and Mental Health Service Administration provides information on medication assisted treatment, or MAT, including training courses for buprenorphine use and opioid prescribing courses. They also provide guides for medication assisted treatment of opioid use disorder that highlight contraindications, warnings, and other concerns and briefly address who ideal candidates would be for each medication. They do not state that any one medication is appropriate over another for all patients. The website provides additional information on medication assisted treatments for providers and patients, and many of these resources are available to guide prescribers, as they select a treatment option for both the induction and maintenance phase, as well as assist in navigating the legal requirements related to the use of these medications were needed.

We have the various medications that fall under this therapeutic class review, along with whether or not they are available in generic form, and their respective indications. So, we have buprenorphine sublingual tablets. We have Sublocade. We have Bunavail, Suboxone, Zubsolv, buprenorphine/naloxone sublingual tablets, Lucemyra, Evzio, Narcan, which is the nasal spray, naltrexone hydrochloride tablets, and lastly Vivitrol. So, I will give you a second to kind of absorb these medications. That'll give you a little bit of background on their mechanism of action. So buprenorphine is a partial agonist of the mu-opioid receptor and an antagonist of the [inaudible] receptor. Naloxone is similarly an antagonist of the mu-opioid receptor. The buprenorphine/naloxone was coformulated in order to prevent patients from abusing buprenorphine in combination with other opioids. Naltrexone is an opioid antagonist with

the highest definity for the mu-opioid receptor. Lucemyra is a central alpha-2 agonist that reduces the release of norepinephrine and decreases sympathetic tone when it binds to the neurons. It targets the symptoms of opioid withdrawal caused by noradrenergic hyperactivity. As one can imagine, these medications are scheduled. So, buprenorphine is a Schedule 3 controlled substance under the CSA and has the same potential for abuse as other opioids. Both buprenorphine and buprenorphine/naloxone combo can be used for office base detoxification from opioids and maintenance treatment for opioid dependency by specially trained and registered physicians. Like methadone, buprenorphine can suppress opioid withdrawal symptoms and block the effects of other opioids. Some additional information for these is, buprenorphine, as with other opioids, may cause central sleep apnea and sleep related hypoxemia in patients at a higher risk for sleep related breathing disorders, as opioid doses increases. A safe opioid taper is recommended in patients who present with CSA.

Moving onto the next slide, for the REMS program, so there is a buprenorphine containing transmucosal products for opiate dependence, REMS, that includes the following medications, buprenorphine tablets, buprenorphine/naloxone combination sublingual film and tablets, buprenorphine/naloxone sublingual tablets, such as Zubsolv and buccal film, which is Bunavail. Other elements in place to ensure safety, buprenorphine and buprenorphine/naloxone produce use include verification of safe use conditions and patient monitoring. Sublocade has a REMS program to ensure the healthcare setting and the pharmacy is certified, and that the injection is dispensed directly from the pharmacy to a healthcare provider to avoid the risk of serious harm or death due to IV administration. There is a shared REMS for Suboxone and Subutex branded products; however, only the Suboxone film remains available, and the branded tablets have been discontinued. For Probuphine, it has its own REMS program where the buprenorphine implant has a select requirement for both prescribers and for surgeons who implant or remove the insert to further ensure safety of use. Naltrexone ER injectable suspension, or Vivitrol has a REMS program consisting of a medication guide and a communication plan. Ultimately, the goal of these REMS is to mitigate the risk of overdose, abuse, and misuse. Each include a medication guide, an implementation system, and elements to

ensure safe use. The REMS program consists of enrollment by the wholesaler, the healthcare setting, and a pharmacy to control distribution and administration.

According to the American Society of Addiction Medicine in 2015, the published guidelines for the use of medications in the treatment of addiction involving opioid use, they state that the choice of medication should be a shared decision between the clinician and patient and should consider patient preferences, treatment history, and treatment setting. Buprenorphine and methadone are the standard treatment options for managing the acute withdrawal from opioids. Buprenorphine may not be appropriate for patients with an active alcohol disorder or sedative drug disorder. Methadone is recommended for patients who may benefit from additional supervision. Oral naltrexone requires special attention to medication adherence and may require observed administration for some patients. Lucemyra is the only FDA approved nonopioid treatment for the management of opioid withdrawal symptoms. In 2017, ASAM adopted guidance on the appropriateness of drug testing to guide clinicians in the clinical setting and emphasized that the frequency and duration of testing should be individualized. Acute symptoms are typically managed in an inpatient setting for close monitoring. So, alpha-2 adrenergic agonists are often used in combination with other agents to target multiple withdrawal symptoms. Following the acute withdrawal period, there is no consensus on the ideal duration of maintenance therapy despite the availability of multiple guidelines and resources for the initiation and management of medications for opioid dependency.

Continuing on with guidelines, first we have CDC in 2016. They have guidelines for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care. These guidelines are intended to encourage appropriate opioid use and help curb the opioid epidemic. Regarding medications for opioid dependence, the CDC states prescribers should offer treatment for opioid use disorder, such as MAT. Buprenorphine and methadone may be used in pregnant patients, but they state that oral or longacting injectable formulations should be reserved for nonpregnant adults and those who are highly motivated. The CDC released an updated statement in 2019, hence the bold, regarding the intent of the 2016 guidelines to advise primary care

providers treating adults with certain types of chronic pain. They recommend emphasizing the careful tapering of opioids to avoid withdrawal symptoms in current pain patients and individualized assessment of risk and benefit for continued high-dose treatment. The Surgeon General of the U.S., last year in 2018, issued an advisory on naloxone and opioid overdose. In support to access naloxone for patients, healthcare practitioners, friends, family, and community members who may come into contact with patients on prescription high-dose opioids, illicit heroin or fentanyl, or patients with opioid use disorder. Lastly, WHO, World Health Organization, in 2014 published guidelines on the identification and management of substance use disorder in pregnancy. They state pregnant women should be encouraged to use opioid maintenance treatment whenever available, rather than attempt opioid detoxification. Patients should be advised to either continue or initiate treatment with buprenorphine or methadone.

Moving over to the DHHS, last year, in 2018, they recommend clinicians to coprescribe naloxone to patients who were prescribed an opioid and are at risk for overdose. This includes patients receiving 50 or more MMEs, which are morphine mg equivalents per day with responsible illness receiving a benzo, or with a concomitant nonopioid substance use disorder, such as alcohol. Naloxone should also be prescribed to individuals that are high risk of experiencing or responding to an opioid overdose, such as a family member or friend of a person with an opioid use disorder, including those who have decreased opioid tolerance. For example, after release from incarceration or other controlled settings.

The final guidelines here are the FDA. In 2016, in response to the opioid abuse epidemic, in April of 2016, the FDA announced plans to reassess their approach to opioid medications where they focus on policies to reverse the epidemic of deaths associated with opioid use. Plans include the use of an expert advisory committee prior to the approval of an opioid without abuse deterrent properties. The formation of the pediatric advisory committee, who will review pediatric labeling for new products, and updated REMS requirement, and improvement in in-access to abuse deterrent formulations, naloxone, and other treatment options for patients with opioid use disorders. In addition to the CDC and FDA advisory committee focus on the opioid epidemic, the FDA has also

awarded a contract to the National Academies of Science Engineering and Medicine to develop evidence based guidelines for opioid prescribing and specific acute pain conditions. The goal of this program is to decrease inappropriate opioid prescribing that may lead to excess opioid supply and inappropriate exposure while maintaining access to adequate pain control for patients. Any questions?

Lisa Chew: Any questions? I have a question around the State. Does the State have a policy about dispensing naloxone for patients who are above a certain MME or also receiving benzodiazepines based on the recommendation of the DHHS?

Ryan Pistoresi: So, this was a topic that was discussed as part of the 1427 implementation for the new board's opioid prescribing rules. So, some boards did adopt to have a requirement to have the prescription be available. Other ones did not. I think it's just up to the prescriber to say, here's the prescription. You can fill it at the pharmacy and then ultimately up to the pharmacy to then dispense that. Then, I don't believe that we have any PA criteria on the naloxone. So, it's really up to the boards and that kind of is the limit where the State has gone for dispensing naloxone, or requiring a prescription for naloxone, not the dispensing. That's a separate one.

Lisa Chew: Any other questions? There are two stakeholders. We have Dr. Valerie Ng and Dr. Paul Thompson. Again, please state your name, who you represent, and you'll have three minutes.

Valerie Ng: Members of the DUR board. Good afternoon. My name is Valerie Ng. I'm a pharmacist with Indivior's Managed Care Medical Science team. Thank you for allowing me to share with you information and updates on Sublocade. So, Sublocade, which is the first and only extended release formulation of buprenorphine administered once a month, is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with an oral or transmucosal buprenorphine containing product followed by dose adjustment for a minimum of seven days. Sublocade should also be used as part of a complete treatment plan, which includes counseling and psychosocial support. Adverse reactions commonly associated with Sublocade were

headache, nausea, vomiting, constipation, increased hepatic enzymes, injection site pain, and injection site pruritus. For complete information and additional safety data, please refer to the prescribing information on Sublocade. So, based on published data, the minimum threshold of buprenorphine plasma concentration to block the subjective opioid effects, requires a minimum of 2 ng/mL. Sublocade was specifically designed to achieve and maintain a sustained buprenorphine plasma concentration at levels known to block the likely effects of opioids and control the withdrawal symptoms over the full monthly dosing interval. We continue to collect data on our clinical trial participants through our Recover Study. Our 12-month post-completion data was recently presented at two national congresses and we're thrilled to report that 51% of all clinical trial participants demonstrated complete sobriety at 12 months after the end of the Sublocade clinical trial participation. Additionally, 75% of patients who received 12 months of Sublocade sustained abstinence for one year post-clinical trial. Separately, a study found that the competitive inhibition of buprenorphine, most notably at concentrations of 2 ng and 5 ng/mL reduced the magnitude of fentanyl-induced respiratory depression. In closing, we support the elimination of prior authorization for all formulations and medications for opioid use disorder, and this is consistent with the recommendations from the National Academy of Medicine and American Society of Addiction Medicine, as it truly represents the best interest of patients who seek recovery, and families who suffer with them. We hope that the committee will help ensure patient access to quality care through the elimination and minimization of barriers to treatment for patients and families suffering from OUD. I'd be happy to take any questions anybody has.

Lisa Chew: Any questions? Okay. Thank you.

Paul Thompson: Hi. My name is Dr. Paul Thompson. I am a pharmacist medical science liaison at Alkermes. Today, I'm here to provide information about Vivitrol. I do know that Vivitrol has been on the preferred drug list, but just wanted to give the DUR group an update. Vivitrol is a once monthly extended release formulation on naltrexone administered by intramuscular injection. It must be administered by a healthcare professional. The active ingredient in Vivitrol is naltrexone, which is an

opioid antagonist, so a blocking agent. I will highlight a few clinical points today. For opioid dependence, it is indicated for the prevention of relapse to opioid dependence following opioid detoxification. The Samson guidelines recommend that OUD medications should be available to patients across all settings and at all levels of care. All patients considering treatment should be educated about the effectiveness, risks, and benefits of each of the different three OUD medications, including methadone, buprenorphine, as well as naltrexone and nonmedication options. For opioid dependent patients, and for those even being treated with alcohol dependence, patients should be opioid free for seven to ten days before initiating Vivitrol to avoid the precipitation of withdrawal, which may be severe enough to require hospitalization. Vivitrol is not a controlled substance and is not associated with any dependence or tolerance. It is not aversive therapy, meaning it doesn't cause a disulfiram like reaction, as a result of opioid use or alcohol ingestion. There is no withdrawal syndrome associated with the use of Vivitrol. The main study that led to Vivitrol's approval for opioid use disorder was a 24-week study of placebo controlled multicenter double blind, 250 detoxified opioid dependent patients. The percentage of subjects achieving opioid free weeks was significantly greater in the Vivitrol group compared to the placebo group. Complete abstinence was sustained by 36% of the patients in the Vivitrol group opposed to 23% of patients in the placebo group. Looking into adverse events, the most common adverse events associated with Vivitrol for opioid dependence were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Clinically significant adverse reactions that may be associated with Vivitrol use include accidental opioid overdose, injection site reactions, precipitated opioid withdrawal, hepatotoxicity, depression, suicidality, eosinophilic pneumonia, and hypersensitivity reactions. Following Vivitrol treatment, opioid tolerance is reduced from pretreatment baseline. So, patients can be potentially vulnerable to potentially fatal overdoses at the end of the dosing interval. Also, attempts to overcome that opioid blockade effect may also result in an opioid overdose. Other than that, when reversal of the Vivitrol blockade is required for pain management in an emergency situation, patients that are on Vivitrol, recommendation for pain management include regional analgesia, as well as nonopioid analgesics. So, other than that, that's kind of the update I wanted to provide on Vivitrol today. I do appreciate that

it is still maintained as a treatment option for patients with opioid use disorder. I would like to ask the DUR group if you have any questions. Thank you.

Lisa Chew: Thank you. I'll just move on to the motion.

Donna Sullivan: So, I just wanted to go over the drugs that we have preferred in these classes. So, at the bottom, we have the naloxone, the vials, and the syringes that are the generic naloxone are preferred. Naltrexone tablets, the Narcan liquid nasal spray is also preferred, as well as Vivitrol. None of those require any prior authorization. Then, for the buprenorphine products, we have the buprenorphine naloxone sublingual tablet preferred, as well as the Suboxone film. It's the brand name film that's preferred over the generic at this point in time. All of the others are listed as nonpreferred. They do require prior authorization for their specific dosage form, and then the medical necessity for that specific dosage form. Then Lucemyra is nonpreferred, as well, on PA for medical necessity.

Alexander Park: So, the Lucemyra is not part of the motion, but it's considered part of that substance abuse class?

Donna Sullivan: It's actually in the, so when you say not part of the motion, yeah. It's in the review from Umang. So, I think we could add it to this particular motion, since we did review it. I didn't realize that it was in the Magellan review. So, that was just my oversight. So, we can... it's just substance use disorder other.

Alexander Park: You allow clonodine as an off-label alternative in that class?

Donna Sullivan: Clonodine is covered right now with no prior authorization. So, yes.

Alexander Park: Yes.

Donna Sullivan: Which is why this is on prior authorization.

Alexander Park: I move that all products in the drug classes listed on slide 29 are considered safe and efficacious for their medically accepted indications

and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products within their respective drug class, before a nonpreferred drug would be authorized, unless contraindicated, not clinical appropriate, or only one product is preferred.

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. We're running ahead of schedule, should we keep going?

Donna Sullivan: Unless you guys need a break.

Lisa Chew: Anybody need a break? Okay. We'll keep going. Does Umang need a break? Okay.

Umang Patel: No. Thank you, though. Alright. So, the next one we have is prostatic hypertrophy agents, or BPH agents. So, benign prostatic hyperplasia is one of the most common conditions in aging men, roughly 14 million men in the U.S. have symptoms related to BPH; 50% of men demonstrate histopathologic BPH by age 60. This number increases to 90% by the age of 85. The symptoms of BPH are induced by hyperplastic changes in prostate tissue, leading to prostatic enlargement. The resulting obstruction increases urinary outflow resistance and results in an impaired detrusor muscle response. Although prostatic enlargement is mediated by epithelial and smooth muscle cells, the etiology of initial hyperplastic changes is currently unknown. Patients with BPH may present with bothersome lower urinary tract symptoms or LUTS resulting from irritation, urinary frequency, nocturia, urgency, incontinence, and/or obstruction, difficulty initiating urination or passing urine, weak stream, involuntary postvoid dripping of urine, and sensation of incomplete bladder emptying. Most men with BPH experience only mild or moderate symptoms of obstruction. Severe BPH, more likely to occur in men over 60 years of age, can lead to urinary retention, renal

insufficiency, urinary tract infections, hematuria, and bladder stones. More serious complications, such as uremia and irreversible bladder dysfunction are uncommon.

So, moving onto the next slide here, we have all of the medications that make up the BPH class. They are broken down into four subclasses. We have alpha-blockers, which consist of alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin. All of these, except for Cardura XL are available in generic form, and they are all indicated for BPH with Cardura and terazosin being indicated for hypertension, as well. We have five alpha reductase inhibitors being made up from dutasteride and finasteride. Both are available in generic formulation, and they do have very specific BPH indications, as well.

Moving forward, we have combinations. So, we have five alpha reductase inhibitors and alpha blocker combinations being Jalyn, so that's dutasteride/tamsulosin combination available as generic, as well. The last subclasses are PDE-5 inhibitors, or Cialis. Again, generic formulation available, and specific BPH indications, as well.

Just to give a little bit of background on some of these medications, for the mechanism of action, administration of alpha-1 blockers relaxes both the bladder neck and the prostatic smooth muscle. So, it decreases the pressure in the bladder. So, it helps improve urinary flow there. In terms of pregnancy, women who are pregnant or may become pregnant should not come into contact with dutasteride, so Avodart, Jalyn, or finasteride, because the possibility of fetal anomaly to a male fetus may occur. The five alpha reductase inhibitors, so again, dutasteride and finasteride, are pregnancy Category X. So, it is very important to keep that in mind.

Moving forward to the guidelines, by the American Urological Association in 2010, which was reaffirmed in 2014, patients with mild symptoms of BPH, so an AUA symptom score of less than 8, and in patients with moderate or severe, which is an AUA symptom score of greater than 8 who are not bothered by their symptoms, for example, they do not interfere with their daily activities of living, should be managed using a strategy of watchful waiting. For alpha adrenergic blocker therapy, it is an appropriate treatment option for patients with moderate to severe

LUTS secondary to BPH. The guidelines state that alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate treatment options for patients with LUTS secondary to BPH. Although there are slight differences in the adverse event profile of these agents, the guidelines state that all four agents have equal clinical effectiveness, and Rapaflo did not have published peer review studies prior to the deadline for the literature evaluation for the guideline update. The guidelines also state that five alpha reductase inhibitors, such as finasteride and dutasteride are appropriate for, and are effective treatments for patients with LUTS associated with demonstrable prostatic enlargement, but they are not appropriate treatment for men with LUTS who do not have evidence of prostatic enlargement. Five alpha reductase inhibitors may be used to prevent progression of LUTS secondary to BPH, and to reduce the risk of urinary retention and future prostate related surgery. The patient should also be advised of the disadvantages of this therapeutic approach. For example, side effects, such as sexual dysfunction, and the need for longterm daily therapy in comparison to a reasonable estimate of his baseline risk of progression, for example, retention, and the risk associated with BPH related surgery so an informed decision may be made. Lastly, combination therapy utilizing an alpha adrenergic receptor blocker and a five alpha reductase inhibitor presents an appropriate and effective treatment for patients who not only fully exhibit LUTS symptoms, but they also have definitive prostatic enlargement. Any questions?

Lisa Chew: Any questions? There are no stakeholders.

Donna Sullivan: In this class, we have the alfuzosin preferred, as well as dutasteride, finasteride, and tamsulosin are all preferred.

Lisa Chew: Okay. Thanks, Donna.

Virginia Buccola: I move that all products in the prostatic hypertrophy agents drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products with the same indication before a

nonpreferred drug would be authorized, unless contraindicated and not clinically appropriate, or only one product is preferred.

Diane Schwilke: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. We'll move onto androgens, testosterone. There are no stakeholders for this class.

Umang Patel: Okay. Thank you. So, our final therapeutic class review will be androgen testosterone, or androgenic agents. So, a quick overview, male hypogonadism is caused by insufficient production of testosterone and characterized by low serum concentrations and may present as testosterone deficiency, infertility, or both. Approximately 20% of men between 60 to 69 years old and 30% of men 70 to 79 years old have serum testosterone levels below normal range. Symptoms at presentation will primarily depend on the patient's age at the time of disease onset, but it can include impotence, decreased libido, fatigue, loss of energy, mood depression, regression of secondary sex characteristics. Potential risks due to male hypogonadism can include osteoporosis, sexual dysfunction, depression, and cardiovascular disease.

So, the first we have androgenic agents, these are all topical. So, we have AndroGel, Fortesta, Testim, Vogelxo, Natesto, Axiron, and Androderm. All of these, except for Natesto and Androderm are available in generic form. They are approved for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, such as primary or secondary hypogonadism, which is congenital or acquired.

The next slide has the dosing and availability. We're not going to go over this, but again, this is available for your review.

Then, here we have oral preparations. So, due to space, I did put dosing and availability here, but just to focus on indications, we have Anadrol-

50, Methitest, oxandrin, and Striant. So, you can see their respective indications here.

Moving forward to the guidelines, the Endocrine Society in 2018 for the treatment guidelines for hypogonadism recommend a diagnosis of hypogonadism be made only if the patient has symptoms of testosterone deficiency and clearly and consistently low serum testosterone levels, typically based on repeated fasting morning total T levels. Additional diagnostic evaluation should be performed to determine the cause of androgen deficiency. The guidelines recommend against testosterone therapy without further urological evaluation in patients with palpable prostate nodule or induration, or prostate specific antigen 4 ng/mL, or a PSA 3 ng/mL in men at high risk of prostate cancer, such as African-American or men with first-degree relatives with prostate cancer. Again, testosterone treatment in patients with hematocrit greater than 48%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, associated with benign prostatic hypertrophy and uncontrolled or poorly controlled congestive heart failure. Testosterone treatment is aimed at inducing and maintaining secondary sex characteristics and improving their sexual function, sense of well-being, and bone mineral density. Treatment goals are continuation of normal activities of daily living and decreased risk of secondary complications, such as infertility, osteoporosis, fatigue, and mood disturbances. The target testosterone levels while on therapy should be in the midnormal range, and you should monitor serum testosterone hematocrit and prostate cancer risk during the first year of treatment. Use of testosterone in men 65 years of age or older is not recommended due to unclear risk versus benefit profile in this population. ES also recommends against testosterone therapy in men who are planning fertility in the near future, or in patients with breast or prostate cancer. While Endocrine Society provides advantages and disadvantages of each formulation, no preference of any testosterone replacement product is provided. The choice of formulation should be based on patient preference and drug pharmacokinetics, adverse profile, treatment burden, and cost. Testosterone transfer to another person who is in close contact as a potential adverse event for the transdermal gel formulation.

The final slide, according to the American Urological Association, 2018, they provide a treatment algorithm evaluating and managing testosterone deficiency. They recommend a total T-level of less than 300 ng/dL based on early morning tests taken on two different days to support a diagnosis of low testosterone in symptomatic males. Adjunctive testing, so serum luteinizing hormones, serum prolactin, serum estradiol, hemoglobin, hematocrit, and PSA may be considered. Measuring the total T-level is recommended in patients with a history of unexplained anemia, bone density lost, HIV or AIDS, chronic narcotic use, male infertility, pituitary dysfunction, chronic corticosteroid use, and exposure to chemotherapy or testicular radiation. In patients who are candidates for testosterone deficiency, they recommend a cardiovascular disease risk assessment be performed in patients at high risk for a cardiovascular event should be referred for further evaluation. Lastly, topical injectable formulations can be considered without preference of one product over another. Any questions?

Alexander Park: It's interesting that the intramuscular preparations are not reviewed. Are they falling out of favor?

Donna Sullivan: The injectable, we actually include the injectables in our PDL. So, they are listed. Did you not cover the injectable?

Umang Patel: So, for our classes, the primary androgenic agents that Magellan focuses on are oral and topical. We can provide a list for the injectables, as well, but it would just be one of those categorized lists that I've provided in the appendices before.

Alexander Park: I see.

Donna Sullivan: We have included them, considered them included them in this list with the testosterone supinate, I believe, is the injectable form. So, it's preferred, and it doesn't have prior authorization. So, we actually would... it's cheaper than topical. So, that would be the preferred for hormone replacement requirements. So, what I have posted up here, we prefer the Androderm patch, in addition to the injectable testosterone that I just mentioned, and the generic gel pump, and the gel packets are also preferred. Questions?

Alexander Park: Umang, did anything come up in your review about the oral drugs. The convention has always been that they're such a high first pass metabolism on the oral testosterone that it's not generally favored.

Umang Patel: Absolutely. So, when it came to guidelines, everything was very in favor of topical over oral. So, because of that, the process of elimination, I think it was more favored to not oral, so topical or injectable.

Alexander Park: Thanks.

Nancy Lee: To kind of follow up on that, it sounds to me that there are differences in terms of the harm profile between topical and oral. Would you say that that's correct?

Umang Patel: I think both safety and efficacy, yes. There is a difference between oral and non-oral formulations.

Nancy Lee: In terms of the harms and potential side effect profile. So, then, that would probably change our motion slightly?

Donna Sullivan: How would you recommend that we change it? It doesn't say they're equally safe and effective.

Jordan Storhaug: It sounds like the oral medications, I think we would probably recommend, would be behind the prior authorization, which you guys are already doing.

Donna Sullivan: They're already on prior authorization. I mean, all of the testosterone products, except for the injectable, require prior authorization.

Jordan Storhaug: I think right now, that's for cost reason. I think the point that's being brought up is, there is actually a medical reason to keep those behind prior authorization, as well. So, even if the orals became more cost-effective to give, we wouldn't want to switch to those being the preferred medication.

Donna Sullivan: I understand. Yes. The criteria that we require, it's not just based on dosage form for this. There is a whole... we actually do have a policy that's published where they have to show that it's truly a testosterone deficiency, but to your point, we will make sure when we update the policy that we put the tablets on a position... I guess the question is, do you never want them used? I mean, is that essentially what you're trying to say, or...

Lisa Chew: On one of the tables for the oral testosterone, it looks like the indication is more than just hypogonadism. There is aplastic anemia, Fanconi Anemia. I don't know the pathophysiology of why they would use an oral versus an intramuscular.

Nancy Lee: I guess because of all those different indications, it's not that I don't want them used, but maybe for hypogonadism, specific for hypogonadism, may not be, I guess, the preferred, since there is potential greater harm with oral agents compared to the topical or injectable agents, aside from the other indications.

Alexander Park: Umang, could you go over the harms for me? I thought it was primarily just a lack of efficacy because of the first pass metabolism. I'm not as up on the safety issues.

Donna Sullivan: I don't know if it's broken out by... did you have it in your presentation, Umang?

Umang Patel: No.

Donna Sullivan: When you said that you thought there was a difference in harms, where was that coming from?

Nancy Lee: Through the oral possibly having higher cardiovascular.

Donna Sullivan: Okay. I'm just looking at Micro Medics, and unfortunately, they don't break it out by the dosage form.

Petra Eichelsdoerfer: I believe there are also some concerns about liver complications, as well as the cardiovascular, and the issue with the liver is that with first pass, it's coming straight out of the gut and going straight to the liver.

Donna Sullivan: So, we'll look into that. When we update our policy, we'll make sure that we position the tablets in the appropriate position behind topicals and injectable.

Nancy Lee: Based on that, I move that all products in the androgens testosterone drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the Health Care Authority. The testosterone products may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Alexander Park: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. I think that the Drug Utilization Review Board is now adjourned. There is something at 3:00?

Leta Evaskus: The Emerging Therapies Meeting is scheduled to start at 3:00, and we are not going to be able to start it early, because we have some people calling in. So, the committee, if you would like to stay, please do. If you don't want to, you can leave, as well, but for all the stakeholders here, we will start at 3:00 for the Emerging Therapies Workgroup.

Lisa Chew: Thank you.