Washington State Pharmacy and Therapeutics Committee and
Drug Utilization Review Board
December 20, 2017

Leta Evaskus:	Okay. It's 9 o'clock. We are ready to adjourn… or convene.
Michael Johnson:	Welcome. Welcome to the Washington State Pharmacy and Therapeutics Committee through the Health Care Authority. We have a few things to go over before we get started. We will start with introductions. This is a recorded meeting so before speaking, please introduce yourself. We're start over here to my left.
Fran McCaugh:	Fran McCaugh, Pharmacy Clinical Programs Manager, CHPW.
David Johnson:	David Johnson, Molina Healthcare.
Dale Sanderson:	Dale Sanderson, committee member.
Nancy Lee:	Nancy Lee, committee member.
Amber Figueroa:	Amber Figueroa, committee member.
Catherine Brown:	Catherine Brown, committee member.
Jordan Storhaug:	Jordan Storhaug, committee member.
Michael Johnson:	Michael Johnson, committee member.
Lisa Chew:	Lisa Chew, committee member.
Po Karczewski:	Po Karczewski, committee member.
Diane Schwilke:	Diane Schwilke, committee member.
Susan Flatebo:	Susan Flatebo, committee member.
Leta Evaskus:	Leta Evaskus, Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Leta Evaskus: And we have some people on the phone. Could you introduce yourselves?

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

Amy Irwin: Good morning. This is Amy Irwin, Health Care Authority.

Charity Harris: And Charity Harris, Health Care Authority.

Stephanie Christofferson: Hi, it's Stephanie. I'm with Magellan.

Jaymie Mai: Jaymie Mai from Labor and Industries.

Donna Sullivan: And this is Donna Sullivan. Normally we don't have people on the phone, but due to the I-5 closure the folks that were coming from Olympia we just told them that they could call in so they didn't have to deal with the traffic trying to get back this afternoon. So I just want to let you know that's why we have more people on the phone than usual.

Michael Johnson: Very understandable. This is my last committee. I did a six-year term. And so because of that we are going to voting on the next chair and the next vice chair. So I think that's our first agenda topic.

Leta Evaskus: Yeah. So do you guys have nominations for the chair?

Michael Johnson: I'll nominate Lisa Chew.

Diane Schwilke: I'll second that.

Leta Evaskus: Are there no other nominations?

Michael Johnson: Any other nominations?

Leta Evaskus: Do you want to do a vote?

Michael Johnson: And you're fine with doing that?

Lisa Chew: Yeah.

Michael Johnson: This is how I got the role. So what I hear is a nomination for Lisa Chew and she is agreeable to doing the… being the chair starting next month. So all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. It's unanimous. Congratulations.

Leta Evaskus: Now nominations for a vice chair.

Michael Johnson: I'll nominate Dale Sanderson.

Nancy Lee: I second that motion.

Michael Johnson: Any other nominations for vice chair? All right. That's it. So all in favor of Dale for Vice Chair say aye.

Group: Aye.

Michael Johnson: Okay. All opposed same sign. All right. Congratulations, Dale. All right. With that done we'll go ahead and start the atopic dermatitis and I think, Stephanie, I heard she's on the phone?

Leta Evaskus: Marian from OHSU is going to present first.

Michael Johnson: Oh, okay.

Marian McDonagh: I am here.

Michael Johnson: We have your first slide up. You can go ahead and start.

Marian McDonagh: All right. So this is our report on treatment for atopic dermatitis. Slide 2.

These are our key questions for this report as is typical and includes all of the drugs in the class and then we have questions on effectiveness, efficacy and harms. And also looking for any evidence in subgroups and on the efficacy and effectiveness we had subgroup questions specifically on the location of the affected body areas and also the amount of body surface area involved and the duration of treatment. Next slide.

This is a quick summary of our methods. So the searches were conducted in September and all the drugs that are included in this report are listed in the table. We had one injectable drug, dupilumab, a monoclonal antibody. And then there are three topical drugs – crisaborole PDE4 inhibitor and then two calcineurin inhibitors – pimecrolimus and tacrolimus. And way back in 2008 we had a report that was only on those two topical calcineurin inhibitors. So in a way this is an update of that report adding in these new drugs. So this report included both adults and children with any severity of atopic dermatitis. The comparative [inaudible] were head-to-head comparisons among the drugs, but we were also looking for comparisons for the topical steroid or with placebo and typically for the topicals those were vehicle placebos. We had a minimum of three weeks duration of treatment. Next slide.

A quick overview of the findings of where the evidence is. We tried to organize the results of this report by the patient population for the place in therapy. So starting with patients with treatment-resistant symptoms we found eight trials of dupilumab only in this population. Then we have the group of patients with moderate to severe symptoms. Here we have the topical calcineurin inhibitors, the TCIs only and here we have both placebo and corticosteroid comparisons. And then in mild to moderate symptoms is where we find the crisaborole studies – three of those. More topical calcineurin inhibitors studies here as well. In the previous report we did have some studies that were

contributing to some evidence about different locations on the body for where the affected skin was. Next slide.

We'll start with the results for the treatment-resistant patients… patients with treatment-resistant symptoms and here this is dupilumab versus placebo. We had four good quality studies and four fair quality studies. These were all in adults with moderate to severe atopic dermatitis and the definition of treatment-resistant symptoms were inadequately controlled disease using topical treatments or in whom topical treatment was inadvisable. That last part wasn't defined as to what that meant. The studies were small to large, 31 to 740 patients. They ranged from short-term four weeks to a year, 52 weeks. Six of the trials compared dupilumab versus placebo and then two compared dupilumab plus corticosteroid to corticosteroid alone plus placebo. Next slide.

We'll look at the results for response. So dupilumab increased response compared to placebo in the short-term, 4 to 12 weeks. This was a statistically significant difference. You can see the percentages there. The definition of response generally in this report is a score of 0 or 1 on the Investigator's Global Assessment. So it means essentially disease clearing or almost clearing. So the comparisons to placebo only. So this is monotherapy in five trials. The relative risk was 4.1 so four times as many patients achieved treatment response and with add on so a topical corticosteroid plus dupilumab versus a steroid alone, the relative risk was 3.94 so pretty similar in terms of the benefit. Next slide.

We're looking at other outcomes here. So this is just looking at the change in symptoms and here dupilumab improved all of these various measures of proven improvement more than placebo in all cases. So they are symptoms using the EASI scale, which is a continuous measurement scale for symptoms, pruritus and then body surface area affected. Also there was a study that looks at quality of life and measures of anxiety and depression and found dupilumab improved those more than the placebo, but I would note that the absolute differences are small. Next slide.

We're looking at the adverse events, the harms with dupilumab compared to placebo. So we found no differences in withdrawal due to adverse events. The most common adverse events with dupilumab were injection site reactions followed by nasopharyngitis and headache. But all of the… [inaudible] had higher rates than the placebo groups. And there was increase in the incidence of any adverse event or serious adverse events with dupilumab and in fact the absolute rates were slightly lower than in the placebo groups for those two types of outcomes.

So if we look at slide 8; here we have… looking at the one study that was 52 weeks in duration this was a good quality trial. They were looking essentially at flares. So fewer patients had flares at… with weekly or every other week dupilumab and with placebo. So 13% and 14% for the weekly and every other week versus 41% in the placebo groups. So that was significant. We would have hoped to have gotten better information about the somewhat longer term adverse event profile from the study, but we really didn't report any adverse events in a way that was useful for that kind of information. Let's move to slide 9.

So moving on now back to the group of patients with moderate to severe symptoms looking at topical calcineurin inhibitors versus each other. So there was no difference or overall conclusion that there is no difference in response rates between the two drugs in the shorter term. So if you look at the bullet points there you'll see that we had some differences in the findings depending on how the measure was estimated. So looking at the pooled relative risk it is 0.73 which favored tacrolimus. But if you look at the absolute difference there is no statistically significant difference. So that usually is what we need to take the first [inaudible] with a grain of salt. But as a follow-up we also did a network meta-analysis using all of the head-to-head evidence, as well as the placebo or corticosteroid controls evidence to try to get a better estimate and here it was clearly not statistically significant. So our conclusion is at this point in time there's no obvious difference between the drugs for response. For symptom

improvement on the EASI scale tacrolimus was superior by 11 to 16%. Body surface area – the better quality studies also find tacrolimus to be superior. But pruritus we had too limited of evidence to make any kind of conclusion on that. Next slide.

So here looking at other outcomes, quality of life, and adverse events. There were no differences found between the two drugs in any of these outcomes. Next slide.

So this is looking at the same population – moderate to severe symptoms and looking again at the topical calcineurin inhibitors. But here we're looking at the TCIs versus corticosteroid. So here we found really good quality systematic review that had 12 trials in it, almost 7,000 patients. We also found additional two poor quality trials and one fair quality trials that were no included in that review. The follow-up ranged from very short two weeks to 260 weeks in the systematic reviews. And if you look at that second bullet down response of… to treatment success was not significantly different between corticosteroid and the combined group of the [inaudible] inhibitors. With the rates of 72 versus 68% between the groups. So in the systematic review we included… they did a subgroup analysis stratifying the two drugs separately and also the… their findings did not change—that the TCIs were not significantly better than the corticosteroid. Similarly then system improvement was also not found to be different between TCIs and corticosteroids in the moderate to severe populations. Let's go to slide 12.

Looking at adverse events for the TCIs compared with corticosteroids. There is no differences in withdrawals due to adverse events or severe adverse events. There were more overall and specific treatment-related adverse events of TCIs and in particularly the skin burning on application and pruritus, the itching with application with the TCIs was greater than with the corticosteroids. Let's move to slide 13.

Now looking at response symptoms and adverse events in this group was mild to moderate symptoms. So here's the only place

where we have evidence on the new drug, crisaborole. This is comparisons with placebo vehicle comparisons and as I looked it up at the top of the slide there were no head-to-head trials with crisaborole, only these three fair quality placebo-controlled trials, two in children and one in adults. So response to treatment was greater with crisaborole. You can see 44% versus 21% and then crisaborole also increased symptoms more than placebo using different methods of measuring symptom improvement. Application site reactions were the most common adverse event [inaudible] across these trials with a higher percentage in the crisaborole group, 4.6% versus 1.7 in the placebo group. Slide 14.

So looking at the TCIs, the topical calcineurin inhibitors in this population, mild to moderate symptoms, [inaudible] a head-to-head trial in children with mild disease only. So here there was no difference in response between tacrolimus and pimecrolimus. Symptom improvement had mixed findings. Body surface area affected there was no difference. Pruritus tacrolimus was better, but it was a small difference and then the EASI scale for measuring symptoms tacrolimus was significantly better when improving symptoms. Adverse event withdrawals were greater however with tacrolimus. It is a very small difference. As you can see the relative risk is only 0.05 and then application site reaction with skin infections, acne and herpes simplex were not different between the groups although they were numerically more frequent with pimecrolimus than with tacrolimus. Slide 15.

Again, in the mild to moderate symptom population, still looking at the TCIs in adults. Again, there was one trial. This was mild to moderate disease. Here was have response tacrolimus was superior to pimecrolimus with 45.7 versus 27.1% of patients [inaudible] response. Symptom improvements across the different scales tacrolimus was found to be [inaudible]. And then no differences in adverse event withdrawals, but more patients reported burning with tacrolimus than with pimecrolimus in the adult population. Slide 16.

Staying with this same population, mild to moderate… patients with mild to moderate symptoms. So we conducted a network meta-analysis to look across the two topical calcineurin inhibitors, crisaborole and placebo on the outcome of response. Again, this is using the head-to-head studies as well as placebo-controlled trials. And so we found that all of the drugs were superior to placebo. So you can see on the… list in the table there, the very bottom row is placebo versus each of the drugs. And they are all better than placebo in this outcome measure. Tacrolimus resulted in more patients achieving response, then crisaborole or pimecrolimus and crisaborole was superior to placebo, but similar to pimecrolimus. Again, this includes indirect comparisons in that network meta-analysis. We usually call that kind of evidence low strength. Slide 17.

We're looking at the risk of lymphoma with the topical calcineurin inhibitors, which is a concern that was raised in our previous report. We reported on that as well. So we're updating that evidence here. In total there were 9 cohort and 19 case-control studies, and 1 good quality systematic review. For patients with a chronic dermatitis regardless of treatment have a small increase in lymphoma. [inaudible] cohort studies so the odds of increased risk of lymphoma is 1.43. However, the evidence was not really conclusive in the TCIs, specifically tacrolimus. So with tacrolimus there were two studies in the systematic review and the pools [inaudible] were 3.13, but it was not significant… was not significantly increasing the risk. There was one additional study that was not included in these [inaudible] increased the risk and the odds ratio was also 3.13. So the data that we were provided and allowed [inaudible] of three studies [inaudible] saying that there is some difference here, one study finding a significant difference in [inaudible]. With pimecrolimus on the other hand there are two studies that found… that pulled [inaudible] 1.58 so no significant difference there and two additional studies that we found also found no increased risk. So in the review they did a [inaudible] based on adults and children and found, again, no significant difference in increased risk of lymphoma with tacrolimus. Slide 18.

The summary for dupilumab is that in the case of treatment resistant symptoms there was no evidence comparing dupilumab to any other treatments. Evidence was only in patients with failure or intolerance to topical treatments. In the short-term (3 to 12 weeks), depending on what [inaudible] to placebo. Dupilumab also resulted in fewer flares than placebo over 52 weeks. And most common adverse events reported were injection site reactions.

So the summary on slide 19 for crisaborole, mild to moderate symptoms. There is no evidence comparing crisaborole to any other drugs for atopic dermatitis or in patients with more severe disease. Based on three placebo-controlled trials [inaudible] treatment response, symptom improvement, and quality of life were all better with crisaborole than placebo. Our network meta-analysis also found crisaborole was similar to pimecrolimus and inferior to tacrolimus in this population. Application site and reactions were more common with crisaborole than placebo.

And then the summary on page 20 is looking at the topical calcineurin inhibitors in cases with moderate to severe disease. Most studies found no difference between the TCIs on most outcomes. Treatment response and symptom improvement were not found different compared with the topical corticosteroids and the TCIs caused more adverse events, particularly the application site reactions. Sometimes in the general populations patients with atopic dermatitis had a slightly increased risk of lymphoma. Evidence does not find that pimecrolimus increases this risk, but the evidence on tacrolimus was inconclusive. And that is the summary of this report.

Michael Johnson: Thank you, Marian. Any questions from the committee? It doesn't look like there are questions from the committee. Thank you, Marian. We'll go to the… go to the next topic. I think we're doing Stephanie.

Leta Evaskus: Yes, Stephanie from Magellan is going to present.

Stephanie Christofferson: Yes.

Michael Johnson: Stephanie, we have your first slide up. You can start when you're ready.

Stephanie Christofferson: Okay. So for my portion of today's reviews I'll just be doing a high level overview of the different products in the class pointing out any significant items that have developed in the past year or so within the drugs or within the class of medications. I'll briefly talk about the… also about the immunomodulators atopic dermatitis products. The new products in the class include Eucrisa which is indicated for the topical treatment of mild to moderate atopic dermatitis in patients two years and older. And the other new product is Dupixent which is indicated in adults with moderate to severe atopic dermatitis who are not adequately controlled with the topical prescription therapy or who cannot use them. And the medication can be used with or without corticosteroids. All the medications have relatively the same indication with Eucrisa and Elidel being indicated for mild to moderate disease states and the Dupixent and Protopic being indicated for mild to severe atopic dermatitis. Next slide.

With dosages and formulations. Eucrisa, Protopic and Elidel are topical preparations and should be applied to the affected areas twice daily on the skin. I did want to point out there is a type-o on the Elidel under the usual dosage range and in fact it is a topical preparation. And then lastly the newer product, the Dupixent this is a subcutaneous injection every other week and it can be self-administered with proper training to the patient or caregiver and it is available in a single-dose, pre-filled syringe. Next slide, please.

There are no new clinical guidelines for treatment and there are no double-blind direct comparative trials that exist demonstrating a clear advantage of one product over another. According to the 2014 American Academy of Dermatology and the American Academy of Allergy Asthma and Immunology 2012 guidelines they

recommend liberal use of emollients and moisturizing agents as they may reduce the disease severity and the need for pharmacological interventions. Both the guidelines recommend topical corticosteroid standard of care to which in fact other treatments are compared to and Elidel and Protopic in these guidelines are recommended as second line agents for the treatment. And then the two newer products they do differ in the mechanism of action, which can potentially offer patients alternative treatment options. But I did want to point out that Eucrisa and Dupixent were not available at the time of the guideline developments. So they could be considered second line option treatments for patients. That concludes any… again, high level topics I want to discuss on these particular products if there are any questions.

Michael Johnson: Thank you, Stephanie. Any questions from the committee for Stephanie? All right. I think that's it for… I see no questions for Stephanie. Thank you. We have two stakeholders for this topic. The first one is Dr. Shannon Schneider followed by David Gross and we will do it up at the podium. When you get up there just introduce yourself and there's a three-minute time limit. Thank you.

Shannon Schneider: Good morning, everybody. Thank you for having me. My name is Dr. Shannon Schneider and I'm a senior medical science liaison at Sanofi Genzyme. Today I will review the clinical highlights of Dupixent or dupilumab. Please refer to the full prescribing information to fully inform you of the safe and effective use of Dupixent. Dupixent is an [inaudible] four receptor alpha antagonist indicated for the treatment of adult patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids or TCS. Dupixent is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients. In clinical trials the most common adverse reaction in anybody with an incidence of at least 1% are injection site reactions, conjunctivitis, [inaudible], oral

herpes, keratitis, [inaudible], other herpes virus infection and dry eye. Dupixent is available in a single dose, pre-filled syringe for subcutaneous injection. It is intended to be self-administered by the patient and/or caregivers with a recommended dose of 300 mg every other week following an initial loading dose of 600 mg. The approval of Dupixent was primary based on three randomized double-blind placebo-controlled multi-center phase three trials and one Phase 2B dose raging trials. These four studies included 1,472 patients with inadequately controlled moderate to severe AD treated with Dupixent with or without concomitant TCS. In all three phase 3 studies Dupixent alone or with TCS met the primary key… primary and key secondary endpoints. In trials 1 and 2 monotherapy with Dupixent 300 mg every two weeks significantly improved measures of overall disease severity at 16 weeks when compared with placebo. The primary endpoint, which was achieving clear or almost clear skin with at least a two point improvement as measured by the five point IGA scale was met by 38% and 36% of patients in trial 1 and 2 respectively compared with 10% and 9% with placebo. In trials 3, and this was the TCS combination study, treatment with Dupixent 300 mg every two weeks with TCS significantly improved measures of overall disease severity at both 16 and 52 weeks when compared with placebo.

To highlight some important safety information Dupixent is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients. Hypersensitivity reactions including generalized urticarial and serum sickness or serum sickness like reactions were reported in less than 1% of Dupixent subjects. Conjunctivitis and keratitis occurred more frequently in Dupixent treated subjects and it is important to advise patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with a health care provider. Patients with known [inaudible] infections were excluded from participation in these clinical studies.

Thank you for your consideration and I’m happy to answer any questions you may have.

Michael Johnson: Thank you. Next is Dr. David Gross.

David Gross: Good morning. My name is Dave Gross and I'm with the medical affairs division at Pfizer. I'm here today to discuss Eucrisa or crisaborole, which is a topical nonsteroidal ointment for the treatment of mild to moderate atopic dermatitis.

As you know, atopic dermatitis is a common chronic inflammatory skin disease that occurs most frequently in children. The prevalence in children is between 11 and 13% and approximately 90% of the people with atopic dermatitis have the mild to moderate form of the condition. Treatment can be a lifelong commitment with approximately 50% of pediatric patients having recurrent symptoms on into adulthood.

Eucrisa is the first topical prescription treatment for atopic dermatitis in more than a decade. It is the first and only nonsteroidal topical treatment that inhibits the PDE4 enzyme within the skin. The specific mechanism by which crisaborole exerts its therapeutic action for treatment of atopic dermatitis is not well defined. Eucrisa can be applied twice daily to the skin anywhere on the face and the body and it's indicated for topical treatment of mild to moderate atopic dermatitis in patients two years of age or older. There were two multi-center randomized double-blind parallel group vehicle controlled trials which treated a total of 1,522 patients, age 2 to 79 years. 38% of the subjects had an ISGA assessment score of 2, which is classified as mild and 61.5% had a score of 3, which is moderate. Subjects were randomized 2:1 to receive either Eucrisa or the vehicle applied twice daily for 28 years. The primary efficacy endpoint was a proportion of subjects at day 29 who achieved success, which is defined as clear, a score of 0 or almost clear, a score of 1 with a two grade or greater improvement from baseline.

Comparing Eucrisa treated patients to vehicle treated patients there was an improvement in 33% of Eucrisa subjects versus 25 of the vehicle patients in trial 1 and 31.4% versus 18% in trial 2. Efficacy results in both trials were seen in some patients as early

as day eight with 14.5% of Eucrisa patients and 5.5% of vehicle patients showing efficacy. The most common adverse effect occurring in greater than or equal to 1% of the subjects was application site pain which was about 4% in the treatment group versus 1% in the vehicle group. However, study discontinuation rates due to adverse events were the same for both Eucrisa and the vehicle which was 1.2%.

Eucrisa is contraindicated in patients that have a known hypersensitivity to crisaborole or any component of the formulation and in summary Eucrisa is the first and only non-steroidal topical PDE4 inhibitor for mild to moderate atopic dermatitis in patients two years of age or older. Before Eucrisa no prescription options were approved for mild to moderate atopic dermatitis in more than a decade.

In conclusion, I'd like to thank the committee for allowing me to testify and again ask that Eucrisa be considered for the Washington State PDL. I'd be happy to respond to any questions that you may have.

Michael Johnson: Great. Thank you. Go ahead and look at the… consider a motion here. Let's consider a motion here.

Leta Evaskus: We're going to start with the P&T motion and then we'll do the DUR motion.

Michael Johnson: I just have one question for the committee. In looking at the motion we have two calcineurin inhibitors and from the data I see these would be similar. If we had one as opposed to the other would there be any opposition to substitution? So when we look at a motion I mean obviously there's three different classes, but if we have two in the same class would we call that out in our motion?

Donna Sullivan: So are you asking whether or not you need to break these out into subclasses or…?

Michael Johnson: Yeah, I guess that's what I'm asking. Like if… the last two are in the same class. Do we have to break that out or should we address that or say they can be… do we have to somehow call that out?

Donna Sullivan: You could say that they are substitutable among their… I mean I don't think it really makes a difference because of the efficacy. I think that would be up to you whether or not you feel that there is a reason why if one was preferred you couldn't… or non-preferred you couldn't substitute one of the others.

Michael Johnson: So in the motion basically we're saying these can be subject to therapeutic interchange.

Donna Sullivan: If that's what you want to say, yes.

Michael Johnson: Any opposition to that?

Jordan Storhaug: With the three different mechanisms of action I think would be leaning towards not subjecting these to the therapeutic interchange with the exception of the two calcineurin inhibitors, which I think would be reasonable for that. I think as a prescriber these are, you know, different routes and different mechanisms and so therapeutic interchange seems a step more than I initially feel comfortable with.

Leta Evaskus: You could name the two drugs as… that can be subject to therapeutic interchange.

Amber Figueroa: I agree with Jordan. If I prescribe something topical and my patient ends up going home with something injectable that's not okay with me.

Donna Sullivan: I would recommend that you actually call out the mechanism of action that is interchangeable. That way if there is a new product that comes out we could include it.

Michael Johnson: So in the second part we could say that calcineurin inhibitor products can be subject. So we could put that in that motion.

Amber Figueroa: After considering the evidence of safety, efficacy and special populations for the treatment of atopic dermatitis, I move that dupilumab, crisaborole, pimecrolimus, and tacrolimus are safe and efficacious for the treatment of their approved indications. The calcineurin inhibitors can be subject to therapeutic interchange in the Washington Preferred Drug List.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. The motion passes. So now the motion for the DUR portion.

April Phillips: Our recommendation is that all products are safe and efficacious and are eligible for preferred status based on… at the discretion of HCA and non-preferreds require a trial of two preferred products with different active ingredients and same indication.

Michael Johnson: I move that the Apple Health Medicaid Program implement the limitations listed on slide 7 as recommended.

Jordan Storhaug: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. Are you on the phone Marian?

Marian McDonagh: Yes, I am.

Michael Johnson: Okay. Just give us a second to pull up your slides. Thank you. Okay. You can start whenever you're ready.

Marian McDonagh: All right. Thank you. So this is the preliminary update scan number 1 for the report we did on drugs to treat asthma and COPD. Slide 2.

For the history of this report the last full report was update 1 completed in June 2016 with searches through November of 2015. This is the first scan that we completed since that report and the searches for this scan were completed in May of 2017. Next slide.

So this report does include adult or pediatric patients with chronic or persistent asthma and adult patients with COPD. Next slide.

On slides 4 and 5 are the lists of all the drugs that are included. As you all know there are a lot of them. Let's move on to slide 6.

So for this scan for new drugs in this scan there were none approved in the classes that are included in this report, the past report. We note that there were three new biologic drugs approved to treat asthma and those are being reviewed in a separate report that is ongoing and will be completed in the early spring. So there's no drugs to identify in previous scans because there wasn't one. Slide 7.

No new boxed warnings were identified for these drugs. Slide 8.

There are no new comparative effectiveness reviews out there that you might be able to use to form your decision. There was one ongoing report at the agency for health care research and quality and was conducting on corticosteroid, long-acting beta 2 agonists and long-acting muscarinic agents as controlled therapy for asthma, but it didn't seem to include all of the drugs that we would include in this report. Slide 9.

So since the last report there are 10 new trials. Five of those are head-to-head comparisons of devices. So the same drug in two different devices for administration. Three in asthma and two in COPD. There are also five new head-to-head drug trials and all of these relate to the COPD population with one being specifically the asthma/COPD overlap syndrome population. And four of these 10 trials are comparisons that we did not have evidence for in the previous report. Slide 10.

This is the description of the studies that are comparing the devices. There are two comparing tiotropium in different devices, two comparing budesonide in different devices, and one comparing beclomethasone in different devices. You can see the top two, the tiotropium are the [inaudible] COPD patient population. Slide 11.

This is the head-to-head drug comparisons and so these are all in COPD patients. There is a 16-week… I'm sorry, a 16-week trial that includes fluticasone with vilanterol compared to fluticasone combined with salmeterol. And that was the asthma/COPD overlap syndrome patients. Then in COPD alone there is a study of umeclidinium versus tiotropium and then a study of indacaterol with glycopyrrolate combined and salmeterol versus… or with fluticasone. Then a separate study of salmeterol/fluticasone versus tiotropium alone once a day. And then the last study on this slide is umeclidinium with vilanterol versus tiotropium and indacaterol. So those are all the new studies for COPD. Next slide.

The summary then is that there are no newly approved drugs for serious harms boxed warnings since the last full report. No new comparative effectiveness reviews and there are 10 head-to-head trials with four new comparisons. That summarizes the scan.

Michael Johnson: Thank you, Marian. Any questions from the committee? All right. I see no questions from the committee. We'll entertain a motion. Actually, there are three stakeholders. Sorry. The first one is Dr. Judy Kelloway followed by Steven Hall. We'll do this again at the

podium and you have a three-minute limit. Please introduce yourself at the microphone.

Judy Kelloway: Good morning. Thank you for giving me the opportunity to present to you this morning. My name is Judy Kelloway and I'm a health outcomes liaison with GlaxoSmithKline. I respectfully request that this group commission a full review of the respiratory class as there have been several significant changes since the scan was done in May. Most importantly, on September 18th a new medication was approved in this class. The first and only inhaler that contains three medications in one device. Specifically an inhaled corticosteroid, a long-acting muscarinic antagonist and a long-acting beta agonist was approved. This is called Trelegy Ellipta and it is indicated for the long-term, once-daily maintenance treatment of patients with COPD who are on a fixed dosed combination of fluticasone furoate the ICS and vilanterol in whom additional treatment is desired or for patients who are receiving [inaudible] and VI via multiple inhalers. Combining these three medications into a single inhaler allows health care providers to offer patients a treatment regimen that reduce both the number of inhalers and the total doses of inhaled medications per day. While the direct length between Trelegy and improved adherence has not been established, once daily dosings of COPD and use of single inhalers and multiple inhalers have both been associated with greater adherence. Two replicate studies secured the approval of Trelegy by showing significant improvement in lung function and quality of life. Yet the GSK development and program included two additional studies. I'll share one by the spirit of time here.

One is called the Impact Study. It had over 10,000 patients with Trelegy, the triple device and it compared Anoro which is our ICS… excuse me, Anoro which is LAMA/LABA and Breo which is our ICS LABA. The key outcomes were significant reduction in annual rate of moderate to severe COPD exacerbations compared to the ICS LABA and the LAMA/LABA, significant improvement in health-related quality of life, and significant improvement in lung function. Across all treatment groups the most commonly

reported AEs were upper respiratory infections, worsening of COPD, pneumonia and headache. The incidence of serious adverse event of pneumonia was similar between Trelegy and the LAMA/LABA at 4% and a [inaudible] at 3%. Please refer to the package insert for full information.

In November there was also a published comparative effectiveness head-to-head study of Anoro, which is the LAMA/LABA versus Stiolto, which is another LAMA/LABA and this was by Feldman. This was an eight-week crossover study that met its primary endpoint in demonstrating non-inferiority of Anoro compared to Stiolto in improving lung function as measured by FEV1. And furthermore Anoro demonstrated superiority to Stiolto with the difference of 52 mills on [inaudible] FEV1.

Thank you for your time and I hope these status support the need to commission a full assessment. I'll be happy to take the first question.

Dale Sanderson: Is there any advantage to separating the steroid dose from a bronchodilator dose in terms of enabling the steroid to get deeper?

Judy Kelloway: The question is, is there any advantage to separating the inhaled corticosteroid versus the bronchodilator. I've not seen… in asthma patients where they have got more restriction there has been some early studies of that. I've not seen that in COPD and this medication right now was indicated for COPD and usually I mean these are maintenance medications and I don't know if I reiterated but it is one puff once a day. So patients with both asthma and COPD always have a rescue medication if they need it. So I don't have [inaudible] data to support that.

Michael Johnson: Anything else from the committee? Thank you. Next up is Steven Hall followed by Nick Nguyen.

Steven Hall: Good morning and happy holidays. I'm Steve Hall with Buehringer-Ingelheim Pharmaceuticals. I'm testifying today on behalf of our respiratory portfolio. First I'd like to discuss some general characteristics about inhalers. You're likely familiar with meter dose inhalers or MDIs, as well as dry powder inhalers or DPIs. There's a newer category of inhaler out now known as a soft mist inhaler or a slow mist inhaler or simply an SMI. Patient drug formulation inhaler characteristics can often influence the inhaled delivery of drugs and I'd like to talk a little bit about that.

First with patient characteristics studies show that as few as 11% of patients use their inhalers properly. A variety of errors in inhaler technique have been observed. Studies also review that as patients age and as the severity of their disease increases their peak [inaudible] flow or what's known as PIF will decrease and at a PIF rate at or below 60 liters per minute a patient may not achieve optimal clinical benefit from medication inhaled via a DPI since the active drug is not adequately separated from the carrier molecule. Unlike DPIs the SMI does not require a minimum sufficient PIF but works independently of [inaudible] flow rate. If you look at formulation in inhaler characteristics particle size and velocity can influence aerosol deposition in airways. Both the slower aerosol velocity and the smaller particle size will aid deeper drug distribution into the drugs. Studies of multiple devices reveal that with MDIs a typical aerosol velocity, average aerosol velocity is from 2.0 to 8.4 meters per second while the SMI has an average velocity of 0.8 meters per second. Further, the SMI provides a slow moving mist with spray duration of about 1.5 seconds which aids in inhalation coordination, is propellant free and it features a fine particle fraction of about 75%. Studies reveal correlation between fine particle fraction and lung deposition.

So given that background I'd like quickly turn to Stiolto and more specifically the Respimat device. Stiolto Respimat is a LAMA/LABA combination of tiotropium and olodaterol indicated for long-term once daily maintenance treatment of airflow obstruction in patients with COPD which includes chronic bronchitis and/or

emphysema. My intent today is not to review the safety and efficacy data for Stiolto, instead I'll refer you to the true prescribing information, but my focus is on the Respimat delivery system. The Respimat inhaler is a hand-held, pocket sized device that uses mechanical energy to generate a slow-moving aerosol cloud or mist of medication from metered volume of drug solution. Respimat is Buehringer-Ingelheim's platform for all inhaler devices moving forward. We now have it available in all our products and those include Spiriva in asthma, which is 1.25 micrograms per puff, Spiriva for COPD at 2.5 micrograms per puff, Stiolto as I've mentioned is a LAMA/LABA, Striverdi which is a LABA and also Combivent which is a combination short-acting beta antagonist and muscarinic antagonist.

Thank you for your time and consideration and I'd be happy to address any questions.

Michael Johnson: I see no questions. Thank you. So Nick Nguyen.

Nick Nguyen: Hello. My name is Nick Nguyen. I am the director of HEOR or Health Economics and Outcomes Research with Sunovion. Thanks for the opportunity today to present the clinical and pharmacoeconomic profile for Utibron and Seebri Neohaler. Seebri, as you know, is a glycopyrrolate LAMA bronchodilator. Utibron is a combination bronchodilator which is a LAMA and a LABA similar to [inaudible], a neuro that was presented earlier. Both are indicated for the long-term maintenance treatment of COPD and as Utibron contains a LABA in [inaudible] it carries a class-wide box warnings regarding the increased risk of asthma-related deaths.

Patients in the Utibron and Seebri clinical studies demonstrates sustained improvement in lung function, as well as health status in a pooled analysis of data for two 12-week studies, Flight 1 and Flight 2 and this is for Utibron specifically. The results demonstrated clinically meaningful improvements not only in FAV1 but also health-related quality of life as measured by the St. George Respiratory Questionnaire or the SGRQ. It also improved

patient's symptoms and [inaudible] as measured by the TDI, as well as reduction in daily medication use.

These findings are consistent with the 2017 gold report, the updated report that recommends LABA/LAMA combination therapy in patients with moderate to severe COPD to be initiated sooner and before LABA ICS therapy when maintenance bronchodilation is required. Now what's unique about Utibron and Seebri is Neohaler device. I know that we're talking about many different devices out there and there's a lot of different agents in the COPD class right now across different classes. There's no one-size-fits-all device for a patient so I just want to share a little bit of an overview about this device right here. It's a DPI as mentioned before from our colleagues, and it is twice daily, morning and evening. There's capsules in there that you can insert into the device that's clear which provides both visual and audio cues for the patients. So you can actually hear that. The patient also has a taste of [inaudible] which is a sweet taste to it. So the patient can open the inhaler to see if there is any powder left in a capsule providing visual confirmation that the powder has been disbursed. If the powder is left in the capsule the patient should close the inhaler and repeat the applicable steps. As long as the capsule is empty the patient has received the full dose.

In terms of comparative effectiveness analysis for what's for Utibron and Seebri both are considered cost-effective in patients with moderate to severe COPD based on separate comparative effectiveness modeling. Looking at a one to five-year time horizon, for instance, for Utibron demonstrated cost effectiveness based on non-severe and severe COPD exacerbations avoided, as well as another outcome is 100 mil decline and FEV1 avoided as compared to calmly prescribed COPD agents in the model… examined in the model such as Stiolto, Anoro, even Spiriva. Budget impact modeling also for Utibron and Seebri suggests that the addition of either agents results in both neutral and cost savings to the formulary budget. In closing, clinical and health outcomes data have shown that Utibron and Seebri both provide treatment options with high potential value in terms of efficacy

and cost… cost effectiveness. On behalf of Sunovion I respectfully request that Utibron and Seebri be considered therapeutically and clinically similar to other agents within their class and to be added to the preferred drug list for Medicaid beneficiaries of Washington. I'm happy to address any questions you guys may have.

Michael Johnson: I see no questions from the committee. Thank you. Just a note, we have separated these out by products, individual products, and then we will get to the combination products. There are many motions here. Bear with us.

Amber Figueroa: Can you clarify as the first speaker was saying, what happens when there are drugs currently on the market that aren't reviewed in this scan? Do we wait until the next scan? When is that going to come out?

Donna Sullivan: If the new drugs… the biologics they are being reviewed as a separate class. So we'll bring to you… those to you when they are completed and from what I understood there's no new products that were… there were no new products that were identified in this scan for the drug classes that are already listed. So they have already been reviewed.

Woman: [inaudible]

Donna Sullivan: So any drug that is new is just not included as part of the class meaning it is not eligible to be preferred and it is not subject to therapeutic interchange.

Dale Sanderson: It seems like there is a number of differences in terms of the delivery devices here as much as there is the medications. I don't know how that… how we look at that.

Donna Sullivan: I mean I think what you need to do is consider the evidence as it is reviewed in the reports and not the testimony about evidence that has not been reviewed. So any evidence of superiority of a device would need to go through OHSU to be considered.

Leta Evaskus: Since this is a scan, first you'll have to accept it.

Michael Johnson: I make a motion that this scan be accepted as adequate.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. So again, this is the P&T motion, not the DUR motion and for that reason we evaluate the data that we've seen in this scan.

Amber Figueroa: I don't see that the scan addressed delivery modes at all. Are we to assume then that they are equal?

Donna Sullivan: Really the scan is just telling you what's new in the class as far as the drugs that were… the new studies that are being completed. It's not a full evidence review. When you accept it as adequate you're basically saying there's nothing significant at this point in time to go back and do a full class update. So it would… what you're really considering is the prior report plus this additional information.

Lisa Chew: Donna, so you said that the biologics are actually being addressed in a separate report, right?

Donna Sullivan: Yes, that is correct.

Ryan Pistoresi: Good morning. We'll probably have that available at the April meeting along with the quick relief asthma medication. So we'll try to get that to you as soon as the report is finished by DERP.

Lisa Chew: For the inhaled corticosteroid class I move to reiterate the prior motion.

Jordan Storhaug: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. There are six classes here. Long-acting beta agonists are next. Just for everybody the A is for asthma, C is for COPD, these are the FDA indications. So you can see those right there for each product.

Jordan Storhaug: I move that the scan be accepted as adequate for the long-acting beta agonists.

Donna Sullivan: You don't need to accept it for each indication.

Jordan Storhaug: Okay.

Michael Johnson: Is the highlighted product… was that a new product or was that just highlighted on accident?

Leta Evaskus: This is last meetings motion. So I can unbold it now.

Michael Johnson: With nothing new I make a motion that we reiterate the prior motion.

Amber Figueroa: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay.

Catherine Brown: I move to reiterate the prior motion for the leukotriene modifiers.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Amber Figueroa: I move to reiterate the prior motion for the ICS/LABA combinations.

Diane Schwilke: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Lisa Chew: I move to reiterate the prior motion for the LAMA/LABA combinations.

Catherine Brown: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Michael Johnson: I move to reiterate the previous motion for the phosphodiesterase-4 inhibitors.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. Are you still with us, Marian?

Marian McDonagh: Yes, I am.

Michael Johnson: Okay. Just give us a second to get your slide up. One minute here. So now we're looking at long-acting muscarinic antagonists.

Diane Schwilke: I move to reiterate the motion of last time for the long-acting muscarinic antagonists.

Jordan Storhaug: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. So the topic is long-acting insulins. All right, Marian, your first slide is up. You're ready to start whenever.

Marian McDonagh: Okay. Great. Thank you. So this is the first update of our report on the long-acting insulins. Slide 2.

These are our key questions. The typical questions are comparative, efficacy, effectiveness and harms and looking for any information in various important subgroups. Slide 3.

So we included adult or children with Type 1 or Type 2 diabetes and the interventions are listed in the table. There are multiple formulations of insulin glargine. U100 or U300 available in pen or vial. There is also a follow-on glargine product which is also known sometimes as biosimilar although they are technically different according to the FDA. But the Basaglar insulin for example is a follow-on insulin approved as a pen only. Then we have insulin degludec. That is a new 100 or a U200 formulation insulin degludec combined with insulin aspart and then insulin detemir. So those are all included in this report. For this report it

went up through November 2016 and we did receive one dossier of information from Lilly. Slide 4.

So this is the overview of the studies included in the report. There are 61 total studies, 36 of those are new in this update. So 42 of those are head-to-head with 29 new. As you can see we do have several observational studies now to look at for these insulins. Before we get into the results I want to comment. There are quite a few slides in order to just try and get through this sufficiently, I think it's good to summarize that there really were not big differences found in the efficacy measures of the HA1C, the glucose control measures and we didn't find any long-term effectiveness outcomes comparing the drugs to each other. So I'll try to go through the slides more efficiently and focus on the differences where they were found. Slide 5.

We're starting with the most recently approved drugs wherever we can. So insulin degludec versus insulin detemir. Slide 6.

In Type 1 diabetes this is all new evidence on this slide. There were two trials, both fair quality. Again, as I mentioned, they provided low strength evidence as no difference in the glycemic control measures. And as you'll see on many slides the evidence on the adverse events, including the important… potentially important nocturnal hypoglycemia and severe hypoglycemia was insufficient to draw conclusions. Slide 7.

This is going to be the evidence for insulin degludec versus insulin glargine. Slide 8.

This is in Type 1. Patients with Type 1 diabetes so degludec versus glargine once daily and all new evidence. Three good and fair quality trials of just over 1,000 patients providing low strength evidence. Again, there's no difference in glycemic control at treatment durations of 16 to 52 weeks. However, we did find that patients using degludec had lower rates of nocturnal hypoglycemia. So the pooled rate ratio or the relative risk is 0.61. Statistically a significantly lower rate. And again the adverse… the

evidence on other adverse events was insufficient to draw conclusions. Slide 9.

This is looking at the same comparisons, degludec versus glargine in patients with type 2 diabetes. All new evidence here as well based on six trials of over 4,000 patients treated for 16 to 52 weeks. No difference in glycemic control. Based on seven trials we found moderate strength evidence that degludec had fewer episodes of nocturnal hypoglycemia than glargine. Those are similar to the findings we just found and reported on for the Type 1 patients. So the pooled rate ratio here is 0.71. Here, however, we had a little more evidence on adverse events. So the strength of evidence is low. That is an insufficient. We found no differences in the episodes of severe hypoglycemia or withdrawals due to adverse events. Slide 10.

We're looking at the comparison of insulin detemir versus insulin glargine. Slide 11.

The evidence in patients with Type 1 diabetes. Again, no difference in glucose control based on two trials and no difference in evidence of severe hypoglycemic events or withdrawals due to adverse events. Unfortunately, the evidence on differences in nocturnal hypoglycemia was insufficient. And we found… we did find two observational studies looking at perinatal mortality, adverse neonatal birth weight, and neonatal hypoglycemia, but the studies were small and they were pretty flawed and they came to different conclusions with their reasons for the difference not being clear. That was evidence was found and reported on in the previous report, as well. So that's not [inaudible]. Slide 12.

This is looking at detemir versus glargine in patients with type 2 diabetes. Again, so the first line is the six trials that were in the previous report where we did not find any difference in glycemic control. And the next one, four cohort studies are new with over 100,000 patients in four studies. This provides low strength evidence of no difference in the risk of skin cancer in the short-term. It is low strength however for multiple reasons, but largely

because the follow-up duration may not be long enough to identify any differences that… a difference if one existed. So then six trials also provide moderate strength evidence that more patients withdrew due to adverse events with detemir than glargine. So the pulled relative risk here is 2.1 because it's twice as many patients due to adverse events with detemir. Then we have low strength evidence from trials… six trials and six cohort studies of no difference in severe or nocturnal hypoglycemia. So it's mostly evidence that was in the previous report with a little bit of observational evidence added this time. Slide 13.

So this is comparing the two different concentrations of degludec in 200 and 100. Slide 14.

There is a single study. This is new evidence that it was insufficient to draw any conclusions about glycemic control or adverse events primarily because it was too small to provide precise estimates and because there are no confirmatory studies. Slide 15.

We'll introduce the evidence that we found on follow-on glargine versus insulin glargine. So this is the comparison of essentially the biosimilar versus the originator product. Slide 16.

So in Type 1 diabetes we found one trial. Low strength evidence that glycemic control between the follow-on and the originator product did not differ and the evidence on the adverse events, again, was insufficient to draw conclusions. Slide 17.

Looking at the same comparison in Type 2. Patients with Type 2 diabetes, again, a single study. Low strength evidence with no difference in glycemic control and again insufficient evidence to really draw conclusions on the comparison of the adverse events. Slide 18.

This is looking at the two different concentrations of insulin glargine U300 and U100. Slide 19.

In patients with Type 1 diabetes there were four trials that provide low strength evidence that glycemic control, severe hypoglycemia and withdrawals due to adverse events did not differ after two to six months of treatment. These trials also provide moderate strength evidence of no difference in nocturnal hypoglycemia. That was some new evidence there. Slide 20.

Looking at the same comparison glargine U300 versus U100 in Type 2. Patients with Type 2 diabetes. So there were four trials with 2,700 patients that provide moderate strength evidence of no difference in glycemic control. There's low strength evidence from previous evidence that severe hypoglycemia and withdrawals due to adverse events did not differ. But there are three trials with 1,800 patients that provide moderate strength evidence that nocturnal hypoglycemia occurs less frequently with the glargine U300 than with the 100. The rates are 37% versus 50% with a relative risk of 0.74 in favor of the U300. Slide 21.

So this is looking at comparisons of glargine given via pen or even a vial and syringe. Slide 22.

So this is the evidence for both patients with Type 1 and Type 2 diabetes. There were no randomized controlled trials. We only have seven observational studies to go on and there's only 24,000… a little over 24,000 patients in these seven trials. So they weren't large to begin with. So low strength evidence here that the rates of severe hypoglycemia were lower with the pen than the glargine given with the vial and syringe with a relative risk of 0.72. Given that this is observational evidence and that that is not a really large sample size for observational study this is low strength evidence. It could change with additional evidence. Slide 23.

Fixed-dose combination products. This is degludec combined with aspart and the comparison group here is degludec alone. Slide 24.

This is looking at patients with Type 2 diabetes and this is the new evidence. We did have a study but it was insufficient to draw conclusions, again, for the reasons of the overall sample size being too small to provide precise estimates and not having a comparator… I mean a comfort confirmatory trial. Slide 25.

Another fixed-dose combination product degludec/aspart again compared this time with detemir. Slide 26.

Here it is Type 1 patients. This is all new evidence. We had one trial provides low strength evidence that the glycemic control did not differ between the fixed-dose product and detemir. The evidence on the adverse events was again insufficient. Slide 27.

Comparing the same fixed-dose combination product degludec with aspart compared with glargine alone. Slide 28.

The results are in patients with Type 2 diabetes. Again, a single study. Low strength evidence of no difference in glycemic controls between the fixed dose product and the monotherapy and insufficient evidence on adverse events. Next slide.

This is the summary of the key findings. We were trying to do something a little different here to see if we could prevent who wants the summary in a visual way. We were using the color coded table and symbols to try and show you where the evidence is and is not and where the differences are. So let's go to the next slide.

So this is the slide title, the summary of comparative effectiveness glargine and detemir. You can see all the red cells where we did not have evidence, and the yellow cells are where we found evidence of no difference between drugs. So this is looking at effectiveness or efficacy outcomes for A1C in Type 1 and Type 2 diabetes. At the beginning no differences were found. Next slide.

This is the summary of comparative harms for glargine and detemir and again we have a lot of red cells where there are no

comparative evidence. We have orange cells with the I meaning that's where we found insufficient evidence. Several yellow cells where we had evidence of no difference between drugs and then we have the two green cells. So we have the one where glargine via vial or pen had lower adverse events than detemir… I'm sorry, withdrawal due to adverse events from detemir. And then down at the bottom there the glargine given by vial or pen had lower nocturnal hypoglycemia in patients with Type 2 diabetes than glargine U300. I'm sorry, I said that backwards. The arrow is pointing up so the glargine had lower frequency than glargine. Then we go to the next slide.

This is looking at the effectiveness and harms of the comparison of degludec versus detemir or glargine. Here the two cells that are important are the green cells where we see that for nocturnal hypoglycemia degludec U100 had lower incidence than glargine and then at the bottom we have degludec U200 it had a lower incidence than glargine as well for nocturnal hypoglycemia in Type 2 diabetes. So that summarizes the report. It's a lot of information both old and new. So I'll see if there are any questions.

Michael Johnson: Thank you, Marian. Any questions from the committee?

Susan Flatebo: I just wondered if you could define or explain or talk about what the adverse events were that cause withdrawals in these trials?

Marian McDonagh: Yeah, that's a good question because most of the time the overall adverse… they're not always mapped out really clearly what the readings were for the discontinuation other than just that they were listed as an adverse event. So if you map up the overall adverse events frequencies with the withdrawals you can kind of get an idea, but it's not usually spelled out directly. But it typically has to do with things like injection site reactions and sometimes hypoglycemia, but it's not always really clear.

Michael Johnson: Any other questions? Thank you, Marian. There's one stakeholder, Anthony Hoovler. So we'll have you come up to the

podium and we'll have you please introduce yourself and you have three minutes. Thank you.

Anthony Hoovler: Good morning everyone. My name is Anthony Hoovler. I'm a board certified endocrinologist. I'm a senior medical liaison with Novo Nordisk and I'm a Washington state resident. Today I'd like to share some highlights with you regarding Tresiba. Tresiba is a long-acting basal insulin analog indicated to improve glycemic control in patients with Type 1 and Type 2 diabetes from age 1 through adulthood. Tresiba is in fact the only basal insulin approved for both Type 1 and Type 2 diabetes in patients as young as one year of age and of note with the scan, slide 3, methods include a populations and included interventions I will say that only Tresiba and Levemir, that is degludec and detemir are approved for pediatric Type 2 diabetes. None of the glargine-based products including Lantus, Basaglar or [inaudible] have an indication from the FDA to treat Type 2 diabetes in children.

In regards to efficacy there are 10 head-to-head clinical studies in the Tresiba PI. In all nine of the head-to-head studies comparing Tresiba to other basal insulin analogs, Tresiba met the primary objective, but non inferiority in regards to A1C reduction. And in addition, a statistically similar percentage of adult patients on Tresiba achieved A1C values less than 7%. There are many other properties of Tresiba that make it unique within the basal insulin class that has a half-life of 25 hours and a duration of action of at least 42 hours, both of which are the longest in the basal insulin class. It can be administered once daily. However, unlike other once daily basal insulin analogs which by label must be administered at the same time of day, Tresiba may be administered at any time of the day.

Tresiba is available in U100 and U200 formulations. The U100 pen can be used to provide doses from 1 to 80 units. The U200 pen from 2 to 160 units in a single injection and that option to provide 160 units in a single injection is also unique to Tresiba.

The U100 and U200 formulations are a bioequivalent and there is no requirement to perform a dose conversion when using the two pens. The recommended starting dose of Tresiba in insulin-naïve patients is outlined in the PI. For those adults already on basal insulin it is recommended to start Tresiba to one-to-one basal conversion. In pediatric patients it's recommended to start Tresiba at 80% of the total daily long or intermediate acting insulin dose to minimize the risk of hypoglycemia. After being open the Tresiba flex touch pen may be used up to 56 days. That's 14 days longer than any other insulin. So with the data I presented including several characteristics that set Tresiba or insulin degludec apart within the basal insulin class I would respectfully request that you consider adding Tresiba to the Washington PDL. Thank you and I'm happy to answer any questions.

Michael Johnson: I see no questions. Thank you.

Amber Figueroa: After considering the evidence of safety and efficacy and special populations for the treatment of Type 1 and Type 2 diabetes, I move that insulin detemir, insulin glargine, insulin degludec, insulin degludec/insulin aspart combination are safe and efficacious for the treatment of their approved indications. Long-acting insulins can be subject to therapeutic interchange in the Washington preferred drug list.

Dale Sanderson: I'll second.

Amber Figueroa: With the note that I don't think the combination should be subject to therapeutic interchange. I don't know how to gracefully say that. Should we just list the other three?

Donna Sullivan: You could just say that the non-combination products can be subject to therapeutic interchange.

Amber Figueroa: Non-combination long-acting insulin products can be subject to therapeutic interchange. Does that work? Slower?

Donna Sullivan: It might be better to say that the combination products cannot be subject to therapeutic interchange.

Amber Figueroa: Implying that everything else can be?

Donna Sullivan: Yes. Fix my own grammar.

Amber Figueroa: That sounds good.

Diane Schwilke: Or single… just say single agent long-acting insulins can be subject to therapeutic interchange.

Amber Figueroa: Okay. Let's try again. After considering the evidence of safety, efficacy and special populations for the treatment of Type 1 and Type 2 diabetes, I move that insulin detemir, insulin glargine, insulin degludec and insulin degludec/insulin aspart combination are safe and efficacious for the treatment of their approved indications. Single-agent long-acting insulins can be subject to therapeutic interchange in the Washington preferred drug list.

Dale Sanderson: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. Are you still there, Marian?

Marian McDonagh: Yes, I am.

Michael Johnson: Give us a second to get the slides up. All right. We have your first slide up. You can go ahead and start.

Marian McDonagh: All right. So this is the preliminary update scan for long-acting opioids for the treatment of non-cancer chronic pain. If we go to slide 2.

The history of his report is that the last full report, which was update #7 was completed in September of 2015. The last scan was last December and the searches for the scan went through November of this year. Next slide.

We note again that we have included adults with chronic, non-cancer pain. The study designs were limited to head-to-head comparisons only. The included drugs are listed on the table and the long-acting… definition of long-acting here is pretty generous. So I think it's even anything given at least three times a day. So there are a lot of products listed on the table. Next slide.

So the results since the last scan. There are two new formulations—extended release formulations Vantrela ER hydrocodone bitartrate extended release approved in January of 2017 and Arymo ER which is morphine sulfate extended release also approved last January. So for the new boxed warnings there were several. Really generally across the class there was an addition… the warning against concomitant use with benzodiazepines or other CNS depressants. That applied to almost all the drugs in the class. Buprenorphine also had an additional warning of a risk of neonatal opioid withdrawal syndrome. Topical patch of fentanyl had a warning added about increased risk of fentanyl absorption with application of external heat to the patch site. Hydrocodone bitartrate an additional warning was added for the interaction with alcohol and oxymorphone there was a broad warning added about risk of addiction, abuse and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, and interaction with alcohol. Slide 4.

The results since last scan. There are a couple of comparative effectiveness reviews that were produced by the Canadian Agency for Drugs, Technology and Health that are applicable to the topics in this report. Pharmacological interventions for back pain and then also buprenorphine for chronic pain. And then since the last scan there are no new randomized controlled trials that would be included in this report. Slide 5.

The summary is that there are two new drug formulations, multiple new boxed warnings, two new reviews, and no new trials. Cumulatively, however, since the last full report that brings us to six new drugs or formulations or combinations and then two trials and four reviews. That's the summary.

Michael Johnson: Thank you, Marian. Any questions from the committee? All right. I see no questions from the committee.

Leta Evaskus: There are no stakeholders.

Michael Johnson: So we'll go ahead and entertain a motion. I make a motion that we accept this scan as adequate.

Dale Sanderson: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right.

Amber Figueroa: Doesn't buprenorphine come in something other than a transdermal film?

Donna Sullivan: For treatment of substance use disorder there are tablets, the dissolvable tablets.

Amber Figueroa: Their FDA indication is not for chronic pain?

Donna Sullivan: That is correct.

Amber Figueroa: Okay.

David Johnson: Are you referring to like the Bunavail or Zubsolv oral films, which are buprenorphine only products for pain?

Amber Figueroa: I just know there is more than just the transdermal film for that drug. I wasn't sure of the FDA indications.

Diane Schwilke: She's referring to Subutex, I think.

Donna Sullivan: Correct and it does not have a pain indication.

Amber Figueroa: But some oral films do or there's…

David Johnson: There's two newer brand only products—Zubsolv and Bunavail which are buprenorphine monotherapy or buprenorphine only.

Amber Figueroa: But they haven't been reviewed in this scan, correct?

Donna Sullivan: Correct. There is a drug called Belbuca that is a film that is approved for pain. Marian, are you still on the phone? I have a question.

Marian McDonagh: Yes, I am.

Donna Sullivan: Slide 5 says that there are six new drugs or formulations, but only two are called out. Do you know what the other four are?

Marian McDonagh: I was just trying to look at the full scan. I was trying to pull that up real quick and see. If you have that document they would be listed in the full scan. Let me try to get to that. I'm having trouble. I'll get there. All right. It's going to take me a second to find it. That tab just closed. I don't know if Leta might have it from the documents that I sent over?

Leta Evaskus: I'd have to pull it up and look through them as well. In the report?

Marian McDonagh: Yeah. The full scan report would have the findings of the previous scan, as well.

Ryan Pistoresi: I did pull up the report and it looks like the ones from the previous scans are an oxycodone/naltrexone combination called Troxyca,

an oxycodone medication called Xtampza ER, a bupropion medication Belbuca and then a morphine sulfa extended release oral tablet called MorphaBond and those are the other four from previous ones.

Marian McDonagh: Thanks.

Leta Evaskus: What page are those on, Ryan?

Ryan Pistoresi: In the report it looks like they are pages 4 and then on to page 5 under the first results.

Donna Sullivan: Just to summarize, what this means is the buprenorphine product Belbuca, the hydrocodone product Vantrela, the morphine product MorphaBond and Arymo, the oxycodone product Xtampza and the oxycodone/naltrexone combination called Troxyca, they are not eligible to be preferred in the class and they are not subject to therapeutic interchange if that were approved.

Michael Johnson: So for those products we have to put… this goes in our motion?

Donna Sullivan: No. Those products just stay out of your…

Michael Johnson: The motion? Okay. That's clarification. So then with that it doesn't look like there is anything new from the last scan. Okay.

Dale Sanderson: Given the concerns that we have in society at this point, I mean using opioids for non-cancer chronic pain. Is there any place for us to make comments here? Or are we just looking at the drugs themselves?

Donna Sullivan: You're always welcome to make comments. For this review we're really looking at product selection. We have implemented our opioid policy, November 1st, which you might all be aware of so we're limiting, you know, the pill counts for adults to 42 doses and for children 20 and under is how we're defining children, to 18 doses per prescription, unless there is a medical condition that warrants additional use… or additional quantities. For new starts,

as patients are starting to transition from acute treatment to chronic treatment, we are requiring an attestation for those patients so that we're making sure that the non-opioid modalities are also being used before they go to chronic use.

Dale Sanderson: Thank you.

Emily Transue: Any input is always welcome, but I think the role here is really about if an opioid is needed, which ones should be allowed. But we're happy to hear feedback on the policy and other efforts.

Amber Figueroa: I'm happy to report I saw a pregnant lady the other day and she was smoking heroin because she couldn't get pills on the street. So we're doing great work.

Emily Transue: Few steps forward. Who knows how many steps back?

Michael Johnson: So for the P&T motion we're saying they are safe and efficacious when used with extreme medical judgment and guidelines from state and federal organizations. So that's what "safe" means here in the motion.

Donna Sullivan: If you want to put language in there that, you know, they should be used at… you're more than welcome to. I know we did that with the estrogens years and years ago. The motion mentioned something that they should be used at the lowest effective dose or something of that nature. I mean the motion is yours to make.

Michael Johnson: Under that line where it says, "These are safe and effective when used appropriately following…" Can you say following… I mean almost what I just said.

Donna Sullivan: I think used appropriately is adequate.

Emily Transue: You could also say something like have an acceptable safety profile. I can… I would have discomfort with saying this is safe.

Michael Johnson: I just hate to say they are safe, because…

Emily Transue: Right.

Amber Figueroa: I mean I think that's kind of implied. We've gone through a lot of different classes of medications that have some horrendous potential side effects. I think it's implied that none of them are safe. Just like abstinence is the only thing that's 100% for not getting pregnant, right? No drug is 100% for not getting side effects. I think it implies that safety is relative when they are prescribed for their indications with clinical judgment. I opine that we don't need to put anything else in there.

Nancy Lee: You can also change the wording to harms instead of safety. So after considering the updated evidence of harms.

Michael Johnson: With that one word change I think we're reiterating the prior motion. Do you want me to read that?

Lisa Chew: I have a question. Do we need to put in wording about their particular interchange with this class? That they are not subject to therapeutic interchange?

Donna Sullivan: I think it has… it was removed long ago because of the nature of needing a new prescription that you couldn't automatically do interchange because by law you have to have a new prescription, but you can put it in there if you want them not to be interchanged. At this point in time what it means is that they won't be subject to interchange.

Lisa Chew: I'm fine with keeping it the way it is then.

Amber Figueroa: I do kind of… I do feel weird about saying, on that fourth to last line, are safe and efficacious. Are equally harmful?

Donna Sullivan: I think you could just remove the word safe and say efficacious.

Amber Figueroa: Yeah, I agree.

Michael Johnson: Any other comments? You okay with this? I'm going to go ahead and read this. After considering the updated evidence of harms, efficacy and special populations for the treatment of non-cancer pain, I move that buprenorphine transdermal film, transdermal fentanyl, hydrocodone bitartrate, oxycodone/naloxone HCL, tapentadol, oral oxycodone ER, morphine ER, methadone, levorphanol, and oxymorphone are efficacious when used appropriately and have similar adverse effects. There should be more than one oral preferred drug in the long-acting opioid class.

Susan Flatebo: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. I think that brings us to a break.

Leta Evaskus: If everybody would like to call back in at 11:05?

Michael Johnson: We're adjourning the P&T Committee portion. See you at 11:00.

All right. We're going to convene as the Drug Utilization Review Committee.

Leta Evaskus: Stephanie, are you on the phone?

Stephanie Christofferson: I am. Can you hear me?

Leta Evaskus: Yes.

Michael Johnson: We'll do this in small segments and we'll go ahead and start, Stephanie, whenever you're ready. We have angiotensin modulators.

Stephanie Christofferson: Okay. Sounds great. Again, all these reviews will be high level with noting any significant updates or issues within the class for each one of the classes. Next slide.

The first slide takes a look at indications, dosages and availability of all the ACE inhibitors. As you can see from the slide, most of the products do have a generic available for them and almost all the medications are dosed anywhere from once daily up to three times a day, which depends on the indication in which the medication is being used for. Several of the ACE inhibitors, including benazepril, enalapril, fosinopril, and lisinopril have been shown to be safe and effective in children ages 6 to 16 years of age. As you can see from the chart enalapril can be used in children as young as 1 month old. All the medications are available in a tablet formulation and enalapril and lisinopril are also available in solutions. From the asterisk in the column, the first column under drugs you can see also that… most of these medications are available in a hydrochlorothiazide combination formulation. I did want to note that special dosing considerations are needed for patients with renal impairment with actually fosinopril being the exception to that rule. The data from clinical... the data from numerous clinical trials suggests that when given in equal potent doses all of the ACE inhibitors are effective in the treatment of hypertension, the pharmacokinetic and the pharmacodynamics differences really don't support any advantage of one product over another and the majority of patients with hypertension. All the medications have similar incidences or rates of adverse effects and costs and central nervous system effects are the most prevalent adverse reactions to the medication class as a whole. Next slide.

This slide takes a look at the ARBs. Of note, a generic was launched not too long ago for [inaudible] and [inaudible] HTC and so most of these products are available as a generic now. Again, by the asterisk you can see that many of the medications are available in the fixed dose combinations with hydrochlorothiazide. The dosing for the medications ranges anywhere from once to twice daily depending on the medication and indication, again.

The medications approved in pediatrics are candesartan, losartan, olmesartan and valsartan. There have been comparative trials that have been conducted between the ARBs and hypertension. According to the prescribing information all ARBs lower blood pressure to a similar degree. There is some evidence, however, that Atacand, Diovan and Avapro at higher doses offer a greater decrease in blood pressure compared to Cozaar and some trials have indicated that Edarbi lowers systolic blood pressure to a greater extent compared to other agents, but there are no long-term outcome studies with the agent. Next slide.

Next we'll look at the angiotensin modulator combinations. Next slide.

On this slide it takes a look at the ARB combination medications. Of note, Azor and Tribenzor had recent generics launched and Byvalson is a new product in the class. It's actually a fixed-dose combination of Bystolic and [inaudible] and it is indicated for hypertension as initial therapy and also in patients not adequately controlled on the individual components. The chart in the second column lists the classes in which the different agents belong to, along with generic availability and adult dosing which is all once-a-day for these products. Most patients require more than one single medication to achieve their blood pressure goals. And the combinations of an angiotensin modulator with a calcium channel blocker or beta blocker have been shown to be more effective than either agent alone in the treatment of hypertension. So that's what comes, you know, these combination products come into play. And the combination products appear similar in efficacy and safety. However, again, comparative trials are lacking. Next slide.

Here we're looking at beta blockers. Beta blockers with… this table looks at the properties and indications. So you can see both the pharmacokinetic and the indications for these medications in this table all have an indication for hypertension except Betapace and all are similar in efficacy. The beta blockers are actually not an appropriate first line therapy agent for hypertension and they

are recommended only if there is a compelling indication such as heart failure, myocardial infarction, angina, and so on. All beta blockers are equally effective in the treatment of stable angina and reduce the morbidity and mortality and actually are considered the standard of care of patients with a prior MI. From the chart you can also see the acebutolol, timolol, propranolol, tartrate, nadolol and propranolol also have an indication for angina. And then all other indications of the medications have FDA approval for are listed in the last column. I also want to mention that [inaudible] also came out recently with a generic and also that the Toprol XL and propranolol are the only agents with safety and effectiveness data available in the pediatric population. Next slide.

That just rounds out the rest of those medications I just discussed. Next slide.

This looks at the beta blockers dosage and formulations and this slide and the next slide I'll talk kind of as a whole. All the medications with the exception of Bystolic and Sotylize are available as generics and many of the medications, as indicated by asterisks, within the chart are available in hydrochlorothiazide combination products. Atenolol is also available in a fixed dose combination with chlorthalidone and nadolol is available in a fixed-dose combination with bendroflumethiazide. From the charts you can see that most of the medications are dosed either once or twice daily and that propranolol and sotalol are also available in solution formulations. Next slide.

Here are the calcium channel blockers. I guess I'll stop there. Are there any questions to this point? I know this is kind of a long block of products. Okay. So I'll go ahead and continue with the calcium channel blockers. The first slide looks at the indications and this looks at the dihydropyridines. The dihydropyridines are actually potent vasodilators and can increase or have a neutral effect on the vascular permeability. Most have an indication for angina and hypertension with amlodipine and nifedipine also having an indication for vesospastic angina. I did want to mention

that amlodipine has been studied in hypertensive children, but the safety and efficacy of the other calcium channel blockers in hypertensive pediatrics have not been established. Next slide, please.

This slide illustrates the FDA approved indications for the non-dihydropyridines. The non-dihydropyridine verapamil and to a lesser extent diltiazem are actually less potent vasodilators, but they do have a greater depressive effect on cardiac conduction in contractility. Most of the medications, again, have an indication for angina and hypertension with a few having additional indications for vasospastic angina, unstable angina and ventricular rate control. Overall, the benefits of calcium channel blockers and controlling angina and hypertension are clearly documented, but there are no products that have demonstrated a clear clinical advantage over another in the treatment of hypertension. Next slide.

For the next two slides I'll, again, kind of talk to you as a whole. As you can see from the chart most of the medications have generic options available and a lot of them are dosed multiple times per day. They are available in several different formulations including tablets, capsules and there's actually one solution product called [inaudible] and it's a ready-to-use oral solution which is approved for the treatment of subarachnoid hemorrhage and it's actually indicated for… or designed for patients who require a dosage that's lower than the standard 60 mg dose. When it comes to dosage adjustments there are several products that do need hepatic impairment or cirrhosis adjustments. That includes amlodipine, felodipine, nicardipine, nifedipine… there's a lot of different products. So that's something that someone might want to take into consideration when dosing or selecting a product for a patient and then there are a couple of products that also require renal impairment dosage adjustments, which includes nicardipine, diltiazem and verapamil. Next slide.

Again, this slide just rounds out the rest of those products that I just mentioned. Next slide.

So there have been some guideline updates. Not mentioned on this slide, but I think worth mentioning is that the American College of Physician and American Academy of Family Physicians published evidence-based recommendations on the benefits and harms of high blood pressure, which they defined as less than 150 mL of mercury versus lower, which was less than 140 systolic blood pressure targets in the treatment of antihypertensive adults who were ages 60 and older. They recommend initiating antihypertensive therapy in adults 60 years and older when the systolic blood pressure is above 150 with a target of lowering it below 150 in order to reduce the risk of natality and stroke and cardiac events. A stricter goal of less than 140 may be considered in older adults with a history of stroke or transient ischemic attacks in order to reduce the risk for recurrent stroke. And then also a stricter goal of 140 they recommend for older adults at high cardiovascular risk, again, to reduce the risk of stroke or cardiac events. If a pharmacological agent is chosen they recommend that generic formulations be prescribed when available in order to reduce the cost for patients and hopefully aid in adherence just, again, to reduce that barrier to compliance. When it comes to heart failure the American College of Cardiology and the American Heart Association, along with the Heart Failure Society of America updated guidelines in 2016 and then also in 2017. They recommend either an ACE or an ARB or an ARNI in conjunction with evidence-based beta blockers and [inaudible] antagonists in select patients and that's recommended for patients with chronic heart failure with reduced ejection fraction. And then they mention that the ACE inhibitors are beneficial in patients with prior or current symptoms of chronic heart failure with reduced ejection fraction and then, again, ARBs are recommended in patients with prior or current symptoms of chronic heart failure with reduced ejection fraction who are intolerant to ACE inhibitors. In patients with chronic heart failure with the reduced ejection fraction and then New York Heart Association Class 2 or 3 and patients who can tolerate an ACE or an ARB they actually recommend replacing that with an ARNI to further reduce morbidity and mortality, but they also, again, mention that it

should not be administered with an ACE inhibitor or within 36 hours of the last dose in medication. The ARNI should not be used in patients with a history of angioedema. Next in hypertension new guidelines came out by the organizations that are listed there. They first recommend non-pharmacological interventions such as weight loss and healthy diet, sodium restriction, increase in physical activity and so on. In patients with stage 1 hypertension they have an estimated 10-year atherosclerotic cardiovascular disease risk of less than 10%. They recommend nonpharmacological therapy. Then in patients with stage 1 hypertension with a atherosclerotic cardiovascular disease greater than or equal to 10%, again, nonpharmacological therapy should use and then they recommend also adding a hypertension medication and then patients with stage 2, again, nonpharmacological approach and then they recommend placing patients on two different medications and different classes and then also again monitoring those patients. They do again indicate that prescribers should consider patient-specific factors when selection the medication and for initiation of hypertension prescriptions for first line therapy they recommend [inaudible] diarrheic, calcium channel blockers, ACEs or ARBs. They do not recommend the concurrent use of ACE, ARB or [inaudible] inhibitors as it may be harmful. And then they also stated that starting hypertension therapy with two first line agents of different classes is recommended in stage 2 hypertension and an average blood pressure more than 20 mm of mercury for [inaudible] that's greater than 20 or greater than 10 for diastolic above the target levels. Lastly the hypertension recommendations in pediatrics, the American Academy of Pediatrics updated guidelines in 2017. The goal they had stated was to achieve a blood pressure that decreases the risk for organ damage and use and decrease the risk of hypertension that develops in adulthood. Their goal is to get patients to blood pressures of less than 130 over 80 and they also, like adults, recommend lifestyle modification such as diet and physical exercise. For the pediatric population the first line therapies include ACE inhibitors, ARBs, long-acting calcium channel blockers or thiazide diuretics. They recommend starting low with the

dosages and titrating them up as needed and then adding a secondary agent if monotherapy is not working. Beta blockers, they note, are not recommended as initial pharmacological therapy in children due to the side effects of the medication. So that's one they do not recommend.

We'll move on to the anticoagulants.

Michael Johnson: Stephanie, we're going to pause here for a minute for stakeholder comment, but before we do that, any questions from the committee for Stephanie? Okay. So we have one stakeholder, Mary Kemhus. We'll have you come up to the podium and, again, reintroduce yourself at the microphone. You have three minutes. Thank you.

Mary Kemhus: All right. Thank you. So again, I'm Mary Kemhus. I'm a pharmacist with Novartis and I just have a few brief comments today related to Entresto. It's the angiotensin receptor neprilysin inhibitor that has been referenced on the Magellan slide as an army. Just as a reminder it is indicated to reduce the risk of cardiovascular death and hospitalization for patients with heart failure and reduced ejection fraction. The Magellan review highlighted the 2017 HAACC and HFSA guidelines and I just want to reiterate that the guideline is notable because it is the first time that these three organizations have come together to create a guideline for heart failure and it specifically identifies that group of patients that should be switched over to an ARNI or Entresto.

There was another guideline update of note that was just recently published. The 2017 ACC AHA HRS which is the Heart Rhythm Society guideline for the treatment of patients with ventricular arrhythmias who are at risk for sudden cardiac death. This guideline also endorses the use of Entresto to reduce sudden cardiac death and all-cause mortality in patients with heart failure and depressed LV function. So with that being said I ask that you remember that Entresto is now a guideline directed therapy for patients with heart failure, reduced ejection fraction and that Washington Medicaid patients have unrestricted access to this

medication. Thanks. I'm happy to take any questions if you have them.

Michael Johnson: Thank you. All right, Stephanie, we can go ahead and continue.

Stephanie Christofferson: Okay. Next we'll talk about the anticoagulants. The first slide lists the indications of the medications, which include hip replacement, knee replacement, hip fracture surgery and abdominal surgery. There are some additional indications not listed here for each one of the medications. For instance, Fragmin also has an indication for prophylaxis of ischemic complications of unstable angina and non-[inaudible] myocardial infarction when administered with aspirin. It also has the indications for deep vein thrombosis, prophylaxis for mobile medical patients who are at risk for thromboembolic complications, and then lastly also an indication for extended treatment of symptomatic Venus thromboembolism to reduce the recurrence of VTE in patients with cancer. Lovenox also has an indication for prophylaxis of ischemic complications of unstable angina in non-Q wave myocardial infarction in conjunction with aspirin. It also has an indication for DPT prophylaxis to prevent thromboembolic complications in medical patients with severely restricted mobility during acute illness and then lastly it is also indicated for the treatment of acute ST segment elevation myocardial infarction medically managed or with subsequent percutaneous coronary intervention. And then lastly Arixtra also has an indication for treatment of acute PE when initial therapy is administered in the hospital or with warfarin.

Other update about fragment, within the last year, I wanted to mention that the pregnancy and lactation information has been updated. So previously it was assigned with the pregnancy category C, but the labeling was replaced with descriptive text and compliance with the new rule, which now states that it does limit… there's not… not reported a clear association with fragment and adverse development… developmental outcomes. The risks and benefits to both the fetus and the mother, if untreated, should be considered. Also, Arixtra was previously

assigned at pregnancy category B, but its labeling has also been updated to comply with the rule and it now states that there is limited data and it has not been… the data has not reported a clear association with the medication and adverse developmental outcomes. And then also that it… data… limited data suggests that there is low placental transfer of the product. Next slide.

We'll look at the dosage and formulation. All the medications come in pre-filled syringes, as you can see here, and then Fragmin and Lovenox also come in vials. The medications are also administered once daily and Lovenox can be dosed up to twice daily in some indications. As far as duration of therapy most often Fragmin is dosed for up to 10 days, Lovenox for 12 to 14 days, and Arixtra usually around 9 to 11 days. Next slide.

There's no new guidelines to mention here. I just… the most recent guidelines, what we have, are the tenth American College of Chest Physicians or ACCP evidence-based clinical practice guidelines, which those were published in January of 2016. In those guidelines they state that patients undergoing orthopedic surgery, DVT prophylaxis with a low molecular weight heparin, unfractionated [inaudible], Vitamin K antagonist such as warfarin or aspirin, and then also the newer agents such as Eliquis, Pradaxa and Xarelto are recommended post operatively for at least 10 days to up to 14 days. And patients undergoing hip fracture surgery they recommend the use of low molecular weight heparin, Arixtra, low dose unfractionated heparin, warfarin or aspirin for antithrombotic prophylaxis for a minimum of 10 to 14 days. They also recommend initial treatment options for DVT consist of either intravenous or subcutaneous unfractionated heparin. Subcutaneous low molecular weight heparin or Arixtra for at least 5 days or until the INR is at a therapeutic range for at least 24 hours until a patient can be switched over to warfarin. And then lastly, low molecular weight heparin or Arixtra is suggested over unfractionated heparin for the treatment of acute DVT of the leg, acute PE or acute upper extremity DVT of the auxiliary or more prophylactic veins. Next slide.

Now we'll go to the antivertigo agents. There are three classes of antivertigo agents which include the antihistamines, phenothiazines and the anticholinergics. The routes of administration are listed here and as you can see there is injectable, oral, suppository or transdermal ways of administered the medications. The indications vary across the medications from minor motion sickness to more severe nausea and vomiting which can be associated with different procedures. Next slide, please.

Under the usual dose range column you can see the various directions for use for the medication. All the medications are dosed multiple times per day in order to reduce or prevent nausea and vomiting. Again, as you can see in the chart many of the medications are available in ATC formulations for some of the minor conditions. And then generics are also available in all of the medications. Lastly, the availability of dosages are in the far right column. Of course I'm not going to go through all of those, but there are a lot of different availabilities for that. Next slide.

This is guideline updates. There are no new guidelines in particular for these products. The National Conference of Cancer Network did have guidelines in version 2 of their 2017 guidelines that states that patients who receive oral chemotherapy with low to minimum emetic risk that they receive alternative oral agents as needed such as metoclopramide, prochlorperazine or a 5HT3 receptor antagonist. And then for breakthrough therapy treatment for chemotherapy induced nausea and vomiting their general principle is to add one agent from different classes as needed to the existing regimen. Also the American Society of Anesthesiologists published recommendations on the prevention of post-operative nausea and vomiting and within their guidelines they recommend routine assessment and monitoring of nausea and vomiting and then regarding the prophylaxis or treatment of nausea and vomiting they evaluated the antivertigo agents, which included the antihistamines, specifically promethazine and then also perphenazine and prochlorperamide. They rated the medications on quality of evidence. It stated that promethazine

compared to placebo anyway reduced nausea and vomiting. However, new literature they had put in their guidelines was insufficient to further evaluate post-operative nausea and vomiting findings for perphenazine or prochlorperazine. And then for motion sickness they are both non-pharmacological and pharmacological interventions for the prevention… or management, however, none of the therapies are really ideal and the medications used, of course, included the antihistamines, phenothiazines and the anticholinergics, but unfortunately they often times cause drowsiness or similar adverse events. So I'll go ahead and stop there.

Michael Johnson: Okay. Any questions for Stephanie? Looks like there are no questions. There are also no stakeholders so if you want, we can go ahead and continue.

Stephanie Christofferson: Okay. Next I'm going to address the hypoglycemics. I'll go through all the medications at once and then I'll go through the updated guidelines at the very end of this section. The first slide looks at the alpha-glucosidase inhibitors. This primarily consists of two drugs which are Precose and Glyset, which are competitive, reversible inhibitors of the alpha-glucosidase and the agents prevent the breakdown of sucrose and complex carbohydrates in the small intestines. They are there by prolonging the absorption of the productions—the carbohydrates and the glucose. It has a mention that Glyset is also a more potent agent compared to Precose on the milligram per milligram basis. This particular class of medication only has a modest effect on lowering the hemoglobin A1C by about 0.4 to 0.7%. The medications are relatively safe, however, they do have significant GI side effects which could limit their use in patients. Again, both medications are taken with meals and they are both available in tablet formulations. Next slide.

We will look at the meglitinides. Again, all these medications have the same indication, which again is the treatment of Type 2 diabetes of… adjunct to diet and exercise. As you can tell from the chart, all the medications are available as a generic with

Prandimet being the new generic available, which that's a fixed dose combination tablet and the medication has been proven to be bioequivalent to the individual drugs when administered together. I do want to note that with Prandimet and actually with all the drugs containing metformin that in April of 2016 the FDA issued a drug safety communication to clarify that metformin may be safer used in patients with mild renal impairment and in some patients with moderately known impairment. This is actually based on the review of various metformin Stacy studies that included new information that was provided to them. They did require re-labeling for all the products that contained metformin so you might be seeing that change over as the manufacturer's update their package inserts. But I've noticed that some of them have old information. Just FYI when you're taking a look at these products. All the medications are taken three to four times daily with meals and are available in tablet formulations. The safety and efficacy have not been studied in the pediatric populations. When you compare the two products here, Prandin and Starlix there was actually two trials that actually looked at and compared the two products. What was concluded from these was that there was actually a greater reduction in the hemoglobin A1C in patients that were receiving Prandin compared to Starlix. Next slide, please.

We'll take a look at the sulfonylureas. Again, all these products had the same indication for the treatment of Type 2 diabetes either a mono combination therapy and work by enhancing the response of the beta cells in pancreas to glucose. They are all available in generic formulations and they are also all tablets. As you can see from the usual dosage range they are usually administered with the first meal of the day. Safety and efficacy have not been established in the pediatric populations so that might be something to consider when prescribing [inaudible] the medications. And then I also did want to note that hypoglycemia has been a major adverse effect with this class. However, it has been noted that glyburide is associated with the greatest risk for hypoglycemia. But overall, as a class, these medications are safe

and efficacious and well tolerated in the treatment of Type 2 diabetes. Next slide.

These are the TZDs. Essentially the products that you have in this class are pioglitazone and rosiglitazone either in single entity or combination. Again, both of the products are indicated for Type 2 diabetes. The reduction in hemoglobin A1C due to the [inaudible] is expected to be around 1 to 1-1/2%, but in combination with other agents used to lower blood glucose levels including metformin the level of hemoglobin A1C lowering is approximately an additional 1/2 a percent to 1%. Generics are available for most of the pioglitazone products and there are combination products available for those needing multiple medications, which of course could always have an impact on patient compliance. In bio coherency studies all the combination products were bio equivalent to the single agents when administered together. The pioglitazone products are dosed once daily and the rosiglitazone products are dosed twice daily. Again, all the medications are available in a tablet formulation. The safety concerns for both agents are pretty similar. However, I did want to note that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. In 2016 the FDA issued an update safety communication concluding that all pioglitazone containing products may be linked to an increased risk of bladder cancer and then also in 2016 there were results from an observational study that was published on patients that were initiated on antidiabetic medications over a 13-year period, which suggested the risk of bladder cancer increased with duration of time and also the amount or dose of pioglitazone used. But to note is that rosiglitazone does not have an associated risk of bladder cancer. Do you want to go ahead and go to the next slide?

This looks at the guidelines which in 2017 the American Association of Clinical Endocrinologists and the American College of Endocrinology updated the management of diabetes algorithm. The AACE supports an A1C goal of less than 6.5% for most patients, but they also note that a goal of greater than 6.5% up to

8% is okay if the lower target cannot be achieved without adverse outcomes. The first thing that the organization recommends is lifestyle modifications including weight loss. Then if drug therapy is needed then they recommend drug selection and the number of drugs based on the A1C level at the time of initiating therapy. If the A1C is less than or equal to 7.5% the guidelines recommend monotherapy and again in addition to lifestyle modifications and really lifestyle modifications should be carried out throughout anyone that has issues with diabetes. But they do, again, when the A1C is less than or equal to 7.5% they recommend monotherapy with one of the medications there in that first column with actually metformin being the drug of choice. The order of the medications that you see in each column actually represents the hierarchy of use. So again metformin is the drug of choice and then if goals are not met within three months, and they do mention you should assess compliance along with therapy goals or lack of therapy goals, if it's not working then after three months they recommend moving to dual therapy. So patients not having success on monotherapy or patients who have an initial A1C of greater than or equal to 7.5%, the organization recommends dual therapy plus lifestyle modification. They recommend that metformin plus another agent, but they do note that patients who are metformin intolerant, they just recommend that two drugs with complimentary mechanisms of action from different classes be used and then again if the goal's not met after three months of dual therapy they recommend them moving to triple therapy and then still at triple therapy if goals are not met after three months they recommend that insulin therapy be added or therapy be intensified. And then finally patients with an A1C of greater than 9 who are symptomatic they state that they would drive the greatest benefit from the addition of insulin, but if they are presenting without significant symptoms then these patients may initiate therapy at the maximum doses of two products. And then after that the doses may be decreased to maintain control as the glucose levels fall. Not on this chart, but I want to mention that the American Diabetes Association released their 2018 guidelines which are very similar to the guidelines just mentioned and that, again, they recommend lifestyle changes for

all patients. And then if the A1C is less than 9% they state that prescribers can consider monotherapy with metformin being the drug of choice. And then after three months if the goal is not met they move up to dual therapy. And then with the dual therapy what they recommend is ideally metformin with another agent and then… for… again, patients who have not worked with monotherapy. And then patients who are not really diagnosed with a hemoglobin A1C greater than or equal to 9%, those patients also start on dual therapy. And then after three months if A1C levels are not reached then a triple therapy can be considered and then again you wait three months and if that's not working, then they recommend consideration of injectable therapy. And then finally they recommend initiation of insulin therapy with or without additional agents in patients who are newly diagnosed who are symptomatic and/or have hemoglobin A1C greater than or equal to 10% or blood glucose levels greater than 300 mg per deciliter. Unlike the other organizations they don't list the hierarchy or drugs. They just list which medications have the greatest efficacy and the ones that they have stated had the greatest efficacy are classes… the GLP1s, the TZDs, sulfonylureas, and then of course metformin. Any questions there? I know there's a lot to go through there.

Michael Johnson: I see no questions from the committee. You can continue. There are no stakeholders.

Stephanie Christofferson: Okay. Next we'll go to the GI motility. The first slide looks at the indications. So the treatment for irritable bowel syndrome really focuses on the management of symptoms and pharmacological options should be considered as part of a multi-focal approach in order to achieve relief. Linzess and Amitiza are indicated for the treatment of chronic idiopathic constipation and IBS with constipation. However, I did want to note that Amitiza is indicated only for use in irritable bowel syndrome with constipation in women. Amitiza is also approved for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain. Viberzi is actually a newer product in the class and it is indicated for the treatment of IBS-D in adults, both men

and women, which is unlike Lotronex. It is a schedule 4 medication whereas all the other medications in the class are non-controlled medications. As you may now, in July of 2016 a Movantik label was actually updated… was removed to a C2 designation. I just wanted to make sure that was updated. I also wanted to mention that in 2017 the FDA did issue a drug safety communication warning users of an increased risk of serious pancreatitis, which sometimes can lead to hospitalizations or even death with Viberzi, but this occurred in patients that were without a gallbladder. So the FDA does not recommend its use for patients that do not have a gallbladder. Trulance is also a newer product in the class and is indicated for the treatment of chronic idiopathic constipation in adults. Its use is contraindicated in children less than six years of age and actually carries a boxed warning. Linzess is also contraindicated in patients less than six years of age whereas all the other medications do not have safety and efficacy established for them at this time. And then lastly I wanted to mention, for this slide, is that Lotronex is also subject to a REMs program which consists of healthcare provider training to ensure safe use and awareness of ischemic colitis risk in complications of constipation. Even though the patients are no longer required to complete and submit an acknowledgement form, there is a patient education sheet that is still available for prescribers when initiating therapy in their patients. Next slide, please.

I'll address the next two slides together, which it looks like the dosage and formulations. All the medications are available in an oral form and Relistor is actually also available as a daily subcutaneous injection. The dosages range from once to twice daily with the once daily medications being Linzess, Relistor, Movantik and Trulance. And the twice daily medications, which include the Lotronex, Viberzi and Amitiza. The new drug, Viberzi is dosed as 100 mg twice daily with food or 75 mg twice daily for those unable to tolerate the full dose or those taking medications which may interact with the medication and then also patients with mild to moderate hepatic impairment. It is noted in the package insert for the drug that… for patients who develop

constipation greater than four days the medication be discontinued. And then also the other new product, Trulance, is dosed as 3 mg once daily and this medication can actually be crushed in applesauce or water for consumption in individuals who have swallowing difficulties. And then lastly Relistor is now available in a tablet formulation and this is dosed at 450 mg once in the morning. Next slide.

This just rounds out the rest of the medications that we just discussed.

As far as guidelines there's no recent guidelines that have been published. In 2014 in the American College of Gastroenterology provided information on the management of irritable bowel syndrome and chronic idiopathic constipation in an effort to assess the evidence of efficacy of IBS and constipation agents. The organization states that Linzess, Amitiza and Trulance are all effective for CSC and are well tolerated. But there are no comparative studies that are available to guide the agents place in CIC therapy. The clinical trials have shown that all three agents are more effective than placebo in reducing the symptoms of CIC. The 2014 guidelines also recommend laxatives as well as both Linzess and Amitiza in patients with IBSC over no drug therapy and they recommend Lotronex over no drug treatment in patients with IBS-D. These guidelines that were developed in 2014 did not address Viberzi. However, we do anticipate new guidelines for these products sometime in early 2018. Let's move on to ulcerative colitis.

The first slide, again, looks at indications and the medications are either indicated for treatment, maintenance or actually both for ulcerative colitis. And, again, these are listed on the first and second slide. They are both oral and rectal dosage formulations available for the disease state with some of the products having a generic, which is again listed in column two. Mesalamine is listed on the second slide and it is actually available in a delayed release formulation. And then to note there has been a recent change in the labeling for Colazal which has been updated with the

pregnancy and lactation rule. They now advise that there are no adequate or well-controlled studies in pregnant women. Therefore, the drug should only be used in pregnancy if it is clearly needed. Next slide.

Again, this lists the rest of the medications and their indications. Next slide, please.

The next two slides look at the dosage and formulation of the products. As you can see most of the medications here are taken multiple times per day. However, Lialda and Apriso are also indicated as once daily therapy. Oral Colazal, [inaudible] and Delizcol are the only products with an FDA approved indication in children, as well.

On the next slide this looks at the rectal formulations of the products. Budesonide and mesalamine are available in the rectal formulations and the enema and suppository formulations are administered once daily at bedtime and the rectal foam is administered twice a day. There was a meta-analyses that has been performed which assessed the agents in this class. In that meta-analyses it noted that the sulfasalazine products were significantly superior to the mesalamine for maintenance or remission. And then also once daily and conventional dosed mesalamine products were similar efficacy in adherence. And then lastly the meta-analysis concluded that no difference was found for efficacy among the various mesalamine formulations. Next slide.

Again, there are no new studies. According to the 2013 American Academy of Family Physician guidelines they had stated that mesalamine via suppository or enema should be used as a first line agent for patients with proctitis or proctosigmoiditis respectively. And that patients who are unable to tolerate the rectally-administered medications could try oral preparations. However, they do note that response times and remission rates may not be as favorable. Oral mesalamine they also note is effective in patients with mild to moderate ulcerative colitis that

extends from the proximal to the sigmoid colon and that a topical mesalamine may be added if an oral formulation alone is inadequate. And then also they note that short-term courses of oral corticosteroids may be appropriate if the oral plus topical mesalamine therapy is not effective or if a more responsive therapy or response is needed. However, to note though is that budesonide or Uceris was first FDA approved in January of 2013 and its use is not specifically addressed in the guidelines. So I'll go ahead and conclude there.

Dale Sanderson: I have a question on the GI motility section. I was curious that you did not include like gastroparesis either medication-induced or say neuropathy-induced.

Stephanie Christofferson: I'm sorry. Can you repeat the question?

Dale Sanderson: Yeah. So the gastroparesis as an indication under the GI motility. I see patients with medication-induced like gastroparesis and young neuropathy, as well. There can be gastroparesis secondary to the neuropathy and diabetes.

Stephanie Christofferson: As far as including information… in the presentation or?

Dale Sanderson: Are these medications, you know, useful for those kinds of indications?

Stephanie Christofferson: Right. Um, I mean it could be used in clinical practice as far as, you know, what has been FDA approved for. I don't believe that those are actual approved indications, but that doesn't mean that… I mean, of course medications are used off label or for various reasons all the time.

Dale Sanderson: Thank you.

Michael Johnson: Any other questions from the committee? All right. Thank you, Stephanie. I think we'll see you back at 1:00. We will now entertain a motion.

Stephanie Christofferson: Thank you very much.

Michael Johnson: Thank you.

April Phillips: We're making a really quick change to the recommendation to add drug class or subclass in there to be more specific. So our recommendation is products within each class or subclass are considered safe and efficacious and are considered for… are eligible for preferred status within that class or subclass at the discretion of HCA and that all non-preferred products require a trial of two preferred products with same indication, but different active ingredient prior to a non-preferred approval.

And then I also want to mention we previously reviewed like the anticoagulants, but they were only the newer oral formulations and this new round is the self-injectable.

Jordan Storhaug: I was… I'm wondering maybe some comments on Entresto which does kind of have a unique need that some patients would need currently and we're not calling those out and so I'm wondering if that's going to be a disservice to some patients or not?

Nancy Lee: I also consider that as well and in reading the second bullet point where if it's a non-preferred product these patients will likely have been on an ACE or an ARB and then before a non-preferred drug will be authorized unless contraindicated or not clinically appropriate. So I feel like it might be addressed by that bullet point.

Donna Sullivan: We would have it on prior authorization just making sure that it is being used according to label.

Diane Schwilke: I move that the Apple Health Medicaid Program implement the limitations listed on slide 48 for each drug class listed on slide 47 as recommended.

Michael Johnson: I second the motion. All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. I think it is lunch time. So we will reconvene at 1:00 p.m.

Leta Evaskus: Please call back then.

Michael Johnson: I think we will go ahead and reconvene the Drug Utilization Review Committee. Are you on the phone, Stephanie?

Stephanie Christofferson: I am here.

Michael Johnson: All right. We have your first slide up. You can start when you are ready.

Stephanie Christofferson: Okay. All right. The first topic we have is the antiparasitic topical agents. The first slide lists the indications. As you can see here in the second column there are both prescription and over-the-counter products that are available for the treatment of head lice and with some of the products being indicated in patients as young as six months and older. Some of the products, as indicated on the slide, are also indicated for other conditions such as scabies, crab lice, and body lice. And then permethrin also has an indication as prophylaxis indication during times of epidemic. Next slide, please.

Most of the medications are applied topically and removed after 10 minutes and then re-treatment may be allowed afterwards depending on the product. But Ovide and Elimite are applied and left on the hair or body respectively for approximately eight hours and then also re-treatment with these products is also a possibility, if needed. As you can see in the very last column the products are available in a wide variety of different formulations including lotions, creams, shampoo, suspensions and foams. Go ahead and advance to the next slide.

There are no new recent guidelines. The AAP guidelines from 2015 do continue to support a role for topical OTC permethrin

and pyrethrin in the treatment of head lice, but there has been resistance noted to these agents and has been documented in the U.S. Some newer agents may have a role when resistance to permethrin or pyrethrin is a concern or in cases where there is treatment failure. For treatment failure it is not attributed to improper use of the over-the-counter products. Malathion, benzyl alcohol lotion or spinosad suspension should be used. The selection of the agent should be based on safety, efficacy, local resistance patterns and then also of course the patient's age. And then also I've noted that lindane is no longer recommended for the treatment of head lice due to its poor safety and efficacy. A few things to note with the newer products is that Ulesfia and Sklice have not been compared to other agents, but versus placebo it has shown efficacy in head lice. But Natroba has shown better head lice eradication compared to topical permethrin, but of note it has not it has not been compared to other topical prescription antiparasitics. I'll go ahead and continue to the antibiotic topical.

The first slide looks at the indications. Most of the medications, as you can see here, are indicated for minor skin infections and a lot of them are available to patients without a prescription. The prescription products include gentamicin, mupirocin and Altabax. These you can see from that first slide there they are indicated for more significant infections. And then also there is a nasal version of bactroban available for internasal use and is indicated for the eradication of nasal colonization of MRSA in adult patients. Next slide.

Application of the topical products range anywhere from once up to three times daily depending on the product and then as you can see in the third column most of the products are available in a generic and there are several different package sizes in formulations available for patient's convenience. Next slide, please.

There are no new recommendations or guidelines. In 2014 the Infectious Disease Society of America they still recommend for…

recommendations… they recommend oral or topical antimicrobials. The oral therapy is recommended for patients with numerous lesions or if there is an outbreak infecting several people in order to help decrease transmission of the infection. Treatment with impetigo with either mupirocin or Altabax twice daily for five days is still recommended by the Society. When comparing the products Altabax does have an advantage in that it is dosed twice daily compared to mupirocin which is three times daily. However, when using Altabax the total treatment area should not exceed 100 cm squared in adults or more than 2% of the total body surface area in children or adolescents. So that might be a limitation of its use. Next slide, please.

We'll look at the antibiotics for vaginal. The first slide looks at the indications. All the medications are indicated for bacterial vaginosis in non-pregnant women. Because it states non-pregnant women you might be considering what you can use in pregnant women. Literature doesn't support any superiority of oral regimens over the intravaginal regimens and pregnant women can be treated with either oral or intravaginal ones. Metronidazole is a pregnancy category B. Previously clindamycin vaginal cream and the [inaudible] were assigned a pregnancy category B. However, again, in compliance with the new regulations there labeling has been updated. And then clindamycin 2% may be used in second or third trimester pregnancy for the treatment of bacterial vaginosis, but there is no adequate or well controlled studies in pregnant women during the first trimester of pregnancy. Next slide.

Administration of the different products is relatively the same and the length of the therapy is actually what differs between the products ranging anywhere from 3 to 7 days for most products. As you can see from the third column there are generic products available for patients' convenience. Next slide, please.

There are no new guidelines to note. According to the [inaudible] CDC Sexually Transmitted Disease Treatment Guidelines they recommend treatment with… for bacterial vaginosis in non-

pregnant women to include oral metronidazole, matrogel vaginal or Vandazole and then actually also Cleocin. Those recommendations still hold true today. Next slide, please.

We'll review the antibiotics for GI. The first slide looks at the indications and there are a variety of different antibiotics available which are utilized to treat gastrointestinal infections and also bacterial vaginosis. Xifaxan has been shown to reduce the duration of loose stools due to traveler's diarrhea compared to placebo. It's not absorbed systemically so it has other few side effects. It's also been shown to have similar efficacy compared to ciprofloxacin for the treatment of traveler's diarrhea. And lastly it was approved for IBS-D in 2015. Additionally, Xifaxan and neomycin are both approved for hepatic encephalopathy and Alinia is the only drug approved in this review for the treatment of cryptosporidium. Tindamax and oral metronidazole are recommended from the CDC for the treatment of trichomoniasis. They actually had similar efficacy in a single-dose study of the treatment of vaginal trichomoniasis. Both are also oral alternatives to vaginal preparations for the… of the disease state and had similar cure rates, as well. And then lastly there are generic formulations as you can see for many of the medications that are in this review. Next slide, please.

When looking at dosage and formulation, dose ranges with these products from once-daily therapy up to several times per day, depending on the indication being treated and the medication being used. I wanted to mention that Alinia is available as a suspension where all the other products are available in either a tablet or capsule formulation. But I did want to note that the suspension is not bioequivalent to the tablets. Next slide, please.

This just lists the rest of the medications with the dosage formulation. Next slide.

Again there are no new updates. In 2010 the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America guidelines on C. difficile infections in adults

recommend oral metronidazole as the drug of choice for initial episode of mild to moderate C. diff. However, they do note that metronidazole should not be used beyond the first occurrence for C. diff infections or for long-term use just due to the accumulative neurotoxicity. They also note that oral vancomycin is the drug of choice for initial episode when there's a severe case of C. diff. In 2015 the recommendations also addressed trichomoniasis and the treatment guidelines there state that a single oral dose of either metronidazole or tinidazole could be used. And also they recommended that an alternative regimen of metronidazole 500 mg orally twice daily for seven days could be used if the single oral dose of 2 grams could not be tolerated. And then in 2014 the American Gastroenterological Association guidelines on the treatment of IBS recommended Xifaxan and loperamide over no drug treatment at all for the treatment of IBS-D. When looking at a meta-analysis in patients with C. diff it concluded that the drug in the review anyway, that vancomycin was found to be slightly more effective than metronidazole for achieving symptomatic cure and that Dificid was found to be more effective than [inaudible] for achieving symptomatic cure. I'll go ahead and stop there.

Leta Evaskus: There are no stakeholders.

Michael Johnson: There are no stakeholders, but there is a question.

Nancy Lee: Hi Stephanie, this is Nancy. A question about the meta-analysis. Did they include vancomycin in the form of a liquid formulation rather than a capsule?

Stephanie Christofferson: I would have to go back and look. I don't know if the literature I read specifically addressed what formulation it was.

Nancy Lee: Is there a liquid formulation of vancomycin?

Stephanie Christofferson: My research says that it is just capsules at this time.

David Johnson: There's a commercial compounding kit from First… from [inaudible].

Stephanie Christofferson: Okay. It's a compounding kit one?

David Johnson: Yes.

Michael Johnson: I think that the liquid form is what most people use for cost reasons, in our area at least. Any other questions? All right, Stephanie, you can go ahead and continue.

Stephanie Christofferson: Okay. Next we're on the acne agents. So there are, of course, several different products that can be used for the topical treatment of acne. Some products have additional FDA approved indications such as Tazorac, which can be indicated… or is indicated for the treatment of plaque psoriasis and then sodium sulfacetamide sulfur products have an additional indication for the topical treatment of acne rosacea and seborrheic dermatitis. And then sodium sulfacetamide is also indicated for seborrheic dermatitis, seborrheic sicca and treatment of secondary bacterial infections of the skin. There are several different products, of course, to choose from when treating acne and as you can see from the second column most of them have a generic available. In 2016 the FDA did approve Differin 0.1% gel for the treatment of acne without a prescription. I also wanted to mention pediatric usage of the medications since this condition is often times present in the younger population. Benzoyl peroxide the NuOX has been approved for patients as young as 6 years of age. Atralin or tretinoin has been studied in children as young as 10 years of age and then Epiduo has been studied in children as young as 9 years of age. The rest of the products, the safety and efficacy has not been established in patients less than 12. Next slide, please.

That just rounds out the rest of the products available. Next slide.

This looks at the dosage and formulations. The adapalene, tretinoin and the tazarotene products are applied once daily. Of the other products available they can be applied anywhere from

up to one to three times daily. Again, there are a wide variety of product formulations available as you can see in the chart and of course I won't go through all of those, but I'm sure most of you are familiar with what's available. Next slide, please.

This just looks at the rest of the products that are available. Next slide, please.

There are no new guidelines for the topical treatment of acne. The most recent guidelines that we have are from the American Academy of Dermatology and they were published back in 2016. These guidelines recommended benzoyl peroxide or combinations with erythromycin or clindamycin for mild acne or in conjunction with a topical retinoid or a systemic antibiotic if the acne is severe. The guidelines were also updated during that time to include topical dapsone 5% gel as a recommendation for inflammatory acne, which was particularly addressed in the female population. For pre-adolescent acne in children, topical adapalene, tretinoin and benzoyl peroxide were recommended in these guidelines. And the guidelines also state that the topical retinoids play a key role in monotherapy for comedonal acne or as a combination therapy with other topical or oral antimicrobials. Overall, the guidelines recommend combination therapy with different agents that have different mechanisms of actions to target acne pathogenesis in the majority of patients. They also state that evidence of sulfur, nicotinamide, [inaudible], sodium sulfacetamide, aluminum chloride and zinc use for acne treatment is actually limited. Next slide.

This will address the oral antipsoriatics. The first slide looks at the indications of the products and their indications. So for mild to moderate psoriasis it is generally treated with topical agents and phototherapy can be used when the disease is wide spread or unresponsive to topical agents. And then for the systemic agents, as listed here, are usually reserved for patients with moderate to severe disease or in those with psoriatic arthritis. Options for systemic therapy include methotrexate, cyclosporine, retinoids, biologics and the methoxsalen plus UVA radiation. I did want to

note that acitretin is a potent stratagem and carries a black box warning and should not be used in women of child-bearing age or potential. It's contraindicated for use in females who are pregnant or who intend to become pregnant during therapy for a three-year period after therapy. There have been major human fetal abnormalities associated with this use. So when prescribers use the medication they have to have a signed patient agreement, informed consent form, for those patients discussing the risk of birth defects and contraception that should be used and so on. Also of significance with the products is on methoxsalen is that patients should wear UVA absorbing wraparound sunglasses for 24 hours following therapy in order to allow the medication to diffuse out of the limbs. For people wear proper eye protection evidence has shown that there is no significant increase for the risk of cataract development resulting from therapy. Patients who do not wear the protective eyewear they do have an increased likelihood of developing cataracts as the medication may irreversibly bind to proteins and DNA within the lenses. I also wanted to mention on the methoxsalen hard gelatin capsules that they are not interchangeable with the soft gelatin capsules without re-titration of the patient. The soft gel capsules actually produce a significant… a significantly greater bioavailability and quicker for those senses of [inaudible] at the onset… onset time than the hard capsules do. Next slide.

This looks at the dosage and formulation. Soriatane is dosed once daily and is available in gels and capsules and methoxsalen is dosed prior to UV therapy and is weight-based dosing. Again, it is available in either a hard or a soft gelatin capsule. Next slide, please.

There are no new updates, but in the American Academy of Dermatology published guidelines for the management of psoriasis with biologics back in 2008 and then in 2009 they published guidelines with traditional systemic therapies and then in 2010 they published guidelines for phototherapy and photochemotherapy. The 2009 AAD systemic therapy guidelines for psoriasis note that acitretin, methotrexate and cyclosporine

have been used for the treatment of psoriasis for many years with good to excellent results. But that acitretin is the lease effective product as monotherapy, which is why it is often used in conjunction with UVB or Soriatane plus UVA phototherapy. Next slide.

This is the antipsoriatic agents, topical. The first slide takes a look again at the indications and the focus of the review for this particular section will focus on non-steroidal topical agents that have been developed and have demonstrated efficacy in managing psoriasis. Of course therapies for psoriasis are not curative, but they are rather symptomatic management. As you can see from this first slide, most of the products, or many of the products are available generically and nearly all the medications have an indication for plaque psoriasis and then to a lesser extent psoriasis of the scalp. I also want to mention that recently Tazorac… pregnancy classification was redone in order to comply with the pregnancy and lactational updated labeling advised us that product is contraindicated during pregnancy and that women of child-bearing potential should have a negative pregnancy test within two weeks prior to using the product and use adequate birth control during therapy. Previous to the labeling change it was considered a pregnancy category X. Next slide, please.

This slide looks at the application frequencies of the product. Most agents are applied once daily, but calcipotriene and calcitriol are applied twice daily which could impact compliance when dosing patients. Tazorac and the calcipotriene/betamethasone combination product are also indicated in children. The Taclonex ointment or suspension is actually not recommended for treatment when the area is greater than 30% of the body surface area in adults or adolescents. In clinical trials, Enstilar, which is the calcipotriene/betamethasone combination foam did not include patients with an affected DSA greater than 30%, which again might be a consideration when prescribing products. And the very last column you can see there are several different formulations available that prescribers can choose from when making decisions for their patients, but, again, things to keep in

mind or prescribers should keep in mind when selecting a product is disease severity, location, product tolerability and also patient response. Out of all of the different formulations available the ointment has been theorized to be the most effective vehicle for psoriasis due to the collusive nature and moisturizing capabilities. However, there is no proof for that. It's antidotal, but the preference could be low since… in patients just because of an oil-based compound and it is greasier or messier than other choices that are available for the treatment of psoriasis. Next slide, please.

There are, again, no new guidelines. There were guidelines in 2011 that were developed by the American Academy of Dermatology, which indicated that approximately 80% of patients impacted by psoriasis have mild to moderate disease and can be managed with topical agents. The guidelines do state that topical corticosteroids remain the cornerstone of therapy for patients with mild to moderate disease despite the development of newer agents. However, due to the short duration of treatment with the topical corticosteroids and the risks involved with long-term use, they are not considered the first choice… first drug of choice for long-term management of psoriasis and then also the guidelines noted that psoriasis can become resistant to the corticosteroid therapy. So with the guidelines from the AED… AED recommended that the choice of therapy should be based on the individual taking… be based on the individual taking into consideration, again, tolerance, adherence, and adverse effects. Topical therapy should be used in patients with mild to moderate disease and that systemic therapy should be used in patients with severe disease. The guidelines do go further on to say that calcipotriene can be as effective as corticosteroids in some patients and there's evidence that mild to moderate psoriasis is improved when calcipotriene is combined with a topical corticosteroid. I'll go ahead and stop there.

Michael Johnson: There are no stakeholders. Are there any questions from the committee? I think we can continue with the skeletal muscle relaxants then. There are no stakeholders for that topic either.

Stephanie Christofferson: Okay. Sounds good. So the first slide takes a look at the indications. The skeletal muscle relaxants are FDA approved basically to treat two different types of conditions either muscular pain or spasms from peripheral musculoskeletal conditions and then also spasticity from upper motor neuron syndromes. For those conditions, the latter, those medications include baclofen, dantrolene and tizanidine. I did want to mention that dantrolene labeling does have a black box warning regarding a potential for hepatotoxicity. The risk of dantrolene induced hepatotoxicity was… can sometimes be fatal. It appears to be greater in females, patients who are over the age of 35 years old, patients who have multiple sclerosis and then patients that are taking other drugs concurrently; especially estrogen. They also note that the incidence of hepatotoxicity with doses greater than 400 mg per day is higher. Next slide, please.

This looks like the dosage and formulation. Most of the medications, as you'll see here in the second column, are dosed multiple times per day with the exception of the cyclobenzaprine ER, which is dosed once daily. All the medications, again, with the exception of the cyclobenzaprine ER or the Amrix is available generically in which case Amrix is the only product that is brand only. Most of the medication are available in brand… I'm sorry, in tablets or capsule formulation. Next slide, please.

As far as MS there are no recent guidelines that have been published. The National MS Society still recommends that baclofen or tizanidine be used over dantrolene and that dantrolene really is generally used only if the other drugs have not been effective. Again, due to those serious side effects that we mentioned. As far as like pain, the American College of Physicians did release some guidelines in 2017 for lower back pain and they broke it down into two different types—acute or subacute low back pain or chronic low back pain. For acute or subacute low back their guidelines indicate that there is moderate quality evidence that the muscle relaxants improved short-term pain relief compared to placebo after two to seven days and that there

is low-quality evidence that showed no difference between the different skeletal muscle relaxants for any of the outcomes in patients with the acute pain and also that there is low quality evidence showing that there were inconsistent findings for the effect on pain intensity in the combination with a skeletal muscle relaxant plus an NSAID compared to just an NSAID alone. For chronic low back pain the guidelines stated that evidence comparing skeletal muscle relaxants versus placebo was insufficient and then there was low quality evidence showing no differences in any outcome between different skeletal muscle relaxants for treatment of chronic low back pain. They recommend that the choice between an NSAID or skeletal muscle relaxant be individualized on the basis of patient preferences and the likely individual medication risk profile. The guidelines stated that treatment with skeletal muscle relaxants resulted in a small improvement in pain relief. I'll stop there if there are any questions.

Michael Johnson: I see no questions. I think that is all for you, Stephanie. Thank you and have a wonderful holiday season.

Stephanie Christofferson: You too. Thank you so much. Happy holidays!

April Phillips: So with this recommendation we're editing it kind of like the other one, too. This is what happens when you copy and paste or don't. Okay. So our recommendation is that all products are considered… within each class or subclass are considered safe and efficacious within that class or subclass and are eligible for preferred status at the discretion of HCA. We also recommend that all non-preferred products require a trial of two preferred products within the class or subclass with the same indication or active ingredient… and active ingredient… oh, different active ingredient before a non-preferred product will be authorized unless contraindicated or clinically inappropriate.

Nancy Lee: I just wanted to… I looked at the PDL and it looks like one of the ones… the skeletal muscle relaxant Soma was the one that kind of came to mind and I saw the PDL and I would like to note that I

would like to continue to have Soma as requiring a PA and not be considered… due to concerns for safety reasons.

Donna Sullivan: We intend to do that.

Amber Figueroa: I move that the Apple Health Medicaid Program implement the limitations listed on slide 86 for each drug class listed on slide 85 as recommended.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. I think that concludes…

Leta Evaskus: I would like to say thank you to Michael and to Po for your time on the P&T Committee and DUR Board. It is much appreciated.

[applause]

Michael Johnson: All right. Thank you and happy holidays to all. Safe travels – especially if you're heading south.