Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board Special Meeting
October 18, 2017

Michael Johnson: It's 9 a.m. We're going to go ahead and get started. Welcome to the Washington State Pharmacy and Therapeutics Committee. Just a reminder this is a recorded meeting. So before speaking, please introduce yourself at the mic. At this time we're going to do introductions starting on my left. State your name and function.

Petra Eichelsdoerfer: Petra Eichelsdoerfer, pharmacist manager for Washington State United Healthcare.

Yusuf Rashid: Yusuf Rashid [inaudible].

Dave Johnson: Dave Johnson, Molina Healthcare.

Jaymie Mai: Jaymie Mai, Labor and Industries.

Nancy Lee: Nancy Lee, committee member.

Susan Flatebo: Susan Flatebo, committee member.

Dale Sanderson: Dale Sanderson, committee member.

Jordan Storhaug: Jordan Storhaug, committee member.

Catherine Brown: Catherine Brown, committee member.

Michael Johnson: Michael Johnson, committee member.

Lisa Chew: Lisa Chew, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Po Karczewski: Po Karczewski, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Charity Harris: Charity Harris, Health Care Authority.

Michael Johnson: Thank you and welcome. Again, this meeting is going to be a little bit different than prior meetings. We have multiple presentations and Ryan will give us this update.

Ryan Pistoresi: Great. Thank you for that. I would just like to start to say, you know, we've been making a lot of changes, especially with the legislation for the single PDL and so as we've been adapting to some of these new processes we've had to change how these P&T meetings have function. So the last few meetings we've mainly focused on implementing the single PDL and getting a few of those drug classes reviewed. But at this meeting we're bringing back in UMP and L&I, the two other agencies that have traditionally participated in the P&T. So there will be a few different things about this meeting than what we've had in the past few meetings, as well as versus the previous meetings. For these meetings we'll begin each drug class review with the Magellan Review and then have a short Q&A for the presenter. Then we'll be going into the DERP, the presentations from DERP. However, because the DERP annual meeting is during this week there will be no live presenters, but we have arranged for recordings. So DERP will be presented by a recording and if you have questions for DERP I'd be happy to take them down and then ask them and get them back to you after the meeting.

Then after that we'll move into stakeholder comments and then we'll have two sets of motions, one for the Medicaid program and a separate motion for the UMP and L&I programs. So since this is a new process for everyone it may be a little bit rough to start, but we

hope that this process will work as we kind of see this moving forward. And if you have any questions or any suggestions I'd be more than happy to hear it and take your feedback into consideration for our next meeting. So with that I think we can begin the first.

Stephanie Christofferson: I'm here. Can everyone hear me?

Leta Evaskus: Yes. We have the slides up.

Stephanie Christofferson: Okay. Great. I'll take a second and introduce myself. My name is Stephanie Christofferson and I'm a clinical account manager with Magellan and I'm here today just to present the four different classes that we'll be discussing; just a quick clinical overview of each of the different therapeutic disease states and medications associated with them. With that said I'll first start with the platelet inhibitors.

Our first slide that we'll be talking about is just a quick overview of the disease state. So the 2016 heart disease stroke statistics actually site that cardiovascular disease causes approximately 31% of all deaths in the United States. The good news, however, is that death rates attributable to the cardiovascular diseases have decreased approximately 29% in the 10-year period that was examined. This was from 2003 through 2013. But as you know stroke also causes a significant number of deaths and morbidities in the U.S. and is actually the fifth leading cause of death behind heart disease, cancer, chronic lower respiratory disease and access. So the inhibitory effects on platelet aggregation have led to a significant decrease in the rate of vascular events for both primary and secondary cardiovascular prevention trials. Aspirin has actually shown to reduce cardiovascular morbidity and mortality in both the primary and secondary prevention trials. And as you'll see when we go through many of these medications is actually… in many of the combination products that we'll discuss today. However, there was a small percentage of patients with cardiovascular disease that do have aspirin resistance and so therefore maybe at higher risk for cardiovascular events. However, guidelines through the management of aspirin-resistance have not yet to be developed. So other antithrombic drugs have

been developed to improve platelet aggregation and to improve the safety profile of platelet aggregation inhibitor therapy. Next slide.

Next we'll talk briefly about the FDA approved indications. The first slide here, this discusses the three different aspirin products that are available or aspirin combination products. I'm not going to read through all of the indications. I assume most of you know them already, either that or have received these slides ahead of time and were able to review them. But some newer products Durlaza, it's an aspirin, but is an extended release product. However, the medication should not be used in situations where a rapid onset of action is required such as the treatment of acute MI or prior to a PCI therapy. However, once it is absorbed the pharmacokinetics of the medication are similar to the immediate release aspirin products. It's just that the time to maximum concentration with the extended release product is delayed by approximately one hour compared to the IR product. And then also I just want to touch base on a newer product, Yosprala. This is actually a combination product with aspirin and omeprazole and it would be a good product perhaps for persons or patients who are unable to take aspirin or who… just because of the GI side effects or maybe they are at risk for gastric ulcers. Next slide.

This next slide talks about many of the products that are used for anti-platelet therapy and are in most of the guidelines as far as recommendations. Again, I won't read through all the indications, but I will point out some of the more notable items or issues on the products. One thing, Plavix on the clopidogrel widely used medication but one major thing to consider with Plavix is the patient responsiveness to the medication. This can be due to the variability and platelet response either due to adenosine diphosphate, genetic variability and then it does contain some more notable drug interactions; most notably with the PTIs namely omeprazole and esomeprazole. So with clopidogrel how it works, clopidogrel is converted to its active form by the CYP2C19 enzyme. Patients sometimes can have a variance to this enzyme and be poor metabolizers to the drug where they do not effectively convert clopidogrel to its active form, which also of course makes the medication most effective on platelets. So it is less able to prevent

against MI strokes and cardiovascular death. The maximum concentration can actually decrease anywhere from 30 to 50%. So in patients where they might be at moderate to high risk for poor outcomes or also the Asian population, since they seem to have more prevalence of having these issues is that they… the guidelines recommend genetic testing be considered before starting therapy. Then also for… I want to note that on ticagrelor or Brillinta it does have a more rapid onset of action than clopidogrel and then both ticagrelor and prasugrel they can also result in more intense platelets inhibition compared to Plavix. And they are also not as likely to interact with the proton pump inhibitors, which of course may be a consideration when prescribing the medication to patients. And then lastly for Zontivity, which is a newer product, if you read the guidelines the place for therapy has not yet been clearly established or fully addressed in the guidelines. However, the medication has demonstrated benefits, especially in the stable post MI population without risk factors for bleeding. Next slide.

Next we'll just talk about dosing and formulations. As you'll notice within these slides there are different frequencies for dosages for the medications. You've got anywhere from once-a-day therapy to four-times-a-day therapy. You're once-a-day therapies include the Durlaza, Yosprala, Plavix, Efficient and Zontivity. Twice-a-day dosing includes Aggrenox and Brillinta and ticlopidine. And then lastly dipyridamole can be dosed up to four times daily. All of the formulations are available in either a tablet or capsule formulations. However, I did want to note that Brillinta might be used for patients who are unable to swallow as it may be crushed and mixed in water and either then drank or if a patient has an NG tube, it could be administered that way too. Also to highlight is the Aggrenox and Yosprala are not interchangeable with their individual components. So that again might be something to keep in mind. There are some generics available within these medications including Aggrenox, Plavix, dipyridamole and ticlopidine. And then one other thing I wanted to point out is that with Brillinta or ticagrelor the daily maintenance doses of aspirin should not exceed 100 mg daily just because that increased dose of aspirin can decrease the effectiveness of ticagrelor. Go ahead and skip to the next slide.

Again, this just finishes off the dosing and formulations of those last products. And then we can go to the clinical considerations and guidelines.

So I wanted to touch base on the mechanism of action. Within these products there's actually four different mechanisms of actions available. First with the Durlaza and Yosprala those are cyclooxygenase inhibitors and they inhibit the generation of [inaudible] 82, which is a powerful inducer of platelet aggregation and [inaudible] construction. The next one is dipyridamole which is a phosphodiesterase inhibitor. It works by increasing interplatelet [inaudible] 35 adenosine monophosphate levels, which is a platelet inhibitor and by inhibiting that… the [inaudible] 3A adenosine monophosphate levels the degradation of that and then it works on the platelets and… by not allowing them to uptake any of the adenosine into the platelets endothelia cells or the [inaudible] sites. Then the next is the ADP or the adenosine diphosphate receptor antagonists. For these simply put these are medications they call P2Y12 plate inhibitors and they inhibit the platelet action by irreversibly binding to plate ADP receptors and prevent platelet aggregation and activation. And then finally these Zontivity, again, a newer product is a reversal antagonist of the [inaudible] activated receptor 1. It inhibits thrombin-induced and thrombin receptor agonist peptide-induced platelet aggregation.

On the next bullet we discussed already the CYP2C19 issues and then again that was just the patients who poorly metabolize the clopidogrel into its active forms of having the Plavix work less in the patients. Again, patients of Asian descent being the most susceptible patient population that that can take effect on. Also I wanted to mention box warnings. Again, we've already touched base on the Plavix. That has a boxed warning with the metabolism to the active metabolite. Ticlopidine has been associated with severe hematologic effects which have limited its use and then [inaudible] and Brillinta do have a black boxed warning for increased bleeding. Next slide.

For pregnancy considerations Plavix, ticlopidine and Zontivity have a category B. Brillinta is a category C, and then Aggrenox is a D. Yosprala has not actually been categorized, but data on omeprazole has not reported a clear association with birth defects or miscarriage. I did want to note that previously Effient was assigned a pregnancy category B, however, it's labeling has been updated for compliance with the pregnancy and lactation labeling rule, which states there is no data with use in pregnant women to inform of a drug-associated risk. For pediatrics the safety and effectiveness has not been established for most of the medications in this therapeutic class with the exception of dipyridamole being used in patients 12 years of age and older and aspirin. And then according to the 2012 ACCP evidence-based guidelines they do state that aspirin remains the most common antiplatelet used in the pediatric population and then a second line therapy of aspirin cannot be used dipyridamole has been used. But there's relatively little literature reading dipyridamole in pediatrics. For geriatrics no dosage adjustments are needed for most of the products. However, Efficient is not recommended in patients 75 years of age and older. And then just in general additional monitoring may be needed in this patient population just due to their greater sensitivity to the products. Next slide, please.

The guidelines that I'll review today in this therapeutic class as well as any other, I'm really only going to try to concentrate on presenting guidelines that have been updated within the last year just really due to time constraints. The first one that we'll touch base on is the primary prevention of cardiovascular disease, which has been updated in 2016. They do recommend low dose aspirin in adults from the ages of 50 to 59 years of age who have at least a 10%, 10-year cardiovascular disease risk. Also have no increased risk of bleed. They do have also a life expectancy of at least 10 years and they are also willing to take aspirin for at least 10 years. The same guidelines really apply to patients age 60 to 69, as well, with the caveat they just say they are most likely to benefit. And then patients that are less than 50 or older than 70 the data has stated or come back that it is inconclusive as far as the benefit of a daily low dose aspirin. For the acute coronary syndrome treatment and prevention this is also… there's some updated guidelines. In 2016 it really is surrounding the

use of dual antiplatelet therapy. So to touch base on that we kind of have to go back to some of the… what the previous guidelines are. So the 2014 guideline recommends that non [inaudible] aspirin, the chewable, should be given to all non-ST elevation acute coronary syndrome patients without contraindication to aspirin after they present. And then afterwards a maintenance dose of aspirin be continued indefinitely. Individuals who are unable to take aspirin it is recommended that a loading dose of Plavix be used and then a maintenance dose used thereafter. In 20016 ACC and the AHA published guidelines, again, specifically regarding the dual antiplatelet therapy in a wide variety of cardiovascular conditions. In these guidelines it states in all cases where aspirin is used as dual antiplatelet therapy they continue to recommend 81 mg of aspirin daily of maintenance dose. And then patients on dual antiplatelet therapy who are undergoing surgery should really continue to have aspirin. However, if it needs to be discontinued they do recommend it be started as soon as possible after surgery.

The guidelines further state for platelets with… I'm sorry, for patients with anterior MI or… and left ventricular thrombosis or at high risk for left ventricular thrombosis who do not undergo stenting the 2012 ACCP guidelines recommend Warfarin and aspirin for the first three months and then a dual antiplatelet therapy with aspirin plus Brilinta or clopidogrel for up to 12 months afterwards. And then after 12 months they recommend a single antiplatelet therapy with aspirin or clopidogrel. And then the 2016 ACC AHA dual antiplatelet therapy recommendations they also either recommend clopidogrel or Brilinta in combination with aspirin and they also recommend that the duration be for at least 12 months.

The 2013 American College of Cardiology Foundation and the AHA guidelines for management of patients with stemi, they recommend a loading dose of a P2Y12 plate inhibitor for patients with stemi who are going to undergo the PCI in addition to aspirin. The guidelines also recommend the aspirin prior to the PCI and then after the PCI indefinitely. The guidelines also recommend that the use of Effient or Brilinta as alternatives to clopidogrel as needed. Those agents should also be given as a loading dose as early as possible to patients with

stemi or at the time of the PCI. And then after the placement of a drug-eluding stent or a bare medal stent they recommend dual antiplatelet therapy with aspirin indefinitely and a P2Y12 plated inhibitor for at least 12 months.

The 2016 Dual Antiplatelet Therapy Guidelines also recommend this, but with the caveat that it is reasonable to use Brilinta over clopidogrel as a maintenance therapy. And they do also note that in stemi patients with a prior history of stroke or TIA for whom primary PCI is planned Prasugrel is not recommended as part of dual antiplatelet therapy regimen.

For peripheral artery disease the 2016 AHA ACC guidelines state that aspirin alone either from 75 to 325 mg per day or clopidogrel is recommended to reduce the risk of MI stroke and cardiovascular death in patients with symptomatic peripheral artery disease, but the data on the effectiveness of dual antiplatelet therapy in pulmonary artery disease with both aspirin and clopidogrel are limited, but it may be considered in select high risk patients. As far as use of Zontivity in this therapy… or in pulmonary artery disease the guidelines do note that it's just uncertain right now.

That concludes the brief overview of the medications in the class along with some of the guidelines that have come out or updates to existing guidelines within this last year. So at this point I'll open it up to any questions.

Michael Johnson: I see no questions from the committee. Thank you.

Marian McDonagh: I'm going to present the antiplatelet drugs most recent targeted update. It was completed in July 2017.

The key questions are listed here and they are, as usual, our two questions on effectiveness and harms – do the antiplatelet drugs differ. Then a question on any differences based on subgroups. And then lastly a question on the duration of antiplatelet therapy. Next slide.

The search dates for this report go through April of last year and the drugs are listed there and we note that in targeting this to narrow the scope we did a few things like excluding ticlopidine, which is no longer used very often, if at all due to safety concerns. And cangrelor which is an injectable drug only. We narrowed to head-to-head studies only so we're really focusing on the drugs versus each other. So aspirin comparisons are no longer included in the report. There is an appendix in the report that includes information on the studies that did compare these drugs to aspirin. Next slide.

This is an overview of the findings. We had 26 studies included in this update. There are a lot of secondary publications for these studies. There are very large studies so they do tend to have a lot of secondary analyses that get published later. So all of the comparisons that we were able to find studies on are listed here. Most of the evidence in this report is new, as you can see. The underlying studies are new so there is just a few that were in the previous report. So most of these studies had more than 10,000 patients and a few more than 20,000 even almost 25,000 patients and they were pretty good quality. Not all that many were good quality, but fair and good. Mostly always the primary outcomes measures in this trials are a composite measure of three to four cardiovascular outcomes. So you'll see that noted. We also report individual outcomes where they are reported separately. So for example MI or cardiovascular death reported separately to the composite. So let's move on to the findings.

If we go to slide 4, this is our first comparison. So vorapaxar is a drug that is used in addition to other antiplatelet drugs. So it's an add-on treatment. So for patients with baseline atherosclerosis this is a very large trial. The TRA 2P-TIMI 50 trial with over 26,000 patients. Here there are some curious findings. So in patients with prior ischemic stroke not only was there no increased benefit, so no reduction in cardiovascular outcomes, but there was a pretty important increase in intracranial bleeding, which led to a black box warning against using this drug in patients with prior ischemic stroke. Looking at patients who had MI or coronary artery disease at baseline they did have a reduction in the composite of cardiovascular death, MI or

stroke. The rates for those were 7.9% versus 9.5% in the placebo group. But there was increased moderate or major bleeding and that was reported as a combined outcome and so 3.7% versus 2.4%. The results of the analyses also showed that if you were a smaller patient less than 60 kilos there was not a statistically significant benefit whereas for those over 60 kilos there was a significant benefit. So then looking at a separate study, the TRACER trial, 13,000 patients with acute coronary syndrome, there's no benefit on the composite outcome that was used for the primary outcome, but there was increased major bleeding and also adverse event withdrawals with vorapaxar. So our confidence in these findings is low because both of these studies were stopped early for safety concerns.

Now we'll look at the comparison of ticagrelor versus prasugrel. So here we're looking at… the first study is in patients with acute coronary syndrome who were undergoing primarily stenting, but percutaneous coronary interventions. Two smaller studies here that found no significant differences in either effectiveness or bleeding in the short term. However, then there's a large good quality observational study that reported lower rates of net adverse clinical events, major adverse cardiac events, and major bleeding as a composite with prasugrel at 30 days, but not at 90 days. So at 30 days the rates were 6.5% versus 8.4%. So the evidence is somewhat conflicting there since the two trials were smaller trials compared to the 10,000 and above sizes that we see with the other comparisons and also shorter term. So we find this evidence to be insufficient to draw conclusions.

If we move to slide 6 we're looking at the comparison of ticagrelor versus clopidogrel. So this is looking at the PLATO trial. It was a large trial, 18,000 plus patients with acute coronary syndrome and here there were fewer cardiovascular deaths, MIs or strokes as a composite and then separately cardiovascular deaths with ticagrelor. The rates on those were the composite outcome, the rate with ticagrelor was 9.8%. The incidence, I should say versus 11.7% in the clopidogrel group. And for cardiovascular deaths it was 4% versus 5.1%. Now bleeding was similar here. So not a significant difference in major bleeding, but adverse event withdrawals due to other kinds

of side effects was actually greater with ticagrelor at 7.4% versus 6%. Now this study had some controversy in the pre-planned subgroup analysis. This was a study that was done around the world and there was a pre-planned analysis to look at the North American subgroup, which was pretty small, you know, 10% of the overall population. But this subgroup did not have a greater benefit from ticagrelor. There was no significant difference between the drugs. And although the difference… they could be due to chance particularly with the much smaller subgroup and further analysis so a post hoc analysis looking at only the U.S. patients in the North American group found that U.S. patients were really the problem. They were the ones causing this difference in the overall finding and that if you limit the analysis to those in the U.S. who were taking low-dose aspirin rather than high-dose that the overall findings were consistent. So pretty much if you're taking higher doses of aspirin in the United States setting then you're not going to see a benefit of ticagrelor over clopidogrel. But if you're taking the recommended low-dose the findings are consistent. This study found that patients with lower weight or who were not taking a lipid-lowering drug, primary statins, did not have a significant benefit from ticagrelor. So our findings in these… our confidence in these findings is low. Next slide.

This is ticagrelor versus clopidogrel continued, but this is looking at patients with peripheral artery disease. And this is the EUCLID trial again, close to 13,000 patients. Here there is no difference in the cardiovascular death, MI or stroke or in the adverse event the outcome of major bleeding. Our confidence in these findings is high. The stroke incidence was significantly lower with ticagrelor at 1.9% with ticagrelor versus 2.4% with clopidogrel. There was no difference found in MI, CV deaths, cardiovascular death or all-cause deaths as individual outcomes. Significantly more patients discontinued ticagrelor due to adverse events though as we saw in the previous slide. And in this study the rate was 15.4% versus 11.1%. So other kinds of adverse events primarily gastrointestinal were causing these discontinuations. Next slide.

Prasugrel versus clopidogrel. This is our next comparison. So the TRITON-TIMI 38 trial, again 13,000 patients and then separately the

PRASFIT-ACS trial with just 1,300 patients examined patients with acute coronary syndrome who were, again, undergoing PCI. Fewer patients had major adverse cardiac events here. So 11.6% versus 13.7%, but there was more major bleeding with prasugrel at 2.1% with prasugrel and 1.7% with clopidogrel. So differences were not found in the individual outcomes of all-cause mortality or cardiovascular mortality or in adverse event withdrawals. However, the subgroup analyses found that patients with a prior stroke or TIA had net harm with prasugrel. And also patients… smaller patients weighing less than 60 kg had no benefit from prasugrel over clopidogrel. So our confidence in these findings is high for the primary outcome and moderate for mortality outcomes. And then our confidence in the adverse event findings is low. Next slide.

Now we're looking at the comparison of… the combination product of dipyridamole extended release with aspirin compared with clopidogrel. This was looking at the prevention of ischemic stroke, a recurrent ischemic stroke and this was in the previous report. This is the PRoFESS trial with 20,000 patients. So there were no differences found in recurrent stroke, or secondary cardiovascular outcomes or in major bleeding. So those are the findings. The hazard ratio confidence intervals are pretty close to 1. So the difference here is pretty small and [inaudible] borderline. So it could be different if additional studies were done. So more patients withdrew from this study due to adverse events with dipyridamole with aspirin in comparison to clopidogrel. That was 16.4% versus 10.6%. Separately there was a network meta-analysis published that used 38 trials of dipyridamole with aspirin versus clopidogrel. So this is using an indirect analysis approach. 142,481 patients were included in this analysis and the network analysis supports the findings of the PRoFESS trial with no difference in the primary outcomes including ischemic stroke and major bleeding. For our confidence putting these two together, our confidence in the findings for benefits and adverse events for withdrawals is high, but again low for bleeding. Next slide.

Ticagrelor compared with aspirin in patients experiencing stroke. If patients have had a very recent ischemic stroke or were high risk for TIA they were enrolled the SOCRATES trial with little over 13,000

patients. Differences were not found in stroke, MI or death. That's a composite outcome with 6.5% in the ticagrelor group and 7.2% in the aspirin group. There was also no difference in recurrent ischemic stroke or in major bleeding. Patients on ticagrelor were significantly more likely to withdraw due to adverse events. However, with 9.7% in the ticagrelor group versus 7.1% in the aspirin group. So our confidence in these findings is moderate for benefit, low bleeding, and then high for adverse event withdrawals. Next slide.

These are our conclusions. To recap everything we just talked about. So differences between the drugs were mostly not found. So there are few places where you can see clear differences and where they were found, even if they are statistically significant, the absolute event differences are pretty small, less than 1% to about 2% difference. In two cases with differences in benefit there was actually more bleeding. So those were vorapaxar in patients with prior MI or coronary artery disease and the difference between prasugrel and clopidogrel in patients with acute coronary syndrome who were undergoing percutaneous coronary interventions. And the only case of benefit with no increased harm, with was ticagrelor over clopidogrel in patients with acute coronary syndrome. A reminder that the patients in the U.S. had different outcomes than only those with low-dose aspirin had the same benefit. There were a higher number of patients in that subgroup taking higher doses of aspirin than there were in other countries. So other sites around the world. So there were more adverse event withdrawals with ticagrelor than clopidogrel or aspirin, and with dipyridamole extended release combined with aspirin than with clopidogrel. Findings of decreased benefit with lower body weight may indicate a need for weight-based dosing for vorapaxar, ticagrelor and prasugrel. That concludes the presentation of our findings in the most recent update of the antiplatelet report.

Michael Johnson: For this topic there are no stakeholders.

Leta Evaskus: Did any stakeholders come in after I took in the sign-in sheet? Did anybody want to speak? Okay. Thank you.

Michael Johnson: So with that I think we will look at a motion.

Amber Figueroa: I just wanted to make a comment since Marian is not here to talk about her presentation, but she's… when it talked about adverse event withdrawal due to side effects with ticagrelor in a couple of those studies she mentioned on the second one that it was due to GI, but I did look it up and it says greater than 10% experienced dysemia at 13.8% and then bleeding. The 1 to 10% category is a bunch of generic stuff including nausea and diarrhea, abdominal pain not being in there. I had looked it up and maybe somebody else had the same question I did.

Ryan Pistoresi: Would you like me to then raise that question with them and see if we can get a response after the meeting?

Amber Figueroa: [inaudible]

Ryan Pistoresi: Okay. Thank you.

Amber Figueroa: I think what we reviewed last year… I think it all seems fairly consistent with the information that we've reviewed today. Anybody have any other thoughts?

Michael Johnson: I would agree. I don't think there is any new information that would change what we did last time. Any other thoughts from the committee?

Amber Figueroa: After considering the evidence of safety, efficacy and special populations for the treatment of acute coronary syndrome, percutaneous coronary intervention, and peripheral vascular disease, I move that clopidogrel, ticagrelor and prasugrel are safe and efficacious for the treatment of their approved indications. The antiplatelets cannot be subject to therapeutic interchange in the Washington PDL. At this time vorapaxar is included on the PDL as a non-preferred drug. Shall we split them up again or do it all together? Keep going? Okay.

After consideration… after considering the evidence of safety, efficacy and special populations for the treatment of stroke and transient ischemic attack, I move that extended release dipyridamole aspirin and clopidogrel are safe and efficacious. Extended release dipyridamole aspirin and clopidogrel cannot be subject to therapeutic interchange in the Washington PDL for the treatment of stroke and TIA.

I move that ticlopidine products not be put on the PDL due to safety concerns.

Jordan Storhaug: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Great. The motion passes. This gets us to April.

April Phillips: Yes, this is April. So this is where it gets a little different. This part is for the Apple Health PDL and so the recommendation is going to be similar to what you have on the Washington PDL. We might want to change the wording on that a little bit. For the preferred products… or the products to be considered safe and efficacious and that… because I have not created a preferred product list at this time since implementation of this particular class for the Apple Health will not be for a while. We wanted to make the selection of the preferred products a little closer to implementation so we can select the products that are most cost-efficient and with the less harm to the clients that are currently taking the medication at that time. So I don't have preferred products selected at this time. So all of our recommendation is… if the committee feels that they're all comparable then we will make the preferred selection at HCA's discretion and for non-preferred products you need to try and fail all or up to two. So if there is only one then they just try one, but if there are three they only need to try two of the preferred prior to a non-preferred being selected.

Michael Johnson: Just for clarification. So what we just stated for the P&T like, you know, if one is considered not safe or if we say that shouldn't be put on the PDL does that follow suit?

April Phillips: We can change the recommendation on this slide to follow that if that's what the committee agrees with.

Ryan Pistoresi: So just more of a point of clarification, what the first motion is, is more for UMP and L&I in terms of what they will do and their cost analysis and how they will determine which drugs are preferred on the Washington PDL. So this recommendation is more specific to the Medicaid PDL or the single PDL that is being implemented. So there is the opportunity to align them where you see fit or if we do have different recommendations saying, you know, for the Medicaid program we're actually wanting to move in this direction for whatever reason. So there is the opportunity to align them, but there is also the opportunity to accommodate Medicaid or accommodate UMP or accommodate L&I as you see fit.

Leta Evaskus: I did change this recommendation, the first bullet, the antiplatelet products that are considered safe and efficacious and are eligible for preferred status.

Michael Johnson: Any other discussion?

Lisa Chew: I move the Apple Health Medicaid Program implement the limitations for the antiplatelet drug class listed on slide 2 as recommended.

Jordan Storhaug: Can I see that slide first? I'm not sure we… I understand the meaning of it. I think maybe we need to do modifications. So I think maybe it is the antiplatelet products that are considered safe and efficacious are eligible. I think if we just have the *and* there we just kind of have a subject and we don't have an action to that phrase. Is that in line with what we want?

Amber Figueroa: And do we need to refer to the PDL in the motion? That are considered safe and efficacious by who? Or on what authority?

Leta Evaskus: Are you saying that you want to refer to the P&T motion?

Amber Figueroa: Yeah. Well, we need…

Leta Evaskus: Safe and efficacious in the P&T motion.

Amber Figueroa: Yes. Don't you guys think? It's kind of generic the way it is. Considered safe by who?

Ryan Pistoresi: We do intend to have these be reviewed at the same time so both for UMP, L&I and for Medicaid in the future. So we'll have both the motions trying to go parallel with each other. If we happen to update the P&T, but not update this, you know, we'll try to get that to be aligned between the three programs.

Woman: All preferred products up to a total of two seems a little ambiguous. Would it be possible to say two or one, if only one is listed? It just sort of seems like all and total up to…

April Phillips: We can do that. I was just trying to find a way to say one or two, but without telling them they can try one. They have to try two if there are more than one preferred.

Leta Evaskus: Should we say the amount of preferred products minus one is what they have to try?

Woman: That's more confusing.

Emily Transue: It's okay. I rescind my concern.

Michael Johnson: This tells us they can use two or less. So if there are five they only need to try two. If there is one that's less than two.

Amber Figueroa: Maybe if we take out all. A trial of preferred products up to a total of two.

Woman: Or a trial of up to two preferred products.

Amber Figueroa: There you go.

Diane Schwilke: Up to two says they could try one or none.

Woman: And if they wanted to try three they could.

Amber Figueroa: Maybe if we say two preferred products… no, never mind.

Woman: How about of at least one preferred product.

Jordan Storhaug: Conversely we could have left it as it is and then said unless contraindicated, not clinically appropriate, or only one preferred product is available.

Woman: I'm thinking… I'm hoping… I'm assuming what you intended was a trial of two unless contraindicated medically necessary… unnecessary and only one available.

Amber Figueroa: Second line, first word, products.

Ryan Pistoresi: So I think we'll need to then re-read the motion since it was already brought up and then changed.

Lisa Chew: You want me to re-do the recommendation or just the motion?

Ryan Pistoresi: I guess just the motion.

Lisa Chew: I move the Apple Health Medicaid Program implement the limitations for the antiplatelet drug class listed on slide 2 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.

April Phillips: I want to say thank you for dealing with us on our learning curve on this.

Michael Johnson: That brings us to the newer diabetes updates. Will that be Stephanie again? Okay.

Stephanie Christofferson: Yeah. I'm here. So the first slide we'll talk about just the overview of the disease state. In 2015 there were approximately 30 million Americans with diabetes and another 84 million at risk for developing type 2. In fact, each year there's about 1.5 million new diabetic patients per year and the expenditures as far as direct and indirect costs annually are approximately $2 billion. As you know, diabetes is a significant cause of mortality and morbidity in the United States and it does increase a patient's risk of eye and kidney complications, along with nerve damage, heart attack and stroke. As you are aware there are two different types of diabetes – type 1 and type 2. In type 1 patients they cannot adequately produce insulin due to pancreatic defects. Whereas type 2 patients cannot use insulin properly and/or does not produce enough insulin. By far the most prevalent type of diabetes is type 2 with approximately 90 to 95% of all diabetic patients having this type of diabetes. Unfortunately there's no cure for diabetes and therapy really involves just controlling blood glucose levels and trying to manage cardiovascular risk factors. In fact, for every 1% reduction in hemoglobin A1C the risk of developing microvascular diabetic complications is reduced by approximately 40%. Today there's several pharmacological therapies available for patients which are available both in an oral and injectable products. There's combination products and also medication… the combination products also… they offer less frequent dosing than what we've previously had in the past. Next slide.

We will address the FDA approved indications. The first drug class we'll talk about is the amylin analog, which really the only medication in this class is Symlin and it can be used to treat both type 1 and type 2 diabetes. The next group of medications which will address are the DPP4 inhibitors. This includes Nesina, Kazano, Oseni, Tradjenta, Glyxambi, Jentadueto and Jentadueto XR, Onglyza, Kombiglyze XR, Januvia, Janumet, and Janumet XR. This actually… you'll see that

those medications wrap around onto that next slide. But all the medications are indicated to… as an adjunct to diet and exercise to help improve glycemic control in patients with type 2 diabetes. Some new generics came out in the last year including generic for Nesina, Kazano and Oseni. Actually, as far as the medication I am going to talk about today those are the only generics that are available as far as the medications we're discussing today. A new drug within the last year was the Jentadueto XR, as well as Glyxambi for the empagliflozin component of it. That also got a new indication within the last year or so, which is now indicated also to reduce the risk of cardiovascular death in adults with type 2 diabetes that have established cardiovascular disease. However, the effectiveness of the cardiovascular… reducing the risk of cardiovascular death in adults that's not been established with the combination product Glyxambi. I wanted to point that out. Next slide.

Next we'll talk about the GLP1 receptor agonists. This starts with Tanzeum on this page and it will wrap around to the next slide, but these medications that are in this category are Tanzeum, Trulicity, Byetta, Bydureon, Victoza, Xultophy, Adlyxin and Soliqua. They are all indicated, as well as for adjunct diet and exercise to improve glycemic control in adults with type 2 diabetes. Not listed here, but I wanted to point out Victoza also gained an FDA approval for reducing the risk of major adverse cardiovascular events in adults with type 2 diabetes with established cardiovascular disease. Byetta is actually an add-on therapy when metformin, sulfonylurea, [inaudible] or insulin have failed to lower blood glucose sugars. And also the two newer products, the Xultophy and Soliqua these are a product that when there individual components have not adequately controlled a patient's type 2 diabetes then these medications can be indicated to help treat and improve the glycemic control and they combine a GLP1 receptor agonist with a long-acting insulin analog. Next slide.

This slide will address the SGLT2 class, which again will wrap over onto the next slide. In this class the medications included are Invokana, Invokamet, Invokamet XR, Farxiga, Xigduo XR, Jardiance, Synjardy and Synjardy XR. As you can see, many of these medications in this class are combined with metformin and all are indicated again

for adjunct diet and exercise in order to improve glycemic control in type 2 diabetic patients. I also want to point out that Jardiance is also indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes with cardiovascular disease. However, the combination products, the Synjardy and the XR… in reducing the risk of cardiovascular death in adults with type 2 diabetes… and cardiovascular disease has not been established. Next slide.

That just finishes up the rest of the medications that are in the SGLT2 category. Next slide.

We'll review high-level the dosing and formulations available for these products. So for Symlin the medication is given with meals, with insulin as a sub-q injection and it is also available in a pen. For the DPP4 inhibitors, which starts with Nesina on this page and continues through Janumet on the next slide. They are administered orally and are just a once daily. However, medications that do have the immediate release metformin are dosed more frequently as you can see in the table. With these… the medications can be used without regard to meals except when metformin is in a tablet in which case it should be administered with the meal. Next slide, please.

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

Next we will start with the GLP1 inhibitors, which starts with Tanzeum and will end on the next slide with the [inaudible]. The GLP1 agonists are administered by subcutaneous injections and the frequency varies by the product. As you can see in the table Byetta is dosed twice daily. Victoza and Xultophy and Adlyxin and Soliqua are dosed once daily and then the Tanzeum, Trulicity and Bydureon are dosed once weekly. Of note, the longer acting products have a stronger effect on fasting blood glucose levels while the shorter acting agents primarily lower the post-prandial blood glucose levels. And then when you look at these products again you see that there are lots of different combination products and those can be used to help offer an additional mechanism to lower blood glucose for patients not needing hemoglobin A1c levels on monotherapy. Next slide, please.

Starting with this slide with the SGLT2 medications. As you can see there are some renal impairment dosings available which are indicated in the package inserts. All the medications are dosed orally, once daily except for Invokamet and Synjardy which are due to the IR metformin being in the products in which case these medications are dosed twice daily. All the medications available here are available in a tablet formulation. Next slide, please.

That just rounds out, again, the rest of those medications. Next slide.

Next we'll go into clinical considerations first with the amylin analogue. Symlin works by flowing gastric emptying, suppresses glucagon secretion and centrally modulates appetite. Again, the medication can be used in either type 1 or type 2 diabetes. Also, someone can… or should only be considered in patients who have failed to achieve adequate glycemic control on insulin and the medication can be taken with insulin. However, this can increase the patient's risk for hypoglycemia which is a boxed warning for this medication. The A1c lowering capabilities for the medication range from .3 to .6% and the medication has also been associated with weight loss. The pregnancy category is a category C. The safety and effectiveness have not been determined in pediatric patients and for geriatric patients the medication should be used with caution due to the hypoglycemic risks. Next slide.

We'll address the DTP4 enzyme inhibitors. The medications work by increasing and prolonging the action of incretin, which promotes insulin release. The medication is only indicated for type 2 diabetes. There is a relatively low risk for hypoglycemia with these medications, but when used with other products it can increase the patient's risk. The medications do have a moderate glucose lowering effect for the hemoglobin A1c, decreasing it by anywhere from .5% to 1%. In trials there were no major cardiovascular outcomes. Most of the medications are pregnancy category B. This includes Tradjenta, Jentadueto, Kombiglyze XR, Januvia and Janumet. However, Glyxambi is not recommended during the second and third trimesters of pregnancy and this is due to data in animal testing showing

adverse renal effects. Nesina, Kazano, Oseni, Jentadueto XR, Onglyza and Kombiglyze XR comply with the current frequency and lactation labeling rule that [inaudible] just insufficient data to determine a drug associated risk with major birth defects. In pediatric patients the safety and efficacy has not been established and in older patients the medication should be used in caution and renal monitoring should be performed. The medications do have some warnings. Ones to note include hypersensitivity reactions, acute pancreatitis, increased heart failure. This was mentioned with Onglyza and Nesina and the incidence of that was 3.5 and 3.9% respectively. There can be also a decline in renal functions, joint pain, and bullous pemphigoid. The concerns regarding the risk of pancreatitis and pancreatic cancer remain unresolved although recent data had indicated there's a lack of association between the DPP4 inhibitors and pancreatic [inaudible] effects. Next slide.

We will address the GLP1 receptor agonists. These work by enhancing glucose-dependent insulin secretions by the beta cells. They suppress inappropriately elevated glucagon secretion and slow gastric emptying. Again, the medications are only used in type 2 diabetes and the medication has a low risk of hypoglycemia and the A1c lowering capability ranges anywhere from .3 to 1.6%. Unlike other medications in studies the cardiovascular… there's been a 13% relative reduction in composite cardiovascular risk with Victoza and Adlyxin and Adlyxin had a neutral effect. For pregnancy… the medications are pregnancy category C except for Trulicity, Adlyxin and Soliqua and Xultophy, which comply with the current pregnancy and lactating labeling rule. Again, just stating that there is insufficient data to suggest the drug associated risk for major birth defects. There has been no safety and efficacy… safety and efficacy has not been established in pediatrics and there's no special considerations for the older population. As far as warnings there is a warning regarding acute pancreatitis. In fact, Tanzeum, Trulicity, Bydureon, Victoza and Xultophy are subject to a communication plan to inform healthcare providers of the risks of acute pancreatitis. And then also hypersensitivity reactions can also occur with these medications. Next slide, please.

Review the SGLT2 inhibitors. They work by reducing the renal glucose reabsorption in the proximal convoluted tubule which leads to an increase urinary glucose secretion. The drugs are efficacious in lowering A1c, postcranial glucose and fasting plasma glucose and they've actually also been shown to decrease systolic blood pressure. In clinical studies approximately 1… approximately a one-third relative risk reduction for cardiovascular death, hospitalization due to heart failure and all cause death have been seen with Jardiance and this was compared to placebo. Again, that medication is a component of Glyxambi, however, that's not been established as far as an indication with Glyxambi. For pregnancy category C this includes Farxiga, Xigduo XR. Product labeling for Farxiga and the metformin ER combination recommend use during pregnancy only if the potential benefit outweighs the risks. Invokana, Invokamet, Jardiance, Synjardy were all previously assigned a category C, but they've changed their labeling again to match the pregnancy and lactation labeling rule. There's no safety and efficacy studies performed in pediatric patients and with geriatric patients it should be used with caution in this patient population due to hepatic and renal issues. As far as warnings some of the more notable ones include increased risk for urinary or genital tract infections due to the increased levels of glucose in the urine. There's been reports of bone fracture with the Invokana which there is an FDA safety communication that came out in 2015. I'm sure as all of you are aware there's also the FDA communication that came out in 2016 regarding Invokana in combination products with the leg and foot amputation and then also there is an increased risk of ketoacidosis which was also an FDA announcement in 2015. And then also the medications can cause renal impairment. Next slide.

This will wrap up the diabetic section or just the guidelines. For the American Association of Clinical Endocrinologists and American College of Endocrinology the 2017 management algorithm they take kind of a step wise approach. If the hemoglobin A1c is less than 7.5 to start they recommend monotherapy. In patients with 7.5 or higher they recommend starting off with dual therapy and patients with a hemoglobin A1c 9% or more and no symptoms they recommend starting with either a dual or triple therapy and then patients with a

hemoglobin A1c of 9 or more and who also have symptoms they recommend beginning with insulin with or without other agents. They do recommend that metformin be the preferred treatment of choice for monotherapy and also the first line therapy for dual and triple therapy. Agents for monotherapy are recommended in the following order with the highest to lowest recommendation which would include metformin, GLP1 receptor agonists, DSGLP2 inhibitors, DPP4 inhibitors, TZDs, alpha glucosidase inhibitors and then the sulphonylureas. Notably they caution the use of TZDs and sulphonylureas. For the American Diabetes Association they also agree and state that metformin is the preferred first line agent. If metformin can't be used they recommend a sulphonylurea, a TZD, a DPP4 or a GLP1 receptor, especially if weight loss is essential. If metformin fails to produce targeted A1c therapy… or levels after three months of therapy a TZD, a sulphonylurea, a DPP4 inhibitor, an SGLT2 or a GLP1 receptor agonist or insulin should be added. And then if targets are still not achieved after three months they recommend an agent from a different group be added. They… [inaudible] guidelines they don't place any sort of… they don't prefer one medication over another or anything like that. That's just simply their recommendations. And then lastly the American College of Physicians their 2017 guidelines also state that metformin is first line therapy and if that doesn't work then they recommend sulphonylurea, a TZD, an SGLT2 or a DPP4 as second line therapy. So with that said that concludes what I wanted to review with the group for the diabetic medications. Are there any questions?

Michael Johnson: I see no questions from the committee. Thank you, Stephanie.

Stephanie Christofferson: Thank you.

Marian McDonagh: This is the report on newer diabetes medications. It was finalized this month in October 2017. This is update three for this report. If we go to slide 1, the next slide, the key questions are here.

We have a new key question this time looking at the cardiovascular events that are found with long-term use of these drugs. We were hoping to find evidence on monotherapy versus combination therapy,

as well as with and without prior cardiovascular disease and also if there is evidence of a class effect. The next three questions are typical questions on effectiveness, adverse events and subgroups. We were also looking for within class and across class evidence. And also again between monotherapy and combination therapy. Next slide.

This is a quick summary of our methods on the left side of the slide. Search dates are through the end of July. Drugs are in the table. And I will say that we have gotten word that Albiglutide, which is a GLP1 agonist there are plans to remove it from the market over the next several months. That drug still appears in this slide and in the report, but I will not be paying a lot of attention to it today. The combinations we were looking for in this report were direct comparisons between the drugs. For the cardiovascular outcomes we also allowed placebo-controls. We were previously asked to continue looking at comparisons to metformin and then also, as I mentioned, we were asked to look at single drug versus combination therapy. Next slide.

Overall there are 91 studies in this report with 33 of those being new. So on the graph you can see where the evidence… the bulk of the evidence is. There are a lot of placebo-controlled trials relative to the other numbers of studies in the other areas that are all new that are looking at the cardiovascular events. There were five new GLP1 agonist studies looking at within class comparisons. For between class comparisons there were three new DPP4 inhibitor versus SGLT2 inhibor studies. Moving on down we have in combination therapy all of the evidence on combination products with insulins and GLP1 agonists is new. Then we also have new evidence for a combination of SGLT2 inhibitor and a DPP4 inhibitor. And a little bit of new evidence with comparisons to metformin. Next slide.

Looking at the cardiovascular outcomes, again, this is all new evidence. There were eight large mainly good quality placebo-controlled trials. So there are studies that are around, you know, smallest is 3,000 up to over 16,000 patients and ranging in duration from 1/2 to 3.8 years. So the findings are that the SGLT2 inhibitors

specifically empagliflozin and canagliflozin and two GLP1 agonists semaglutide and liraglutide were found to reduce cardiovascular events significantly compared to placebo. So the difference in percentages of those cardiovascular events were at 13 to 26%. We will note though that some of the confidence intervals are close to being non-significant. So for those two GLP1 agonists, semaglutide and liraglutide there were also findings of decreases in nephropathy. So the GLP1 agonist lixasenatide and the DPP4 inhibitors alogliptin, saxagliptin and sitagliptin did not have significant reductions in cardiovascular outcomes and sitagliptin there was also some evidence that the incidence of retinopathy increased with that. However, there was a higher rate of retinopathy at baseline in those patients so that does need to be taken into account. So with DPP4 inhibitors there is also evidence on heart failure. So the risk of hospitalization with heart failure was examined in a placebo-controlled trial with saxagliptin which showed an increased risk and with alogliptin and sitagliptin the studies did not find an increased risk compared to placebo. Now there's two observational studies that provide some evidence that's a little bit conflicting with these findings of the trials. There were no statistically significant differences between saxagliptin and sitagliptin where it is based on the placebo-controlled trial evidence you would have expected there to be a difference. So that reduces our confidence in the findings.

On slide 5 we conclude that a class effect seems likely for the SGLT2 inhibitors and for the DPP4 inhibitors. That being that the SGLT2s reduce cardiovascular events and that the DPP4s do not. Subgroup analysis also possibly suggest that benefit… varies by age, what other medications are used, and the patient's baseline weight and renal function. We also conducted indirect comparison meta-analysis that was consistent with these findings of the trials and our conclusion on class effects. So our confidence in these findings overall is moderate for the composite outcomes, the cardiovascular events, and low for most of the other outcomes. Next slide.

Now we will look at the comparisons within class. The first comparison is the GLP1 agonists compared to each other. There is a total of 11 trials here. We've separated these into the group of trials

that compare newer ATLP1 agonists with liraglutide on this slide and then compared to exenatide on the next slide.

So first of all dulaglutide had less weight loss than liraglutide. But there were no other differences. There was a decreased appetite, however, in liraglutide in Japanese patients. So this was a study conducted in Japan using doses that are approximately half of the FDA approved doses. Now the second bullet is about albiglutide, which as I mentioned is being removed from the market so we'll skip that one. The next bullet is lixasenatide. This is new evidence and lixasenatide actually did better on A1c outcomes than liraglutide. Adverse event withdrawals however were not different and liraglutide had decreased appetite compared to lixasenatide. So the next new evidence is for semaglutide versus liraglutide and here there is some slightly mixed evidence. The A1c outcomes differ… the statistical significance differs based on which specific outcome measure we're looking at. So for mean change in A1c it was -1.7% compared with -1.2% with a difference of 1.3%. And that was statistically significant. The proportion of patients achieving an A1c less than 7, however, 81% in the semaglutide group versus 57 to 59% in the liraglutide groups and that was not statistically significant, but you can see that the absolute difference is fairly large. So semaglutide also had better weight change outcomes, but more withdrawals due to adverse event than specifically GI adverse events. So our confidence in these findings is low to moderate for A1c, low for weight and adverse events. Next slide, slide 7.

So this is the GLP1 agonists again, but now these are studies that are comparing newer drugs to exenatide. So dulaglutide and liraglutide were found to have better A1c outcomes than exenatide. No difference in other outcomes. Then on the second bullet albiglutide and exenatide extended release were not different to the twice-daily form of exenatide on any of the outcomes that we included. So our confidence in these findings is again low to moderate for A1c, low for weight and adverse events. Now the DPP4 inhibitors compared to each other there are only two trials and differences were not found between the drugs. SGLT2 inhibitors we found no studies comparing those drugs to each other. Moving on to slide 8.

This is the between-class comparisons. This is the DPP4 inhibitors compared with the FLP1 agonists. So mostly this evidence is old. It was in the previous report and only the top bullet is new. So we can summarize that mostly these studies find that the GLP1 agonists had better outcomes on hemoglobin A1c measures and on weight. However, the GLP1s had more adverse events and mostly those were found to be gastrointestinal adverse events. Next, slide 9.

Between class comparisons, again. This is DPP4 inhibitors versus GLP1 agonists again. This is the… the comparison here however is the DPP4 inhibitor saxagliptin and previously, on the previous slide, all of the comparisons were with sitagliptin. So here liraglutide, the GLP1 agonist improved A1c in the mean change, but not the proportion of patients achieving an A1c less than 7%. Liraglutide did have greater weight loss, however, and again more nausea. Here there was no difference in the withdrawals due to adverse events though. Slide 10.

This is the comparison of DPP4 inhibitors to SGLT2 inhibitors and its nine trials. So we have some new evidence here. The evidence varies by the specific SGLT2 inhibitor used. All of the trials compared to the DPP4 inhibitor sitagliptin. So canagliflozin did better on A1c outcomes and weight, but caused more genital mycotic infections, quite a lot more. There was some follow-up evidence… extension study evidence at 52 weeks that the differences were maintained. As we found in the previous report, empagliflozin improved weight, but not other outcomes prepared to sitagliptin. And then finally new evidence we have that dapagliflozin was not different to sitagliptin on the outcomes that we were including, but it was a small trial. Slide 11.

This is DPP4 inhibitors versus SGLT-2 inhibitors, but this time the DPP4 inhibitor being compared to is linagliptin. There's no new evidence on this slide. And so the evidence is mixed. So for the comparison of empagliflozin with linagliptin, empagliflozin had better A1c outcomes and weight outcomes, but again more genital mycotic infections. And then linagliptin compared with saxagliptin… sorry, dapagliflozin compared with saxagliptin. Dapagliflozin had better

weight outcomes, but no other differences. In one trial that compared that GLP1 agonist exenatide to the SGLT2 inhibitor dapagliflozin compared to the efficacy types of outcomes. Slide 12.

This is looking at the first of the GLP1 agonist's combination products with a long-acting insulin and these are fixed ratio combination products as a more appropriate term, and not fixed dose. So lixisenatide combined with glargine insulin there were three trials. Here we found that the combination results in better A1c outcomes than glargine insulin alone or lixisenatide alone. And the combination also results in more weight loss than glargine insulin alone. However, lixisenatide alone has better weight loss outcomes than the combination. Withdrawals due to adverse events, the combination was right in the middle of the two with lixisenatide having the highest rates and glargine having the lowest. So our confidence in these findings is moderate for A1c outcomes, low for weight and adverse events. Next slide, slide 13.

This is liraglutide combined with degludec insulin and again we have three trials. Here we also find the combination is better in the A1c outcomes and that there is more weight loss than either glargine insulin or degludec insulin alone. But again more with the GLP1 agonist alone, liraglutide. Here the finding is that there was less hypoglycemia with the combination than with glargine insulin alone. But more with liraglutide. There was more withdrawals due to adverse events compared to glargine alone or liraglutide alone. The combination also had more nausea than either of the insulins alone, but less than liraglutide alone. And that difference is quite large, 20% versus 9%. So we here moderate strength confidence in the A1c findings, but low again for weight and insufficient for adverse events in this case. Slide 14.

These are the oral fixed-dose combination products. The first comparison is SGLT2 inhibitors combined DPP4 inhibitors and the comparisons are all versus the monotherapy of the components or in some cases dual therapy with metformin. So the first line is an old finding canagliflozin combined with linagliptin had better A1c and weight outcomes than the component monotherapies. The next

several lines are new evidence. It's dapagliflozin with saxagliptin and those were given in these studies as separate products, but they are the same components and same doses as one of the combination fixed-dose combination products. And then metformin was given along with that. So that's triple therapy and the comparison was to the two components either dapagliflozin or saxagliptin alone given with metformin. So dual therapy versus triple therapy. Triple therapy had significantly better A1c outcomes than dual therapy. Dual therapy using saxagliptin had significantly less weight loss than the triple therapy. And there were more genital infections with either of the dapagliflozin regimens. So either the combination of all three drugs or just dapagliflozin with metformin. So our findings are low to moderate… our strength, our confidence. Let's move to slide 15.

We'll look at some more of the oral fixed-dose combinations. Here there is no new evidence on this slide and all of the combinations were better on hemoglobin A1c outcomes, but there were mixed findings on weight. So for example in the top line SGLT2 inhibitors plus metformin, canagliflozin with metformin improved weight both hemoglobin and A1c and weight more than the monotherapy components. Second line, the DPP4 inhibitors combined with other oral diabetes medications, so alogliptin with metformin improved A1c and weight more than the component monotherapies. Linagliptin plus metformin and sitagliptin plus metformin improved A1c outcomes but not… the weight findings were mixed. So better in one trial and not better in another. And finally alogliptin plus pioglitazone improved A1c more than the component monotherapy, but higher dose combination therapy had more weight gain than the monotherapies. That is from a single trial. So our confidence in these findings is low to moderate. Slide 16.

This summarizes the evidence on our comparisons with metformin and as I mentioned at the beginning there's just a little bit of new evidence here. So with DPP4 inhibitors compared to metformin new evidence found that linagliptin reduced A1c less than the… higher dose metformin, 1000 mg twice a day. No differences were found in other outcomes. The older evidence found that sitagliptin reduced A1c more than metformin, but weight loss was greater with

metformin and no other outcome differences. Saxagliptin did not lower A1c more than metformin, but metformin reduced weight more. And no other differences. So GLP1 agonists compared to metformin, exenatide extended release was not different to metformin on any outcome. Dulaglutide was better on A1c outcomes, but not different on other outcomes. And the SGLT2 inhibitors, HbA1c outcomes were not different, but weight loss was greater with the SGLT2 inhibitors, dapagliflozin, empagliflozin and canagliflozin. Slide 17.

All right. We have a few conclusion slides here because it's a lot of evidence in different categories. So on this slide the cardiovascular outcomes to summarize they reduced cardiovascular events with the SGLT2 inhibitors canagliflozin and empagliflozin and also with the GLP1 agonist's semaglutide and liraglutide. And to remind you the differences were 13% to 26% reductions. There was no effect on CV outcomes with the GLP1 agonist lixisenatide or with three of the DPP4 inhibitors. With heart failure the DPP4 inhibitors saxagliptin may increase heart failure for… due to… hospitalization due to heart failure compared to placebo but there was no significant difference versus sitagliptin in an observational study. Next slide.

The summary of the evidence for within-class comparisons. Here I would remind everybody that the differences in the overall reduction in A1c is typically pretty small even if it's statistically significant. So often times less than 1% and up to close to 2% reductions. So with DPP4 inhibitors there was no difference. [inaudible] was found with saxagliptin and sitagliptin. With GLP1 agonists the newer drugs semaglutide and lixisenatide were better on A1c outcomes than liraglutide. Semaglutide was also better on weight and adverse events. Liraglutide was better than dulaglutide on weight only. And both dulaglutide and liraglutide were better than exenatide on hemoglobin A1c outcomes. So some differences across the GLP1 agonists there for at least the short-term outcomes. Slide 19.

These are conclusions summary on the between class comparisons and here the greater than symbol means better than. So for SGLT2 inhibitors versus DPP4 inhibitors the SGLT2s were better on A1c and

weight outcomes, but were pretty consistently had a higher infection rate… genital infection rate. GLP1 agonists versus the SGLT2 inhibitors there's not a lot of evidence, but no differences found between exenatide and dapagliflozin. So for DPP4 inhibitors versus GLP1 agonists the GLP1 agonists were mostly better on the A1c outcomes, as well as weight. However, the GLP1 agonists had more withdrawals due to adverse events and GI adverse events. Slide 20.

Fixed-dose combinations. The summary here is that for GLP1 agonists plus insulin the combination products are better on A1c outcomes, but weight is better with the GLP1 agonists alone. Liraglutide plus degludec insulin was better on withdrawals due to adverse events and nausea, but had less hypoglycemia. SGLT2 inhibitors combined with DPP4 inhibitors were better on hemoglobin A1c and weight outcomes. SGLT2 inhibitors combined with metformin specifically canagliflozin combined with metformin was better on again A1c and weight outcomes than the monotherapies. DPP4 inhibitors combined with metformin. Alogliptin plus metformin was better on A1c and weight. And either linagliptin or sitagliptin combined with metformin were better only on A1c outcomes than the component monotherapies. Now the summary for comparisons of these drugs with metformin. Metformin reduces A1c better than linagliptin, one of the DPP4 inhibitors or a similar amount to other DPP4 inhibitors. For the GLP1 agonists dulaglutide was better on A1c outcomes, but exenatide extended release was not different to metformin. And the SGLT2 inhibitors, the A1c outcomes were not different, but weight loss was greater with the SGLT2s. That concludes the presentation – the summary of our findings in the report on newer diabetes medications.

Michael Johnson: We have three stakeholders. I'll just reiterate. It's a three-minute limit. The first person will be Anthony Wheeler followed by Toby Damron and we'll do it up at the podium because this is recorded. So we'll go ahead and call Anthony Wheeler to the podium. Thank you. Again, please introduce yourself and state where… who you represent.

Anthony Wheeler: All right. Good afternoon. My name is Anthony Wheeler. I'm an employee of Eli Lilly & Company and I'm going to provide just a few comments on Trulicity. This is part of the GLP1 class of drugs and this one is administered once per week. I know that this drug has been reviewed by the committee before. So I'll just provide a few updates on recent research. There's now eight completed randomized controlled clinical trials for Trulicity. The most recent was a study looking at treatment using Trulicity in combination with insulin glargine. These studies also had several different comparators including liraglutide or Victoza, twice daily exenatide which is Byetta. And also a study looking at Trulicity versus insulin glargine. And then another recently published study is a real-world evidence study where patients who receive Trulicity were significantly more likely to be adherent and persistent to this medication after six months from starting it compared to patients who receive Victoza or Vivarium. Trulicity has a proven safety and tolerability profile that's similar to the other drugs in its class and you certainly can see the full prescribing information for all the safety details. Lastly, Trulicity is available as a once weekly injection. It is delivered via a single use pen device and it has a hidden, pre-attached needle inside. There's no reconstitution or mixing necessary to use the device. So it's pretty easy to use. So thanks for listening. I'm happy to try to answer any questions you have.

Michael Johnson: Thank you. Next is Toby Damron followed for Sarah Gray.

Toby Damron: Good morning. My name is Toby Damron. I'm a pharmacist and medical liaison with Novo Nordisk and today I would like to share some highlights and some significant label updates regarding two medications. Both Victoza and Xultophy 100/3.6. In order to cover both medications appropriately may I request a few more minutes than the three allotted?

Michael Johnson: It's three minutes total.

Leta Evaskus: You can have extra time.

Toby Damron: Okay. Thank you very much. So starting with Victoza, Victoza is a GLP1 receptor agonist indicated as an adjunct diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Victoza is now also approved in the U.S. to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. This latter indication is based on data from the LEADER trial. The LEADER trial was a landmark cardiovascular outcomes trial of 9,340 adult patients with type 2 diabetes randomized to maximum tolerated Victoza versus injectable placebo both with standard of care. Eighty percent of the enrolled population had established vascular disease, chronic kidney disease stage three or greater, or New York Heart Association class two or three heart failure. The trial was randomized, double blinded in both event driven and time driven with the median follow-up of three and one-half years. The primary composite outcome in the time to event analysis was the first occurrence of death from cardiovascular causes, non-fatal cardio infarction or non-fatal stroke. At the end of this trial there was a statistically significant 13% reduction in the primary endpoint with Victoza. In regards to the individual components of the 3 point composite there was statistically significant 22% reduction in death from cardiovascular causes with Victoza compared to placebo. The rates of non-fatal mild cardio infarction and non-fatal stroke were numerically but not statistically lower with the Victoza group compared to placebo. A summary of the LEADER trial is now sited in section 14.2 of the Victoza PI. Of not, though there are cardiovascular outcomes trials published for two other currently-approved GLP1 receptor agonists, to date Victoza is the only agent in this class which has shown cardiovascular benefit. In regards to addition recent label updates Victoza was not previously recommended as first line therapy for type 2 diabetes. However, this limitation of use has been removed from the label. As a reminder, Victoza is not insulin and should not be used in patients with type 1 diabetes.

Similar to other longer acting GLP1 receptor agonists there is a boxed warning for Victoza regarding a potential risk of thyroid C cell tumors and as such patients with personal family history of medullary thyroid carcinoma and patients with MEN2 should not use Victoza. As with all GLP1 receptor agonists the Victoza label includes warnings and

precautions regarding pancreatitis. Discontinue Victoza promptly if pancreatitis is suspected and do not restart Victoza if pancreatitis is confirmed. For additional safety information, I refer you to the PI. With the data I presented including a new indication to reduce the risk of major adverse cardiovascular events in patients with type 2 diabetes and established cardiovascular disease, I respectfully request consideration that Victoza be added to the preferred drug list. Thank you.

Then to cover Xultophy, if I may. Xultophy 100/3.6 is a combination of insulin degludec, a long-acting human insulin analog and liraglutide, a GLP1 receptor agonist. This medication is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin, less than 50 units, or liraglutide less than or equal to 1.8 mg daily. There is a REMS in place for Xultophy 100/3.6 to inform health care providers of the potential risk of medullary thyroid carcinoma and acute pancreatitis. There is also a boxed warning with Xultophy 100/3.6 in regards to risk of thyroid C cell tumors and as such patients with a personal or family history of medullary thyroid carcinoma in patients with MEN2 should not use Xultophy 100/3.6. I would refer you to the PI for additional safety information.

A comprehensive phase 3A clinical trial development program evaluated the safety and efficacy of Xultophy 100/3.6 in adult patients with type 2 diabetes inadequately controlled on oral diabetic drugs, basal insulin or GLP1 receptor agonists. In the three efficacy studies sited in the PI, patients treated with Xultophy 100/3.6 achieved greater reductions in A1c compared to those comparators. Those comparators were liraglutide in study A, insulin degludec U100 in study B, and insulin glargine U100 in study C. Of note, mean end of trial A1c values in Xultophy 100/3.6 of all three of these efficacy studies were less than 7%. In addition, a greater percentage of patients treated with Xultophy 100/3.6 achieved an A1c goal of less than 7 versus comparators.

The recommended starting dose of Xultophy 100/3.6 is 16 units. This is 16 units of insulin degludec and 0.5 mg of liraglutide given

subcutaneously once daily at the same time each day with or without food. The dose should be titrated by two units upwards or downwards every three to four days until desired fasting plasma glucose is achieved. The maximum dose of Xultophy is 50 units. This is 50 units of insulin degludec and 1.8 mg of liraglutide. Xultophy 100/3.6 is supplied in a 3 mL pre-filled disposable, single-patient use pen with each pen containing 100 units per milliliter of insulin degludec and 3.6 mg per mL of liraglutide. After first use the pen can be stored for up to 21 days. The concurrent use of basal insulin and GLP1 receptor agonists is now established treatment regimen and it is included in the 2017 ADA, EASD physician statement on the management of hyperglycemia in patients with type 2 diabetes. Given the data I've presented today I respectfully request consideration that you add Xultophy 100/3.6 to your preferred drug list. Thank you very much for your time.

Michael Johnson: Thank you. Next up is Sarah Gray followed by Brent Wright.

Sarah Gray: Good morning. My name is Sarah Gray and I'm a senior medical science liaison with Janssen Scientific Affairs. I'm here to discuss canagliflozin commercially known as Invokamet. So Janssen has recently announced the primary results of the… of canagliflozin's cardiovascular outcomes trials referred to as the Canvas program, which studied over 10,000 patients with type 2 diabetes and either a history of cardiovascular disease or multiple CV risk factors. The Canvas program showed that canagliflozin treatment led to a 14% reduction in major adverse cardiovascular events compared to standard of care. Notably cardiovascular death, myocardial infarction and stroke evenly contributed to the overall [inaudible] risk reduction. In light of these findings Janssen has recently filed for a cardiovascular indication with the FDA. In the Canvas program canagliflozin also sustained positive effect on glycemic control, blood pressure and weight for up to 6-1/2 years demonstrating wide ranging durability. Exploratory end points in the Canvas program showed that treatment with canagliflozin led to a 33% reduction in hospitalization for heart failure and a 40% reduction in a renal composite of severely reduced filtration, end stage renal disease and/or renal death. The adverse events in the Canvas program were

consistent with previous findings with the exception of an increased risk for lower limb amputations mostly affecting [inaudible]. The canagliflozin showed a rate of 6.3 amputations per 1,000 patient years compared to 3.4 with placebo. Now while the data did not provide a mechanism for this imbalance the highest incidence occurred in patients with a prior history of amputation irrespective of treatment. The label has been updated to reflect this new information and no contraindications were added. Notably no increases in amputations were observed across the 12 completed phase 3 and 4 clinical trials. A recent analysis of a large U.S. claims database also showed no increases in amputations with canagliflozin compared to other anti-hyper glycemic agents including agents within the class.

The Canvas program results add to the benefits previously demonstrated, but with canagliflozin which is the only SGLT2 inhibitor that has shown superiority to both [inaudible] and sitagliptin in head-to-head studies. With the totality of evidence in support of a positive risk benefit profile for this medication I respectfully request the committee to consider adding canagliflozin to the Apple Health Medicaid PDL. Thank you for your time.

Dale Sanderson: You mentioned the increased risk of leg and foot amputations. Any sense of the mechanism of that?

Sarah Gray: Unfortunately, no. I mean we've looked at a number of baseline characteristics, you know, in reality it was 187 patients. So we're really looking at small numbers trying to sort out, you know, what could be influencing this. We are currently looking into real-world databases to try to look for larger numbers and see if (1) if this risk can be picked up, and (2) if there is some data that can point to a mechanism. But currently it is just unknown.

Michael Johnson: Thank you. Last up is Brent Wright.

Brent Wright: My name is Brent Wright. I'm associate director of health economics outcome research for Boehringer Ingelheim. I'm here to represent empagliflozin. Just a quick update, as you all know, we did receive a

change in our label December 2nd, 2016 from the FDA, which now reads, "To reduce the risk of cardiovascular death in adult patients with type 2 diabetes the [inaudible] cardiovascular disease." This came from the Landmark trial from [inaudible]. It is important to note there was a couple of numbers that came up. I'm not sure where they came from, but I just want to make sure we're kind of clear on where those came from. The 3 point [inaudible] for the [inaudible] Rag trial which included cardiovascular mortality, non-fatal stroke and non-fatal MI was 14% relative risk reduction. It is very important to note this was 100% driven by cardiovascular mortality, which had a relative risk reduction of 38%. This was also mentioned in placebo and it is important to that this was standard of care. The placebo was a standard of care and it was the standard of care across whatever country the trial was carried out. A couple other points to note. We do not have any black boxed warning at this point although we did submit all of our information to the FDA and they did not find it necessary to add a black boxed warning. We do not have any warnings around fractures and to date we are the only SGLT2 that has shown statistically significant findings in reduction of cardiovascular mortality in patients with established cardiovascular disease. Also to note the empagliflozin trial has been added to all [inaudible] containing drugs, but there has not been any direct study showing that those drugs will have the same effect as the [inaudible] Rag trial. Thank you for your time. If you have any questions, I'd be glad to answer them.

Michael Johnson: Thank you.

Amber Figueroa: In reviewing what we've done in the past I'm wondering what everyone's thoughts about maybe adjusting it now that there is some cardiovascular risk reduction.

Ryan Pistoresi: First I just wanted to mention that you may notice that there are a few more drugs in the current motion for this class. What we've done previously in the classes is that we've had the combination drugs be separate because we had previous motions that they were not preferred on the PDL. And so they had been set aside in a different class so that way we could review the single ingredients and have the

combo separate. But in the last time we reviewed this class, in October of last year, we decided to add the combinations in at that time and at that time that was a separate motion. So in order to accommodate how we included that in on the PDL we decided to add the combinations in with the other drugs. So now they are done by drug class which is how they are reflected on the Washington PDL document that we post every quarter. So that's why this is a little bit different. You may see a lot more drugs now than in the previous ones. We did have cardiovascular outcomes presented at the last one, but I don't believe that we had any type of motion with any type of cardiovascular data. That was more presented as supplemental data to DERPs original report from 2016. So if you want to, you do have the opportunity to add that into the motions.

Nancy Lee: I would like to propose when we talk about it, that we talk about individual agents first and then add on the… talk about the combination products afterwards.

Michael Johnson: Just a question to the committee. Do we want to call out the cardiovascular mortality agents separately in our motion?

Amber Figueroa: My concern is that if you're using a specific agent for cardiovascular risk reduction and there is something in here that says that they are therapeutically interchangeable to another medication that does not have that indication then we may not be getting the risk reduction that we're seeking.

Nancy Lee: I think if we kind of go through it by class like DPP4 inhibitors first there's no cardiovascular outcome data for that. We can go through that class and then we can move on to the GLP1 agonists which has some cardiovascular like the LEADER trial and then we can go into the SGLT2 and discuss the cardiovascular and kind of divvy it up that way, that's what I would recommend.

Michael Johnson: So what I'm hearing is this class… the four individual agents have no change.

Nancy Lee: For DPP4 inhibitors, yeah.

Michael Johnson: So then potentially we could reiterate the same motion for those four agents.

Nancy Lee: That's correct.

Amber Figueroa: Ryan, are we asking that the combo all be included in that, right?

Ryan Pistoresi: I believe that you could just say the names of the drugs as they are in the ingredients. I don't think you have to read every single combination because all the combinations have one of those ingredient names in it. So I think if you say, you know, linagliptin, the saxagliptin, the alogliptin and the sitagliptin we understand that to be all the drugs here listed on the side with those ingredients that are being reviewed.

Woman: Do you want to say and all combinations?

Ryan Pistoresi: Yeah. Or that could be a good… you could say, and all combinations with these ingredients or all drugs containing… actually, I do believe there's one that is… yeah, so there is a dapagliflozin/saxagliptin combination that is in with the SGLT2s. So just a heads up that there will be one other DPP4 in the SGLTS2 motion.

Amber Figueroa: I recommend taking the linagliptin and pioglitazone combo empagliflozin down to the other class then and taking it out of DPP4 because that's one of those with the decreased cardiovascular risk reduction. So if we're going to include that in that grouping it should be down with the other category instead of here. It can go either way, but it might be better classified in the other one.

Ryan Pistoresi: I think that was an oversight.

Susan Flatebo: Another option would be to separate them out as far as those agents that reduce… or improve glycemic control in patients with diabetes and then those agents that reduce cardiovascular events in patients with diabetes. I mean we could call that out as two separate, you

know, I don't want to say indications, but that could be another option.

Ryan Pistoresi: Are you saying that you'd like to have two separate motions like two different conditions for the recommendation for the PDL? Or was it something else?

Susan Flatebo: No. Just if we want to call out those separate agents that reduce the cardiovascular events. If we want to make those separate as far as another drug class to review.

Michael Johnson: Another way to do that, in our motion we could particularly call out that one of the agents with proven cardiovascular benefit should be included on the PDL. That's another way to do it without listing individual agents.

Nancy Lee: The other thing I wanted to just kind of mention is that the agents that have cardiovascular outcomes are in patients with underlying established cardiovascular disease. So I just want to make that clear, as well. So a lot of these patients have had diabetes for greater than 10 years, more than 60% or 50% have underlying cardiovascular disease. So these are patients who are higher risk.

Ryan Pistoresi: So going back to your original question, what Michael just said where you say one of the drugs that is proven to have cardiovascular benefit is, you know, needs to be preferred on the PDL. Does that satisfy it or is there something else that you would like?

Amber Figueroa: I think it also needs to say something about not interchangeability.

Ryan Pistoresi: Okay.

Amber Figueroa: So that doesn't apply to this class of drugs. We're kind of jumping ahead. Copy that and take it out… there you go.

Michael Johnson: Any further discussion on the wordage of this?

Amber Figueroa: There's a couple of typos. On the drug list four down I think that's supposed to be a T-I-N at the end. Then if you continue to the next column it's T-I-N on the alogliptin too.

Ryan Pistoresi: So since we have some of these that are in the SGLT2s instead of saying all combinations containing these drugs should we say and combinations listed in the drugs reviewed column? So that way we know that the other ones that have the SGLT2 components are not subject to tip like this one.

Leta Evaskus: All combinations in the DPP4 inhibitors?

Michael Johnson: All listed combinations. You could potentially say all listed combinations in this class.

Amber Figueroa: After considering the evidence of safety, efficacy and special populations for the treatment of diabetes, I move that DPP4 inhibitors linagliptin, saxagliptin, alogliptin, sitagliptin and all listed combination drugs in this subclass are safe and efficacious. DPP4 inhibitors can be subject to therapeutic interchange in the Washington preferred drug list. Therapeutic interchange is allowed only within each diabetes subclass.

Nancy Lee: I second that motion.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Nancy Lee: For the GLP1s I… if we can remove the albiglutide since it is no longer going to be available.

Ryan Pistoresi: On the column to the left are the drugs that have been reviewed in this class to show that has been reviewed. So the way that I would recommend that is to say that albiglutide cannot be preferred. And so that way it shows that we did review it, but since it is being

discontinued by the manufacturer that we shouldn't prefer it when we do our cost analysis.

So just reading the language up there at the bottom, at least one drug with cardiovascular benefits needs to be preferred on the PDL and not subject to TIP. Should that not subject to TIP be referring to the drugs or just that one drug, if there is one drug? Just the way it's written I'm not sure if we would interpret that as, you know, just the drug itself or if there would be…

Michael Johnson: I would say just that one drug.

Ryan Pistoresi: Just that one drug. If there is one drug or…

Michael Johnson: Most agents… if you have two cardiovascular drugs it would be those two. Does that make sense?

Ryan Pistoresi: So just looking at the DERP review it said the semaglutide and liraglutide. So if we were to prefer if someone were to do one TIP would apply within that group or not?

Michael Johnson: I think you could substitute it with another agent with cardiovascular [inaudible].

Ryan Pistoresi: Within that? Okay.

Susan Flatebo: I just think maybe what Nancy said that we should maybe say at least one drug with cardiovascular benefits may be preferred in patients with a cardiovascular history. Do we want to call out…

Woman: We won't call out patient…

Ryan Pistoresi: Yeah. So the way that the motion is written is it says that one of these drugs will be preferred on the PDL, but do you want it to be preferred for use in that specific patient population rather than just being preferred in general?

Woman: Well, if it has cardiovascular benefits isn't that calling out patients with cardiovascular…

Woman: No, it's not. I would say with established cardiovascular disease is what's been studied in patients with underlying established cardiovascular disease. Not…

Amber Figueroa: One of the stakeholders said that it was… those including, I think, two or more cardiovascular risk factors.

Woman: Looking at the baseline demographics for Canvas, for [inaudible] Rag and for Leader trial more than 60% of patients had established cardiovascular disease.

Ryan Pistoresi: So Leta and I we kind of word-smithed what I think you're trying to say and we wrote it up there on the screen for you to read. So is this the correct interpretation of what you are looking for right now and then obviously there is the opportunity for more discussion to, you know, make this more clear and to what you intend as the P&T Committee.

Amber Figueroa: I still think we need to say something in there that there could be therapeutic interchange among any of the drugs with cardiovascular benefit.

Lisa Chew: I just have a question about whether the prescribing certain drugs for patients with proven cardiovascular disease lies here in the P&T section or is it more of a criteria regarding prescribing what the utilization…

Ryan Pistoresi: What we are looking at are just the recommendations for the [inaudible] to then go and see what drugs we then go through with our cost analysis. So if we do have a condition like this on the PDL we set it to another status so that way it is treated differently in the cost model, because it is being used for a certain subset of patients. Now it doesn't mean that it can't be used outside of those patients, but we'll treat it differently when we are building that model. I think this is okay and I'm just trying to think of another drug class where we

have a similar type of condition. But I can't think of one off the type of my head.

Nancy Lee: For the last paragraph what are committee thoughts about adding something about minimal harms, as well? I'm kind of thinking ahead for the SGLT2s with the cardiovascular benefits, but then one has unclear potentially high risk of harms with toe amputation and fracture risk and so I don't know if this… putting that information here for the future? I don't know.

Amber Figueroa: I think we have to be careful to not be too detailed. Not saying that the risk doesn't exist for that medication, but trying to keep it generalized as a class, you know, if you think about specific medications a lot of them have specific badness associated with it. I'm not minimizing that. I'm just thinking that when we're trying to keep a general overview of it. I also had a question about including in the first paragraph stating that albiglutide is safe and efficacious, but yet it is going to be pulled from the market. Do we want that up there?

Ryan Pistoresi: Right. So we can remove that because down at the bottom we do say albiglutide cannot be preferred on the PDL. So we do recognize that it is being discontinued. So we can remove it from that list because that first list is kind of saying these are all eligible.

Jordan Storhaug: I guess I have questions on the practicality of putting so many stipulations on the therapeutic interchange and whether or not it is actually going to be possible for people to have those level of details when deciding if they are able to exchange these medications.

Michael Johnson: What do you think?

David Johnson: I mean the therapeutic interchange is going to happen at the retail pharmacy. I never had a problem with it when I was doing it. But this is probably more complex than what it has been in the past. Realistically it didn't happen that much and I think in today's environment most retail pharmacists are going to not use it and call the provider.

Petra Eichelsdoerfer: The other thing that… again, similarly this is based on my experience, a lot of the pharmacists who may be practicing the therapeutic interchange may also be in a clinic setting where the provider is directly upstairs or across the street. They are very close and accessible and they may even have access to the electronic health records.

Leta Evaskus: I'm going to add in after this list of drugs, and all combinations listed in this subclass. Is that okay?

Ryan Pistoresi: Yeah.

Amber Figueroa: Jordan, I understand what you're saying, but I can't think of a different way to do it. You know, if I have a patient who's recently had an MI and been found to be diabetic and I specifically want them on this medication I can't think of a different way to do it to where that medication would be covered and not switched to something else.

Diane Schwilke: I mean you can always do DAW1, do not sub, if you specifically want that. And honestly from my perspective in most retail pharmacies I don't think therapeutic sub is used very often by the pharmacist. So I don't think it is going to be a huge issue with stuff getting changed all the time. It's just not something they do. I think in settings like mine where you do have the electronic health record you're probably most apt to do it in those settings as a pharmacist, but I think most retail pharmacists are not going to do it, just period. They're going to send a prior auth or a message to you. That's just the reality. Even though it's an option I just don't think it's widely used. But if you want to make sure you can always use that "do not sub" or whatever. Sign on the opposite side. Check the box or whatever.

Ryan Pistoresi: Do you want us to then maybe remove that? Or are you just noting that there are difficulties with the…

Diane Schwilke: I don't think it needs to be removed. I'm just saying that's probably the reality. I don't know if that helps anybody on the panel. I think

that is the reality of practice, just giving a perspective of… I kind of have dispensing and clinical both sides to my job. I see both sides.

Amber Figueroa: I think it's important that it stay in there whether or not providers choose or realize that they can do DAW or pharmacists realize that they can or can't do therapeutic interchange. I still think for the… what our purpose here today is, is to make sure that one of those is covered on the PDL. How a provider a patient choose to access that since there are multiple avenues.

Ryan Pistoresi: I think what I hear you saying is that we need to have one of these drugs at least preferred, but we don't necessarily have to have that TIP in there. So that way instead of having that opportunity for therapeutic interchange you would know that it is preferred and you could still write, you know, the DAW if you need it.

Jordan Storhaug: I think the net effect is that these drugs that have the cardiovascular benefit are in settings where they don't have the ability to get the whole story. These drugs will just be effectively not subject to therapeutic interchange because they may not have the information to know the situation and are not going to be able to make the switch without contacting the physician for more information. So the benefit is that we will have… we will be guaranteed that people won't be switched off these cardiovascular drugs, but the negative effect is that there is less opportunity for people to use the therapeutic interchange. And what I'm hearing is that… in either case probably doesn't matter too much because it's not used very often except in settings where the clinical information is available.

Lisa Chew: Ryan, you were saying though if one of those cardiovascular drugs is a preferred there would be no reason to do a therapeutic interchange. Is that what you're saying?

Ryan Pistoresi: Right. I'm saying if we just leave it as, you know, at least one of these drugs must be preferred then that way, you know, any time you would prescribe that drug with cardiovascular benefits for those people, you know, it wouldn't be ever subject to therapeutic interchange. It would just be a preferred drug. And also for ease of

implementation, you know, when we're doing the programming not having to have that separate TIP subclass in there would be easier for us to then administer it. So I think it would get one of these drugs, or both, on the PDL.

Amber Figueroa: So the second paragraph there would be gone. There would be no therapeutic interchange among this class.

Ryan Pistoresi: I was actually looking at the third paragraph where it says, you know, one of these drugs must be preferred and then these drugs would be subject to TIP within that class. That's kind of where I was looking at removing that TIP stipulation.

Michael Johnson: So I think what you're saying is if we just state that one of these agents needs to be on the preferred drug list that's all we need to say.

Ryan Pistoresi: That's what I believe that you're looking for just after Jordan's comments.

Michael Johnson: I think that's reasonable to make it simple. It gets us the medication and it doesn't delay, you know, with prior auth and all of that. We could modify that paragraph.

Ryan Pistoresi: The third one.

Amber Figueroa: So just to clarify if I wrote a prescription for semaglutide nobody would therapeutically interchange it even though the second paragraph says therapeutic interchange is allowed?

Ryan Pistoresi: It would depend on what the preferred drug is. So if it was the liraglutide or the semaglutide. So if there was one of those preferred, let's say the liraglutide is preferred and you wrote for semaglutide. It could be tipped into whatever the preferred one is.

Amber Figueroa: But it wouldn't be tipped into exenatide?

Ryan Pistoresi: If exenatide was a preferred drug there is a possibility that it could be, but that just depends on what is the preferred drugs and if we have multiple for this class. Is that not what you were…

Amber Figueroa: It's not… it doesn't fall within those two that have the cardiovascular benefit. So if there's a chance that if I write for liraglutide and it could be subbed for exenatide and I wouldn't even know, I'm not okay with that as a prescriber.

Jordan Storhaug: I think I feel differently about it in that I think that the level of complexity that we're adding to that isn't necessary and I think providers will be able to either choose the appropriate medication for that… more the pharmacies who are making this interchange will have the information to know to choose the cardiovascular interchange that is selected, that is preferred.

Amber Figueroa: So you're saying what you write down you're okay with them getting something else?

Jordan Storhaug: If I write the preferred they won't be getting anything else.

Ryan Pistoresi: So what was mentioned by Diane you can also write the DAW, do not sub, if for whatever reason that specific drug that's non-preferred you were looking to, you know, prescribe rather than any of the preferred products. So I think that kind of supplements what Jordan was…

Amber Figueroa: I thought there were multiple preferreds here.

Ryan Pistoresi: There could be. There's going to be at least one preferred given that there is the condition. I mean theoretically there originally could have been no preferred products or they all could have been preferred, but from now moving forward at least one of those drugs will be preferred and one of those drugs will be the two that was listed in the DERP report. Does that clarify it or make it more…

Amber Figueroa: It clarifies it for me. I'm going to vote nay, but that's okay.

Ryan Pistoresi: Okay.

Jordan Storhaug: So after consideration the evidence of safety, efficacy and special populations for the treatment of diabetes, I move that GLP1 agonist's dulaglutide, exenatide, exenatide XR, liraglutide, semaglutide, and all combinations listed in the subclass are safe and efficacious. GLP1 agonists can be subject to therapeutic interchange in the Washington preferred drug list. Therapeutic interchange is allowed only within each diabetes subclass. At least one drug with cardiovascular benefits needs to be preferred on the PDL for patients with proven cardiovascular disease. Albiglutide cannot be preferred on the PDL.

Catherine Brown: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign.

Amber Figueroa: Nay.

Michael Johnson: Okay.

Lisa Chew: I hate to do this, but I don't think we list the lixisenatide in the paragraph.

Ryan Pistoresi: Good catch.

Leta Evaskus: Jordan, do you want to read it again?

Jordan Storhaug: I don't think… with that understanding… I mean do you think that you have a different motion now that we added it? It was just an oversight on our end. Okay.

Dale Sanderson: This is a small thing. Is there a reason why diabetes is capitalized in all of these paragraphs?

Ryan Pistoresi: I think it was just kind of an oversight. So we did change it to lower case and we can change the… we can change it in the other ones. It was just an oversight. Thank you.

Nancy Lee: I think the wording can be similar to the GLP1 section and then I guess the other question I had is background information regarding the last sentence of canagliflozin and dapagliflozin can be subject to therapeutic… I don't know where that… what the basis for that is or the history for that is.

Michael Johnson: I had the same, you know, the empagliflozin is not listed. Was there a reason?

Ryan Pistoresi: I don't have… we don't have a reason listed and I think it may have been from the original report prior to getting that cardiovascular information there may have been not as much data that was presented in the DERP review from 2016. So we can certainly take that out.

Amber Figueroa: In the previous one didn't we say that it wasn't subject… that it was subject to therapeutic interchange for the cardiovascular benefit?

Woman: Do you want to add that to this one too?

Amber Figueroa: No, I don't. I want to know if I'm going to vote yes or no.

Ryan Pistoresi: I think we finalized with no therapeutic interchange within the… yeah.

Jordan Storhaug: I think we would like to take that third paragraph and apply it to the SLGT2 section, as well.

Nancy Lee: It's T. SGLT2 inhibitors.

Michael Johnson: Any other discussion?

Diane Schwilke: If nothing else, after considering the evidence of safety, efficacy and special populations for the treatment of diabetes, I move that canagliflozin, empagliflozin, dapagliflozin and all combinations in this

sub class are safe and efficacious for the treatment of their approved indications. SGLT2 inhibitors can be subject to therapeutic interchange in the Washington preferred drug list. Therapeutic interchange is allowed only within each diabetes subclass. At least one drug with cardiovascular benefits needs to be preferred on the PDL for patients with proven cardiovascular disease.

Jordan Storhaug: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign.

Amber Figueroa: Nay.

Leta Evaskus: It's 11:45. We missed our break so why don't we just go straight into lunch and come back in an hour? So we'll be back at 12:45.

Michael Johnson: We'll be adjourned until 12:45.

Leta Evaskus: Stephanie are you still on?

Stephanie Christofferson: Yes, I am.

Leta Evaskus: Do you want to call back in at 12:45?

Stephanie Christofferson: Sure thing.

Leta Evaskus: Thank you.

Stephanie Christofferson: You're welcome. I'll talk to you guys in a bit.

Michael Johnson: Welcome back. We're going to reconvene the Washington State Pharmacy and Therapeutics Committee and I think we will start with April.

April Phillips: So our recommendation for the Apple Health Medicaid single PDL is for the newer diabetics. We are going to continue with the EA for the Symlin for type 1 diabetes. We also recommend that the products are considered safe and efficacious within the same subclass and are eligible for preferred status. Similar to the previous recommendation the non-preferred products require a trial of two preferred within that same subclass before a non preferred in that subclass will be authorized unless contraindicated or not clinically appropriate unless there's also… also if there's only one, they only need to try one product.

Per the previous P&T recommendation we've noted one drug with cardiovascular benefits must be preferred on the PDL.

Jordan Storhaug: April, I wonder if there is any recommendations on how people move between the subclasses in this category?

April Phillips: You mean if somebody is on a DPP4 and wants to go to an SGLT2? They are considered separate. So if they want a DPP4 that's non preferred they have to try a DPP4 that is preferred. Same with the SGLT2.

Jordan Storhaug: I guess the question would be will all subclasses have a preferred drug on it?

April Phillips: Yes.

Jordan Storhaug: I move that the Apple Health Medicaid Program implement the limitations for the newer diabetic drug class listed on slide 4 as recommended.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign.

Amber Figueroa: Nay.

Michael Johnson: It passes. So Stephanie, just give us a minute to get your slides up.

Stephanie Christofferson: Just let me know when you're ready.

Michael Johnson: All right. We're ready.

Stephanie Christofferson: All right. The next topic we have is the bladder relaxant preparations. The first slide will talk about the overview of the disease state. So overactive bladder or OAB is a chronic, debilitating syndrome that's usually characterized by urinary urgency with or without urge incontinence usually in combination with urinary frequency and nocturia. Overall the prevalence of overactive bladder occurs equally in men and women and more women actually suffer from urinary… I'm sorry, overactive bladder with incontinence. The prevalence of OAB is almost 20% in patients 60 years of age and older. In the resting state the pressure within the bladder is lower than the urethral resistance and as urine accumulates in the bladder urethral resistance decreases the detrusor muscle and the bladder contracts and it causes the bladder to empty. However, patients that have OAB there's an over activity of the detrusor muscles that cause spasticity which results in higher bladder pressure and then urgency and urge incontinence. So in order to combat that the way that the antimuscarinic medications work is by relaxing the detrusor muscles to help prevent the muscle contraction. Next slide.

We will address the FDA approved indications. So I put these in a chart. Hopefully it makes it a little bit easier to see which medications have indications… FDA approved indications for what. But as you can see most of the products in this category have the same indications, which is the treatment of over-active bladder with symptoms of urge, urinary incontinence, urgency and frequency. And then oxybutynin has a couple extra indications here – one being the release of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflux neurogenic bladder and then with the oxybutynin ER it is also indicated for the treatment of

pediatric patients age 6 years of age and older with symptoms of detrusor over activity associated with neurological condition. There are several generic medications available in the class which include Enablex, the Ditropan, Detrol LA and the trospium and trospium ER. Also, just as a side note, Oxytrol is available as an NPC. However, it's not been approved for use in men due to concern of prostate-related complications. Next slide, please.

We will talk about the dosing and formulations. So dosing frequency varies amongst the products. Many of the products are available to be used once daily. This would include Enablex, Toviaz, Myrbetriq, Ditropan XL, Gelnique, VESIcare, Detrol LA and trospium ER. Twice a day dosing of medications include Ditropan, which can actually be dosed up to three times a day, Detrol and trospium. And then we've got twice weekly availability with the oxybutynin transdermal product. As you can see, based on this chart, many of the products have dose adjustments for hepatic and renal impairment patients. Most of the medications are available as an oral tablet or capsule formulation. But Ditropan does have a solution available and as I mentioned before there is an oxybutynin transdermal gel and patch for those unable to either swallow or tolerate some of the oral medications. Next slide, please.

We'll go on to the clinical considerations and guidelines. So with the mechanism of action the antimuscarinic medication activity is focused on the muscarinic receptors located on the detrusor muscle. There are five known muscarinic receptor subtypes which are labeled M1 through M5, but the subtype 3 is thought to be the subtype primarily responsible for normal maturation contraction. However, it is unclear of selective antagonism of M3 receptor improves patient tolerability or clinical efficacy, but it has been known that non-selective antimuscarinics may produce adverse effects consistent with anticholinergic actions and then central nervous system and the GI track. Myrbetriq is a beta-3 adrenergic receptor agonist which relaxes the detrusor muscle during storage phase of the urinary bladder fill void cycle thereby increasing bladder capacity. So it works a little bit differently. As far as warnings, all the medications are contraindicated in patients with uncontrolled narrow-angle glaucoma

or gastric or urinary retention except for the Myrbetriq. CNS side effects are common except for the Myrbetriq and as less [inaudible] at the [inaudible] and [inaudible] since the medications don't seem to cross the blood brain barrier or CNS system. Most of the medications, like I said, are anticholinergics and have the expected adverse effects of dry mouth and constipation. With the oral oxybutynin products having the highest anticholinergic effects. The incidences of the adverse effects are also higher with the immediate release products compared to the extended release products. [inaudible] still have the same side effects, it's just in clinical trials it is shown to be to a lesser degree compared to the IR products. Myrbetriq is not recommended in patients with severe uncontrolled hypertension as the medication may increase the systolic and diastolic blood pressure in patients. And then finally the transdermal Oxybutynin may transfer to other people with skin-to-skin contact so it's been suggested in order to minimize that after the medication has dried, is to make sure it is covered with clothing and be sure that patients, of course, wash their hands immediately after application. Also of note is that the transdermal gel is alcohol-based and therefore it can be a flammable product. Next slide, please.

As far as pregnancy, oxybutynin is a pregnancy category C while… I'm sorry, pregnancy category B, while all other drugs in the class are a pregnancy category C. The two oxybutynin products, the IR and the ER are indicated for… indicated in children ages 5 and 6 respectively whereas the other products have not had their safety or efficacy studied. In the geriatric population for patients greater than 65 years of age there was not an overall difference in safety or efficacy with Enablex, Myrbetriq, VESIcare, Detrol, trospium or Toviaz. However, on patients 75 years of age and older the incidence of adverse drug reactions are higher with trospium and Toviaz and then with the oxybutynin products just as a word of caution in older patients just due to the greater sensitivity patients have within this population to the product it is suggested that the medication be started on the lower end and increased slowly just to monitor for those side effects. Next slide.

We'll briefly touch base on some of the newer guidelines. The American Urology Association actually recommends non-pharmacological interventions as a first line therapy such as bladder training, bladder control strategy, public [inaudible] muscle training and fluid management. If that doesn't work the oral antimuscarinics including Enablex, Toviaz, oxybutynin, VESIcare, Detrol or trospium should be offered as a second line therapy and then the guidelines state that the Myrbetriq can also be used as a second line as it has similar efficacy to… of the antimuscarinics. The American College of Physicians also recommends the non-pharmacological therapy as first line therapy. They state that if that's unsuccessful then the pharmacological therapy should be used as second line therapy. The authors of the guidelines concluded the pharmacological agents were similar in their effectiveness at managing urgency, urinary incontinence and had a moderate benefit in reaching continence rates. The guidelines don't state which medications are superior compared to another, but did note that VESIcare had the lowest risk of discontinuation resulting from adverse drug reactions and that oxybutynin had the highest risk of discontinuation. When looking at Enablex and Detrol compared to placebo they found that discontinuation was about the same. So overall there is little to no difference in efficacy among the agents when comparing the immediate release… or even when comparing the immediate release to the extended release really the difference becomes in the variations of adverse effects. The class could be therapy interchangeable with the final selection really depending on the individual patient preferences in the requirements and response and tolerance to the medications. So with that I'll go ahead and end my portion and open it up to any questions.

Dale Sanderson: The problem is, you know, these are being used in older people and yet they have such an anticholinergic load to any continence.

Stephanie Christofferson: Certainly. Yes. You know, again, first I think, based on the guidelines, you try to do the non-pharmacological approaches and then, again, if that doesn't work then try to pick a medication with the lowest adverse drug reaction profile. That would be my personal recommendation. Probably medications like oxybutynin knowing

that, you know, their anticholinergic effects are pretty high. I don't have the statistics right in front of me but I know compared to all of the products that those were certainly an issue. So I would avoid ones with known issues and maybe try to stick to ones that have less CNS penetration, maybe something like the VESIcare. Again, you know, probably with a lot of patients and a lot of different drug classes there is probably going to be a trial and error to see what works best for patients.

Dale Sanderson: Thank you.

Stephanie Christofferson: You're welcome.

Marian McDonagh: Hello everyone. This is the drug class review preliminary update scan number 4 for the overactive bladder drugs. Slide 2.

You will see the history of this report. The last full review was a summary review done in 2013, but we did do an expanded scan that was done specifically for Washington State in January 2016. So the searches for this scan were completed through August of this year. Next slide.

Here are the inclusion criteria. The review covers adults with symptoms of urge incontinence or overactive bladder. There's quite a list of drugs there now. They are all included in this report. Slide 4.

There are no new FDA approved drugs since the last either expanded scan or the summary review. There is a drug that was approved in Canada and the company had indicated that they were going to be seeking approval in the U.S. I checked the FDA website yesterday and did not see that it has been approved yet. And there were no new boxed warnings for this group of drugs. Next slide.

There are some new comparative effectiveness reviews, so other systematic reviews out there that could be sued to help you… inform your decisions. One is from the Agency for Health Care Research and Quality and the other is from a Canadian organization. And then

there's also another one from AHRQ that is ongoing that is an update of a previous report that is specific to women. Next slide, slide 6.

This summarizes the new studies that have been found since the last report. Accumulatively there are 14. There are 6 new in this scan and there are additionally some new placebo-controlled trials. Next slide.

We see that there is a couple of slides here that show the table of studies that have been published since the expanded scan was produced. So on this slide the underlined studies are those that are new to this scan. So you'll see that there is a study of Mirabegron versus extended release Tolterodine that was conducted in Asian countries and then down at the bottom of the slide there is a study conducted in Turkey that was Solifenacin and Fesoterodine and then another one Solifenacin versus Mirabegron that was specifically in women. Slide 8.

Here we have some new studies. Solifenacin versus Mirabegron or the combination of Solifenacin and Mirabegron and this is in elderly patients. And then near the bottom of the slide we also have another study that was conducted in Iran that is comparing two of our older drugs. Slide 9.

This is just the summary. So since the last report no new drugs or boxed warnings. Two new comparative effectiveness reviews are available. They are from 2016 now. So they aren't super new. And total cumulatively there are 14 new head-to-head trials. Eight of those are comparing newer drugs in this group compared with older drugs – fesoterodine, mirabegron, and then the combination of solifenacin and mirabegron. That concludes the scan presentation.

Michael Johnson: There are no stakeholders for this topic.

Leta Evaskus: This is a scan so you need to accept it or not.

Michael Johnson: I propose that we accept this scan as adequate.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. Any discussion on this? I don't think there is any discussion so I'm going to reiterate the previous motion. So after considering the evidence of safety, efficacy and special populations for the treatment of overactive bladder, I move that darifenacin, fesoterodine fumarate, flavoxate, mirabegron, oxybutynin-gel/patch/tab, solifenacin, tolterodine and trospium are safe and efficacious. These drugs can be subject to therapeutic interchange in the Washington preferred drug list. Immediate release formulations cannot be interchanged for once-daily formulations and vice versa. A once daily formulation must be included as a preferred drug on the Washington preferred drug list.

Susan Flatebo: I second.

Amber Figueroa: Just a point. I don't know if we want to include it, but this is pediatric… has pediatric indication and the oxybutynin solution isn't included there. Just says gel/patch/tab.

Michael Johnson: Is that covered, you know, the safety, efficacy and special populations. So that would be pediatrics.

Ryan Pistoresi: Was the solution new? I don't see it on the fourth quarter PDL that we published. I see the gels. I see the ER tabs. I see patches. So is the solution then a new formulation?

Amber Figueroa: I don't think so. It's listed on the Magellan on slide 7 under the oxybutynin ER.

Leta Evaskus: Stephanie, do you know if the solution is new?

Stephanie Christofferson: It is not.

Ryan Pistoresi: We just haven't listed it.

Michael Johnson: It may have been an oversight last time. It's been on the market.

Ryan Pistoresi: I guess, you know, we could maybe just remove that gel/patch/tab or you already added solution. I guess that's fine then. We have the ingredient name up there, but we haven't specifically called out the solution or had that solution on the PDL. So we can make sure that it's on there.

Dave Johnson: Is there a clarification since the Oxytrol patches are available OTC and Rx in our… there's a horrific difference in cost, which would be preferred or covered?

Ryan Pistoresi: The one for the Medicaid PDL will be covered in the next section by April. So this is just kind of more for what UMP has. Thanks for bringing that up so we can get to that when we get to the Medicaid one.

Michael Johnson: I think there was a motion that was seconded. With the addition of the word "solution". No other comments. All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. Now on to April.

April Phillips: So for the Apple Health PDL our recommendation is that all products are considered safe and efficacious within their specified duration of action. So the immediate release versus the long-acting and are eligible for a preferred status at the discretion of HCA. We'd like a trial of at least two preferred with different active ingredients with the same duration of action of the non-preferred that's being requested.

Amber Figueroa: So going to the issue of the OTC formulation.

April Phillips: With that it would be based on the cost benefit and client disruption if they are currently on the OTC then, you know, it's preferred. Sorry,

I'm having an issue thinking. So our preferred status at that would be determined at a later time if it was preferred or not.

Jordan Storhaug: I think the clarification is, will OTC be considered separately from the Rx formulation and the cost benefit analysis?

April Phillips: I believe it would be considered part of it if the OTC is cheaper. It's similar to some of our other Washington PDL if the OTCs are cheaper than the prescriptions then they'd be considered included in that class.

Amber Figueroa: So keeping it generic and letting you guys decide based on the cost analysis is probably best. I move the Apple Health Medicaid Program implement the limitations for the overactive bladder drug class listed on slide 8. It says 8 at the bottom. Is it a different slide set?

April Phillips: Sorry, that's me. I was having a last-minute numbering issue.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. Are you still there Stephanie?

Stephanie Christofferson: I am.

Michael Johnson: Okay. We're just pulling up the slide. Just give us a second.

Ryan Pistoresi: Just to let you know, if you look at the agenda this one is just the Magellan presentation. So there is no OHSU presentation for this and that also means that this is not a class for UMP or L&I. This is just going to be a Medicaid specific class. Going into this presentation we'll have that mind frame and it will switch again later on. We'll try to preface each of these drugs classes now of which program it is for.

Michael Johnson: Stephanie, your first slide is up. Go ahead and get started when you're ready.

Stephanie Christofferson: Sounds good. The last topic I have for today is the topical steroids. Next slide, please.

We'll just touch base first on the overview of the disease state. As you're probably aware topical steroids are used for a large variety of conditions including atopic dermatitis, psoriasis, seborrheic dermatitis. The selection of the medication and the potency has to… the first [inaudible] of the medication and where it's going is… on the body is on the potency of the medication, the medication efficacy, the severity of the disease, location, surface area or the affected skin, the duration of therapy, the medication vehicle meaning cream, ointment, solution, patient preference and then also you have to take patient age into account. Next slide, please.

Next we'll look at the PDA approved indications. The first group we have here are the low potency steroids. I won't of course read through all of these, but you can see that many of the products have the same FDA approved indications with Verdeso, Capex shampoo and Derma-Smoothe having some different indications compared to the other products that are in the low potency category. Next slide, please.

The next slide looks at the medium potency products. Again, like the low potency products all of them have [inaudible]. The more indications with really the two outliers being the Cutivate and the Locoid products having additional indications for atopic dermatitis. For those patients is a patrons age of 3 months and older. Next slide, please.

This slide and then the slide right after it deals with the high potency products. Again, all the products are basically approved for the same FDA indication being that corticosteroid response of dermatosis, but then you've also got the Sernivo and Topicort which have the additional indication of plaque psoriasis in patients 18 years of age and older. Next slide, please.

That just rounds out, again, the rest of the high potency products that are available in the marketplace. Next slide.

The last category we have is the very high potency products. Again, most of them having the same indication, again. And then we see some additional products that do have an indication for plaque psoriasis. Overall, short-term durations of treatment, especially with the high potency medications have greater efficacy when they are compared to their less potent counterpart. However, the high potency topical corticosteroid do have an increased risk of side effects. Dermatological effects such as [inaudible], atrophy, anaphylaxis have occurred in patients as well as non dermatological specs on linear growth rate, bone density and then the hypothalamic pituitary adrenal access suppression, which can limit the long-term use of the products. However, the incidence of that occurring are relatively low. But also keep in mind is that the increase incidence of the adverse dermatological sects are positively correlated with the medications frequency and duration of use. So as you'll see later on the guidelines they really try to limit or the suggested guideline recommend that the duration of use be short-term. Go ahead and advance to the next slide.

We'll talk about dosing and formulations. So in general the low potency medications are applied anywhere from two to four times daily, which really depends on the medication and again all of them are approved for short-term duration. When you look at the low potency medications you can see there are a variety of different formulations available including creams, ointments, lotions, foams, body oil solutions, and then there are also some convenience kits in here that put together a couple of different products or medications together and just kind of… a patient convenience package. Next slide.

For the medium potency, again, application from range anywhere from once daily with the Cutivate and Elocon up to four times daily you can see with some of the betamethasone valerate products and the Synalar. Again, duration is short-term for these products. These are also available in several different vehicles such as foams, creams, lotions, ointments and solutions. Next slide, please.

For the high potency products, and this is on this slide and the slide following, again, these products can be applied anywhere from 1 time per day to 4 times per day. They are available in creams, lotions, ointments, spray gels, solutions and kits. This is when we first start to see gel formulations come into play and it has been noted that the cortisone and gel formulations can cause more dryness compared to other vehicle in addition to more irritation to their skin. So it's been suggested that their use be limited to areas such as the scalp or the bearded areas. Next slide.

That just completes the high potency products that are available. Most of these on this slide you can see are kits.

And then lastly on the next slide we have the very high potency. These products, the application frequency is a little bit less applied anywhere from 1 to 2 times daily. These are also available in a wide variety of vehicles such as lotions, shampoos, creams, gels. I won't go through all of those. You can see those on there. But, again, a lot of different options for patients. Next slide.

So for clinical consideration and guidelines. The way the medication works – they work by inducing the phospholipase A2 inhibitory proteins which control the biosynthesis of mediators of inflammation by inhibiting the release of arachidonic acid. It's really a substitution of either like a fluorine atom or acetone group or something like that within the product to make them have… [inaudible] slightly different, which that is what controls their potencies. For warnings, patients with peanut allergies should use caution and not use the Derma-Smoothe products because it does contain peanut oil. So that is something that is a little bit unique and prescribers should probably be aware of. Also of note is that the hypothalamic pituitary adrenal axis suppression, [inaudible] of Cushing's syndrome, hypoglycemia, glucose in the urine and growth retardation in children can result from systemic absorption of the topical corticosteroids. If these adverse reactions are seen the medication should either be discontinued or applied less frequently or, you know, even if it's a higher potency medication substitute lower potency products. All the

products that we've discussed today are pregnancy category C with the exception of the halobetasol propionate which has no data currently available. Next slide, please.

Other clinical considerations in pediatrics specifically is that prescribers should be mindful of the body surface area to weight ratio. This can cause an increased risk of systemic absorption of the product and increase side effects even when using like the same amount of medication in children as prescribers would use in adults. The medications that you see here in this chart show the breakdown of what medications would be appropriate and which age groups. And then the medications listed at the bottom here, I won't read through all of those, it just states within the package inserts that pediatrics should use the least amount possible of these products and the shortest duration as possible. Other products that are not listed on this slide is the… their safety and efficacy has not been established in the pediatric population. Next slide, please.

As far as guidelines from the American Academy of Dermatology the psoriasis guidelines, it states the majority of the patients with psoriasis have a limited disease and most causes 80% of their psoriasis are mild to moderate and they can be treated with topical agents. For more severe disease states these medications should be used in conjunction with UV therapy or systemic medications, but that the use of monotherapy with just topical agents alone in patients with the severe disease state is not routinely recommended. The guidelines actually rank the medications from 1 to 7 and this is based on vasoconstriction of the medication and the efficacy rates differ between the classes and even really between the medications within a certain group and there is just a wide range of efficacy within the products. In large clinical reviews potent and very potent topical corticosteroids were shown to be more efficacious than mild or moderate corticosteroids, which I think would be kind of expected. The choice of appropriate therapy, and the vehicle should take into consideration the disease severity, the location of the disease state, as well as the patient age. The medications, again, should be used for limited amount of time on the face and areas where there is skin-to-skin contact, and especially in infants. In other areas and in adults

guidelines actually recommend mid to high potency agents as initial therapy. It's also recommended that the more potent agents, again, be used on a short-term basis until [inaudible] response after which time patients should be instructed to use the medication intermittently for long-term management. It is also recommended that there should be a graduation reduction of frequency of the usage following clinical response due to the fact that true efficacy and risks associated with the long-term use are not known mostly because the clinical trials have been relatively short in duration and they also are concerned again about the tachyphylaxis, but again that is lacking to show significant problem. The guidelines do not recommend one product over another. For the American Academy of Dermatology for the Atopic Dermatitis guidelines, topical corticosteroids are typically introduced in treatment regimen after failure of good skin care or the use of moisturizers alone and they are efficacious in treating the disease and actually are generally the standard to which other topical anti-inflammatory therapies are compared to. Like psoriasis there's a variety of factors that should be considered when choosing a particular product. We talked about location, patient age and other factors, and, again, the cost of medication could be a concern to the patient. The comparative trials are limited in duration and in scope. Mainly most of the trials compare two, maybe three, different agents. So as a result there is no data to support one or even a few specific agents as being more efficacious than others. So it really comes down to, again, the patient preference along with cost and availability of products. An atopic dermatitis and psoriasis topical corticosteroid use in children should be used with caution for the issues that we talked about as far as increased risk for systemic absorption, again, due to the greater body surface area to weight ratio. However, during significant acute flares the guidelines for atopic dermatitis do recommend the use of mid or high potency steroids for short courses in order to gain rapid control of the symptoms. Again, however, long-term management they recommend the least potent corticosteroid be effective in order to minimize those adverse effects. For acute flairs the use of topical corticosteroids is recommended every day until inflammation lesions are improved and less thick, which can be up to several weeks at a time and after controlling the outbreak the goal is to prolong the period until the next flare and in these

guidelines it is suggested those previously topical steroids they recommend stopping them after improvement of symptoms, and then the patients be switched to moisturizers, but actually more recent guidelines they are suggesting a more proactive approach, which is to use… use the topical steroids for maintenance, especially for patients who experience frequent repeat outbreaks at the same location. What they are suggesting is a schedule of an application of a topical steroid once or twice weekly at the particular locations kind of as a proactive approach in trying to reduce the frequency of those flairs. Like the psoriasis guidelines, the American Academy of Dermatology for atopic dermatitis they also do not recommend one product over another. So with that said that concludes the materials I had for today for the topical steroids. Any questions with that?

Michael Johnson: I see no questions from the committee and there are no stakeholders.

Leta Evaskus: Stephanie, you can sign off now. We're all done with the Medicaid section… or with the Magellan reports anyway. Thank you very much.

Stephanie Christofferson: Thank you. Hope everyone has a great day. Bye bye.

April Phillips: Okay. So for the Apple Health preferred drug list we recommend that all products be eligible for preferred status within their potency level and that a trial of two preferred with different active ingredients in that subclass, potency subclass be tried prior to a non-preferred product.

Amber Figueroa: I move the Apple Health Medicaid Program implement the limitations for the topical steroid drug class listed on the slide previous.

Catherine Brown: I second.

Diane Schwilke: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right.

Ryan Pistoresi: So the next two drug classes that we have are a TIMs scan and then a HEP-C update and both of these will just be for UMP and L&I. So no Medicaid in those.

Marian McDonagh: This is the preliminary scan report for the targeted immune modulators. Slide 2.

The history of this report is that the last full update was #5, finished in June 2016 with searches through January of that year. There have been no other scans. This is the first one since that report and our searches were conducted through June of 2017.

On slide 3 there are all the populations for this report listed.

On slide 4 these are all the drugs that are currently included. Study designs include only head-to-head trials or head-to-head cohort studies.

Now on slide 5 we see that since that last report there have been three new drugs approved – sarilumab, brodalumab and ixekizumab. In addition there are newly approved biosimilar products. Two for infliximab and one for adalimumab. And we also noted that there are two drugs that are in phase 3 in the pipeline and probably coming to market in the not-too-distant future.

On slide 6 there were no new boxed warnings since the last update report.

On slide 7 there was one comparative effectiveness review that was published and is relevant. It is a health technology assessment of ankylosing spondylitis treatment in general and then we note that there is an Agency for Healthcare Research and Quality report that is in progress that is looking at rheumatoid arthritis treatments. Again, not limited to the targeted immune modulators but certainly including them.

On slide 8 we see that since the last report there have been 12 new potentially relevant trials. Three of head-to-head drug comparisons, four of head-to-head device or delivery method comparisons. Four trials of the biosimilars versus their reference product. And then one trial of one of the pipeline drugs compared with a currently marketed drug.

If we go to the table on slide 9 this is all of the new head-to-head trials. The top half of the table are the four head-to-head drug trials. So you'll see that there is three in plaque psoriasis and one in rheumatoid arthritis and then at the bottom these are the head-to-head delivery methods. So we had not had this type of study included in the report previously. So these are… two of these are comparing subcutaneous versus intravenous routes of delivery and one is comparing an auto injector versus a pre-filled syringe.

On the next slide these are the other new trials for the biosimilar drugs. There was one trial of adalimumab and three for infliximab and then as I mentioned there's the one trial of one of the drugs that's in development versus risankizumab for plaque psoriasis.

On slide 11 this is the summary. There are three new drugs, three new approved biosimilar products, two drugs in the pipeline, and then for new evidence there is one currently published systematic review and another one that may be coming soon. Then there are four head-to-head drug trials. One is a new drug, one is a new drug in a new population, and two are new comparisons that are already in the report. Three head-to-head delivery method trials that are all new to this report and then four trials of biosimilars versus reference products which would also be new to this report. And then one trial of the drug in the pipeline. So that concludes the presentation of this scan.

Michael Johnson: We have three stakeholders. We'll call them one at a time. First is Margaret Olmon followed by Chris Conner, followed by Marc Jensen. If Margaret Olmon will come to the front.

Margaret Olmon: Thank you so much. My name is Dr. Margaret Olmon from medical affairs at AbbVie. I appreciate the chance to talk to you about Humira adalimumab today. This will only be a short summary. The full prescribing information is available at RxAbbvie.com. Humira now has 10 indications in its profile which include treatment in moderate to severe active rheumatoid arthritis and psoriatic arthritis for reducing signs and symptoms inducing major clinical response, inhibiting the progression of structural damage, and for improving physical function, for reducing signs and symptoms in ankylosing spondylitis and in moderate to severe juvenile idiopathic arthritis for patients age 2 and older, to treat moderate to severe active Crohn's disease, pediatric Crohn's disease in children age 6 and older, and in ulcerative colitis for inducing and sustaining clinical remission, to treat moderate to severe chronic plaque psoriasis including in patients with fingernail psoriasis and currently Humira is the only FDA approved treatment regimen for moderate to severe hidradenitis suppurativa and uveitis. With long-standing safety data, 71 global trials, 14 years of on market experience and over 1 million patients exposed, Humira has a well-defined, published benefit to risk database. All TNF antagonists carry similar boxed warnings regarding serious infections, tuberculosis and malignancies. Patients starting any anti TNF including Humira should be screened for TB and carefully monitored for serious events.

In summary, the proven efficacy and well established safety profile and maintenance dosing across a wide range of indications are reasons why I respectfully urge the committee to maintain preferred status of Humira. I'm happy to answer any questions you might have and thank you for the time today.

Michael Johnson: Thank you. Next up is Chris Conner.

Chris Conner: Good afternoon. My name is Chris Conner and I'm with Bristol-Myers Squibb and I'm here to make a brief statement today in support of Orencia or abatacept. I'd like to start with a brief mention about an update that's been made to the indication section of our package insert. This is something that wasn't included in table 1 of the most recent scan document. So there have been two changes that I'd like

to draw your attention to. The first is in relation to the subcutaneous formulation and its use in pediatric patients with severe polyarticular JIA. The age for that indication has been lowered to 2 from 6. Secondly, there's been a brand new indication added for adults with active psoriatic arthritis. So again those are two changes that have yet to be reflected, I guess, in the scan report.

Next I'm required to draw your attention to a limitation of use statement that's in our package insert that's related specifically to the coadministration of Orencia with other biologic DMARDS or TNF inhibitors. This coadministration is not recommended and I'm also required to mention that the most common adverse event seen in our clinical trials included headache, upper respiratory tract infection, nasal pharyngitis and nausea. For a full listing I'd refer you to the full product package insert.

In closing, I'd like to just briefly review the results from the long-term randomized controlled head-to-head trial of Orencia or abatacept plus methotrexate versus adalimumab or Humira plus methotrexate both in patients with adult… or in adult patients the rheumatoid arthritis that failed to achieve adequate response on methotrexate monotherapy alone. This is called the Ample study. While this study found no difference in any of the efficacy endpoints, and there were many that ranged from measures of disease activity, measures of remissions, and measures of radiographic progression, this study did demonstrate a statistically significant difference in favor of Orencia with respect to injection site reactions, which was a pre-specified tolerability endpoint. Also at two years the discontinuation due to adverse events was found to be higher in patients randomized to adalimumab or Humira versus patients randomized to abatacept. Lastly, the discontinuations due to severe adverse events was also higher in patients randomized to adalimumab versus those randomized to abatacept. In closing, I'd like to just ask that you consider adding Orencia to the preferred drug list for the UMP and L&I populations. Any questions?

Michael Johnson: Thank you. Last up is Marc Jensen.

Marc Jensen: Good afternoon everyone. My name is Marc Jensen. I'm a pharmacist and an employee of medical affairs with Pfizer. I would really just like to quickly review the latest phase 3 head-to-head trial that was recently published in July in the Journal Lancet. I do have to remind to go to the package insert for full prescribing information. It is approved for the treatment of… Xeljanz or tofacitinib was approved for treatment of rheumatoid arthritis in adults with some caveats and also for a list of our adverse events including boxed warnings. But again I'd like to really focus on this phase 3 trial. It was a 12-month, double-blind, head-to-head, non-inferiority, randomized controlled trial conducted to assist the comparative efficacy of tofacitinib or Xeljanz monotherapy versus combination Xeljanz with methotrexate or adalimumab combination with methotrexate. None of the prior six phase 3 tofacitinib trials that evaluated monotherapy versus combination therapy of tofacitinib. Over 1,100 patients were randomized equally to receive either tofacitinib 5 mg monotherapy, tofacitinib 5 mg combination with methotrexate or adalimumab in combination with methotrexate at its approved dose. The primary end point was proven as signs and symptoms of 50% of American College of Rheumatology score or ACR 50 at six months and at six months those ACR 50 scores or response rates were 38% in those patients who received tofacitinib to monotherapy, 46% in patients who received tofacitinib and methotrexate, and 44% of patients who received adalimumab plus methotrexate. What we found is tofacitinib plus methotrexate was deemed non-inferior to adalimumab plus methotrexate although non-inferiority was not demonstrated for tofacitinib monotherapy versus either of the combination arms. And the proportion of patients who achieved either low disease activity or remission were in general similar to those ACR findings, the ACR 50 findings, higher in the combo, lower in the monotherapy arm. As far as side effects or adverse events the authors noted no new unexpected adverse events or safety issues in any of the treatment arms and most of the adverse events were mild to moderate in nature. The most common adverse events were URIs, ALT elevations, nasal pharyngitis, UTIs and nausea and interestingly enough the incidence of liver function tests the elevations were higher in either of the combination arms versus the monotherapy arm. So the authors concluded that there were similar safety and

efficacy noted with tofacitinib plus methotrexate compared to adalimumab plus methotrexate.

So in conclusion, this is the seventh phase 3 randomized controlled trial with tofacitinib and RA and part of a program evaluating the safety and efficacy of tofacitinib in a wide range of RA patients. This oral medication has been studied in over 6,300 patients with over 21,000 patient years of experience. Xeljanz is a useful option in combination with other non-biological DMARDS or as monotherapy to have available on the PDL as a preferred agent for those patients who cannot tolerate methotrexate or have not adequately responded to methotrexate or biologic-based therapies due to its unique mechanism of action, established safety and efficacy and availability as an oral dosage form. Thank you for your time and I'd like to address any questions you might have.

Michael Johnson: Thank you.

Leta Evaskus: The motion that is in your binders left off the three new drugs listed at the bottom here. They are new this scan, but they are not considered reviewed, so they can't be included in the motion. Sorry, you will need to accept the scan.

Lisa Chew: I move to accept the scan.

Dale Sanderson: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right.

Amber Figueroa: I have a question based on our previous motion and then this email that's in here from the dermatologist in Spokane. It doesn't jive. It doesn't seem to based on what we said here as far as… I don't see that it says that they have to have tried and failed. The email seems to say that they have to…

Leta Evaskus: This email… the stakeholder input seems to be for Medicaid, but we are not reviewing this for Medicaid because they say in the last paragraph on Medicaid or state-sponsored insurance. Okay, I guess it is considered a UMP.

Ryan Pistoresi: For the UMP program the preferred products are Humira and Umbral as what is on the PDL. But if they do try and fail that product they can then step into the other products. They do have different cost sharing tiers because they are the non-preferred drugs, but if you do that and you can demonstrate that it is because of the TNF that they don't respond to a TNF and they have to move into an IL17 or another type of TIMs product that is approved for that, they can. But it is at the non-preferred cost share.

Amber Figueroa: So they have to try both of them? That's the implication here. Or does it depend?

Ryan Pistoresi: If they try and they don't respond they can submit information to UMP saying, you know, we're looking to go to this one. I believe that they have criteria that recommends that they… or ensures that they do the preferred products first, but if they… since they are both TNFs I believe that they just have to demonstrate that they need to move on to the next one. So I believe that PA criteria that exists for these drugs make sure that they are just stepping through the preferreds first and if there is a clinical reason that they can't then they just submit that information.

Woman: Is it possible he's just not aware of this or is it that hard to demonstrate?

Ryan Pistoresi: I'm not sure. I'm not sure it's…

April Phillips: I'm assuming that the author of this email was referred to Washington Medicaid's previous DUR motion which was tried and fail all preferreds with the same indication unless clinically and appropriate contraindicated. So I'm assuming that's what this particular person meant.

Michael Johnson: So it kind of appears that with that information we're probably reiterating the previous motion. Is that correct?

Amber Figueroa: Do we want to… since these are different categories of medications do we want to specify that at least one in every category be covered?

Ryan Pistoresi: So this is… we've mainly been looking at it having the FDA approved indications and using that kind of as our guide for setting up, you know, how this class would be kind of modeled, you know, and how we would then choose the preferred drugs for the list. Doing it by each individual one you're going to be setting up, you know, six or seven within, you know, different subclasses within. I'm not sure how we would be able to necessarily implement that.

Amber Figueroa: So as it stands we have to know the patient's diagnosis then to determine if the medication that the prescriber prescribed is covered or not. Is that what you're saying is that it is based on the diagnosis? Or there are certain medications under each diagnosis?

Ryan Pistoresi: The way that we've figured out which is preferred and non-preferred is that we have to have all of the diagnoses listed in the scan. So rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's, ulcerative colitis and plaque psoriasis. So we do have a preferred product for each of those indications based on our current PDL. So for any of those indications there is a preferred product.

Amber Figueroa: And then what about the uveitis and hidradenitis suppurativa? Humira has the only indication.

Ryan Pistoresi: Yeah, if that is something that you want to add to the scan as ensuring that there would be a preferred product for that indication, you can. It's just that for what we've done traditionally is having the rheumatoid arthritis and the other ones that are listed there.

Michael Johnson: Thinking back on when the last time we did this I don't remember ever talking about uveitis and other indications other than what's here. So I'd hate to try to lump those in.

Ryan Pistoresi: If there are other indications… so if we choose, let's say one drug and it doesn't have an FDA approved indication for that drug they should be able to step into that because there's no preferred product for them and so there shouldn't be any barriers for them to step into that if it is a unique indication that is not already covered by a preferred product.

Amber Figueroa: So translating that – if we don't include that in here the patient will still be able to get the medication?

Ryan Pistoresi: If it's for one that is, you know, preferred or non-preferred, yeah. If it's not one of those covered indications. But if you're trying to prescribe a drug with that indication and there is a preferred product with that approved indication they would have to go through the preferred one. But if it is one that is unique and there are few, you know, in this class that are for very rare, ultra-rare or orphan conditions they don't have to step through those because the preferred products just don't have evidence for working in those diseased states; especially for some of these other non TNF conditions.

Michael Johnson: Any other comments?

Lisa Chew: I agree with keeping the diagnoses as stated up there. In terms of the scan they only included those diagnoses within that scan listed there. So I would keep those… I would not add any additional diagnoses.

Amber Figueroa: Nobody wants to read it. The words are too hard.

Jordan Storhaug: After considering the evidence of safety, efficacy, effectiveness and special populations for the use of targeted immune modulators for the treatment of immunologic conditions for which they have FDA indications, I move that abatacept, adalimumab, alefacept, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept,

golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, ustekinumab, vedolizumab are efficacious. The PDL must include a drug approved for treatment of the following FDA indications (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis) and should include a self-administered agent if indicated. These medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Catherine Brown: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign.

Shelley Selph: This is the third update to the hepatitis C report. Next slide.

Here are the key questions. The first looks at comparative benefits and harms of all oral regimens that contain at least two direct-acting antivirals. This is a change from the previous update where the inclusion of only one DAA was required. Such regimens as simeprevir plus ribavirin or regimens containing interferon are no longer included in this reported. The second key question looks at comparative results based on subgroups of patients. For this update we focused on the effects of disease stage based on degree of either liver fibrosis or cirrhosis, specific prior treatments, resistance conferring polymorphisms, and the effects of higher versus lower viral loads in benefits and harms. We also included the transplant population and those who abuse illegal substances. The third key question examines the relationship between SVR and long-term health outcomes with DAA treatment. Next slide.

We included both adults and children in this review. Although there was no evidence that met inclusion criteria in children that was published through our search dates which were through the first week in August. We recently came across limited information in

children published after our search dates were conducted, which will be included in the next update. In this update we also required trail evidence to be randomized and removed references to single-arm studies. We also required observational studies to have a sample size of at least 1,000. In addition, we followed a more simplified format than was used previously and moved some information to the appendix in order to keep the main report more succinct. Also we completely reorganized the report so now it has fewer sections and subsections, which we believe makes for improved readability. Next slide.

Here are the included drugs. The top two regimens with approval dates given are the regimens new to this update. Next slide.

Here's some general findings. As mentioned we have two new regimens. This update glecaprevir and pibrentasvir as well as sofosbuvir velpatasvir now with voxilaprevir. All included regimens are capable of yielding high rates of SVR in specific populations. Most to all study participants experienced an adverse event during the trials although these events were usually not serious. Longer treatment and including ribavirin and the treatment regimen occasionally resulted in increased risk of experiencing any adverse event. And few to no participants left the study due to adverse events. So that was a rare occurrence. Next slide.

With regards to the regimen approved most recently head-to-head studies indicated no difference between treatments with eight weeks of glecaprevir/pibrentasvir compared with 12 weeks treatment with the 2D regimen. And as a reminder that stands for ombitasvir, paritaprevir and ritonavir and this is in patients who are genotype 1 without cirrhosis. Similarly, treatment with 12 weeks of glecaprevir/pibrentasvir was similar to 12 weeks of declatasvir/sofosbuvir treatment in patients who were treatment-naïve without cirrhosis and were infected with hepatitis C genotype 3. Next slide.

For the second regimen new to this review there were only two head-to-head trials. In both cases sofosbuvir/velpatasvir/voxilaprevir

treatment was compared with dual therapy with sofosbuvir and velpatasvir. Eight weeks of triple therapy was not as good as 12 weeks of dual therapy in patients with genotype 1A. The triple therapy for 8 weeks was similar to 12 weeks with sofosbuvir/velpatasvir in patients who had previously been treated with a DAA and were infected with genotypes 1B, 2, 3, 4 or 6 and also in patients who had genotype 3 hepatitis C along with liver cirrhosis. In a second trial 12 weeks of triple therapy with voxilaprevir yielded improved rates of SVR compared with 12 weeks of dual therapy in DAA experienced patients with genotype 3, but similar benefits and harms as dual therapy in treatment experienced patients with genotypes 1 and 2. Next slide.

Adding ribavirin improved SVR rates when patients were treated with sofosbuvir and velpatasvir and had genotypes 1 through 4 or genotype 6 and when patients with genotype 1A were treated with a 3D regimen for 12 weeks. Next slide.

Extending the duration of treatment to 24 weeks improved rates of SVR with ledipasvir and sofosbuvir when patients were treatment experienced with genotype 1 and also when patients were treatment-naïve with genotype 3. Next slide.

This is the first update that we have included resistance information. We found evidence that having a resistance-conferring mutation polymorphisms, also known as an existence associated variant, resulted in lower rates of SVR when patients were treated with glecaprevir and pibrentasvir and the patients had both NS3 and an NS5A polymorphism. When the patients were treated with 8 weeks of triple therapy with sofosbuvir, velpatasvir and voxilaprevir and the patient had an NS3 polymorphism. When a genotype 1 patient had an NS5A polymorphism and were treated with grazoprevir and elbasvir and when genotype 1 patients without cirrhosis had an NS3 polymorphism and were given the combination of simeprevir and sofosbuvir. Next slide.

Having a higher viral load at baseline increased the risk for it not experiencing a sustained viral response when the treatment with

sofosbuvir, velpatasvir and voxilaprevir lasted for 8 weeks. When grazoprevir and elbasvir were given to treatment-naïve genotype 1A patients and when genotype 1 patients without cirrhosis were treated with 8 weeks of simeprevir and sofosbuvir and also when treatment-experienced genotype 1 patients were given 12 weeks of ledipasvir and sofosbuvir regardless of whether ribavirin was included or not. Next slide.

Having cirrhosis lowered rates of SVR when treatment-experienced genotype 1 patients were treated with 12 weeks of ledipasvir and sofosbuvir. When patients with genotypes 1 through 4 were treated with 8 weeks of the triple therapy with voxilaprevir and when patients with genotypes 1 and 2 were given 12 weeks of dual therapy with sofosbuvir and velpatasvir compared with 12 weeks of triple therapy. Next slide.

New to this report is evidence on the associations between SVR and long-term health outcomes. We now have observational evidence that in patients treated with ledipasvir and sofosbuvir or with the 3D regimen who achieved SVR mortality was decreased. And we also have observational evidence that achieving SVR decreases the risk of hepatocellular carcinoma. Next slide.

Some take home points. Based on one trial each, 8 weeks of glecaprevir and pibrentasvir is similar to 12 weeks of the 2D regimen and 12 weeks of glecaprevir and pibrentasvir is similar to 12 weeks treatment with declatasvir and sofosbuvir. Eight weeks of triple therapy with sofosbuvir, velpatasvir and voxilaprevir was similar to 12 weeks without voxilaprevir in most cases. In some instances SVR is lower in the presence of polymorphisms, higher viral load, and cirrhosis and not on the slide SVR may be increased in some cases with the addition of ribavirin over extending the treatment duration although this may also result in increased risk of experiencing any adverse event. Overall, throughout the report we have low to moderate confidence in our best estimates for SVR and due to sparse data lesser confidence in our estimates for serious harms and for the effect of resistances. Next slide.

Please send us any questions you have via email and this concludes the presentation on hepatitis C. Thank you.

Michael Johnson: We have two stakeholders. The first stakeholder Yusuf Rashid followed by Margaret Olmon.

Woman: Yusuf Rashid is one of our MCOs so I think he mistakenly signed up.

Michael Johnson: Margaret Olmon?

Margaret Olmon: Good afternoon. I'm Margaret Olmon from medical affairs at AbbVie and I want to thank you for letting me speak today about glecaprevir pibrentasvir which is now known as Mavyret. It was recently approved as a once-daily ribavirin free [inaudible] treatment for patients with chronic hepatitis C infection. Mavyret is indicated for the treatment chronic HCV across all genotypes for adults without cirrhosis or with compensated cirrhosis. Mavyret is also indicated for those with HCV genotype 1 infection who previously have been treated with a regimen containing an NS5A inhibitor or [inaudible] inhibitor, but not both. This would include treatment of those with genotype 1 who failed regimens such as Harvoni, Epclusa or sofosbuvir plus declatasvir. It is estimated that Mavyret can treat up to 95% of HCV patients. The vast majority of patients awaiting treatment are estimated to be both treatment-naïve and non-cirrhotic and would be eligible for 8-week treatment duration. Mavyret's clinical program included more than 2,300 patients across nine clinical trials. To summarize, the overall efficacy rates of Mavyret in the modified intent to treat analysis a 99% SVR12 rate was achieved for treatment-naïve patients without cirrhosis across all HCV genotypes treated for eight weeks. A 99% SVR12 rate was also seen in 146 patients with compensated cirrhosis across genotypes 1, 2, 4, 5 and 6 who were treated for 12 weeks. SVR12 rates for genotype 3 patients, the more difficult to treat, with compensated cirrhosis were 100% for treatment-naïve patients treated for 12 weeks and 96% treatment-experienced patients treated for 16 weeks. No dosage adjustments are needed for HCV, HIV co-infected patients and no adjustments are needed for patients who have severe renal impairment including those on dialysis. Relative to safety Mavyret

carries a boxed warning regarding the risk of hepatitis B reactivation in patients co-infected with HCV and HBV as do all the direct-acting antivirals. Mavyret also has two contraindications one for patients with severe hepatic impairment, child pube C and the other for patients taking [inaudible] atazanavir or rifampin. The most common adverse reactions in clinical trials greater than 10% were headache and fatigue and the ease were comparable among patients with compensated cirrhosis and without cirrhosis. I appreciate the committee's time to review Mavyret as a pangenotypic treatment option for HCV patients and respectfully request that Mavyret be considered for addition to the formulary. Thank you so much for your time and I'm happy to answer any questions you might have.

Michael Johnson: Thank you.

Leta Evaskus: Is that all of the stakeholders?

Michael Johnson: Yes.

Nancy Lee: It looks like there are two medications not listed in the second column under Hep-C and genotype 1 through 6. The voxilaprevir triple combination and then the glecaprevir combo.

Ryan Pistoresi: Right. So this is not a scan. This is an update. So for the scans we can just reiterate the same motion, but for this one, you know, if you want to reiterate the same motion that we previously had but add the two new ones we could start there and see if there is any additional discussion, but we'll add those in to be eligible to be preferred… for their FDA approved indications.

Woman: Don't blame me for my pronunciations. Hepatitis C genotype 1 through 6. After considering the evidence of safety, efficacy and special populations for the treatment of hepatitis C, I move that daclatasvir, glecaprevir/pibrentasvir, grazoprevir/elbasvir, ledipasvir/ sofosbuvir, paritaprevir/ritonavir/ombitasvir, paritaprevir/rit/ ombitasvir/dasabuvir, simeprevir, sofosbuvir, velpatasvir/sofosbuvir, voxilaprevir/velpatasvir/sofosbuvir are safe and efficacious for their

FDA approved indications. These drugs cannot be subject to therapeutic interchange in the Washington preferred drug list.

Amber Figueroa: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. That, I believe, will adjourn the P&T Committee and we will reconvene as the Drug Utilization Review Committee. We have two classes to talk about.

April Phillips: We do. These two classes were actually reviewed last month for the preferred/non-preferred status and this is just to allow you to know what our policy is going to be moving forward. This presentation is actually… its flow is a little different. I'm providing the recommendation first and then give you a little bit of background so you can be thinking about it prior to the motion.

Our recommendation for the oral hematologic cancer medications is for prior authorization to include any new and all of the drugs listed on there to follow either the FDA guidelines, NCCN and supported guidelines, the ASCO published criteria. So we're allowing any pretty much published criteria to go for. Next slide.

Magellan presented quite a bit of thorough information last month. So these are kind of just a little reminder. The first slide here is a list of the medications and their subclass name, mechanism of action. So you can kind of see which drugs are in which class as a comparison. Next slide.

So the next couple of slides just kind of give you a general idea of what indications they treated for. Each FDA indication is actually a little bit more specific on it. It was also brought to my attention that there's a couple errors on here. The… for the CMLs Iclusig, I'm probably not saying that right, has an indication for that which is not listed on this particular slide. And it is not supposed to be on the next

slide for the multiple myeloma. So that's pretty much all I have – just general background information and kind of remind you and then let you know what our intended policy is supposed to be.

Michael Johnson: We have two stakeholders. First is Scott Collins followed by Mark Fosdal.

Scott Collins: Hi everyone. I'm Scott Collins with Pharmacyclics. Senior director of market access. I have with me Mark Fosdal. He's our medical science liaison. We're here today to talk to you about Imbruvica. You recently just showed that on the list here under oral hematologic cancers. It's a BTK inhibitor. We have eight indications currently… FDA approved for eight indications. We noticed all indications except for a recent one marginal zone lymphoma, which was FDA approved in January and we also wanted to bring to your attention recently chronic graft versus host disease, which was in August of 2017 and ask if there is any materials or information we can provide regarding both of those disease states and our FDA approval and ultimately ask for coverage. Any questions?

Dale Sanderson: Would these be reflected in the NCCN guidelines?

Scott Collins: They are. I don't believe chronic graft versus host disease is currently in NCCN guidelines.

Mark Fosdal: Current TBHD is not a malignancy in itself. It is a complication of an [inaudible] transplant. There is discussion whether the supportive care of the NCCN guidelines would discuss this, but since it is not a malignancy-treated drug, it's not at this time in the NCCN guidelines, but we are asking that to be considered under supportive care.

April Phillips: Since it is an FDA approved indication it is something that would be considered for approval.

Michael Johnson: Thank you. That was it for stakeholders.

Amber Figueroa: I have a question for you, April. I count up that of all the medications listed on slide 15 there's 13 of the 22 of them require a prior

authorization and without totally taking forever looking through I'm assuming that at least one drug for each of these indications doesn't require a prior authorization?

April Phillips: The list of the drugs that require prior authorization are basically… I've gone through all of our managed cares and ours that require prior authorizations and all of those that are similar for the majority of all of us… are continued prior auth.

Amber Figueroa: So my question is, for each of these diagnoses there is at least one medication that a prior auth wouldn't have to be done in order to treat or not necessarily.

April Phillips: That I'm not 100% sure on. I know during the last meeting our… I believe our preferred status was supposed to be generic and single-source brands on the preferred versus non-preferred, but I'm not 100% sure what would require prior auth or not.

Dale Sanderson: Slide 11 refers to… oh, slide 10?

Ryan Pistoresi: We corrected the slides up here. So they may have the wrong number in your binders, but the correct slide number should be the one on the screen.

Michael Johnson: We don't have that here.

Ryan Pistoresi: Yeah, it's been updated. The slides were updated in some of the numbers then just were out of order. We apologize for that.

Amber Figueroa: I'm sorry, but I have a question. So the recommendation on that very first slide, April, so is the prior authorization criteria for all new in the following oral hematologic cancer treatments will be limited to the indications and dosing from FDA labeling blah, blah, blah. I'm sorry, can you clarify? Are you saying that these 13 drugs require a prior auth?

April Phillips: Yes, these 13 particular drugs require prior authorization and the recommendation is basically to say the prior authorization criteria will not be more strict than the FDA labeling or the NCCN guidelines.

Amber Figueroa: Even if we're using it based on FDA dosing and everything like that, a prior auth would still need to be done?

April Phillips: Yes.

Amber Figueroa: Okay.

Michael Johnson: This is my guess, tell me if I'm wrong, but probably the prior auth that I would imagine… to make sure I'm an oncologist and to make sure that I'm using it for an FDA approved indication, that would really be the only prior auth.

April Phillips: Correct. Yeah. There would probably not really be a tried and failed with this particular group of medications and their indications.

Nancy Lee: To further clarify, I guess I don't know what's currently being done so I guess it sounds to me what is currently being done is prior authorization, especially for these oral [inaudible] agent. So… okay.

April Phillips: Yes. When we had previously spoke with our managed care directors they were… they agreed on the NCCN guidelines as long as…

Susan Flatebo: I move the Apple Health Medicaid Program implement the limitations for the oral hematologic oncology drug class…

Leta Evaskus: I'm sorry. I need to exit out of there to write the motion. Sorry.

Susan Flatebo: I move the Apple Health Medicaid Program implement the limitations for the oral hematologic oncology drug class listed on slide 10 as recommended.

Nancy Lee: I second that motion.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. That brings us to the final topic, which is oncology breast cancer and there are no stakeholders.

April Phillips: Similar to the last class the drugs listed on this particular slide here are once again the managed care all have in common of which are currently on PA and so for all new, and the following ones, the prior authorization criteria would be limited to the NCCN guidelines FDA labeling. So no real difference than what's currently going on. Next slide.

Similar to the previous lists the mechanism of actions and which drugs kind of fall under each mechanism of action and then next slide.

This kind of gives you a little idea, once again not very specific, but a little idea of the drugs that could potentially treat these parts… or these breast cancer drugs.

Amber Figueroa: I realize that we haven't discussed grandfathering in any of our motions today.

April Phillips: For the oncology ones in our last… last month when we discussed this they were grandfathered.

Michael Johnson: Further discussion? Okay. I'm read this one. I move the Apple Health Medicaid Program implement the limitations for the oral breast cancer oncology drug class listed on slide 15 as recommended.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. That's it. Any other business?

Ryan Pistoresi: I was just going to say we appreciate your support and thank you for working with us as we go through this new process and I'd be happy to follow-up offline if you have any recommendations or suggestions for, you know, what we can do for the next meeting. Our next scheduled meeting is for November 17th and I believe that will just be more of a single PDL meeting. We probably won't have anything for UMP or L&I for that meeting, but we do expect some new reports from DERP. So we will probably be back to this similar format for our December meeting. So thank you again.

Michael Johnson: Thank you everybody. The meeting is adjourned.

April Phillips: I also wanted to thank you guys for dealing with me while I give this presentation. I didn't have Donna to hide behind.