

**Washington State Pharmacy and Therapeutics Committee  
Drug Utilization Review Board  
P&T Meeting Notes  
June 20, 2018**

Dale Sanderson: This is Dale Sanderson. I would like to convene the Pharmacy and Therapeutics Committee. And if we could start with introductions.

Lorena Wright: I'm Lorena Wright from Coordinated Care.

Yusuf Rashid: Yusuf Rashid, Community Health Plan of Washington.

Petra Eichelsdoerfer: Petra Eichelsdoerfer, United Healthcare.

David Johnson: David Johnson, Molina Healthcare.

Catherine Brown: Catherine Brown, committee member.

Susan Flatebo: Susan Flatebo, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Dale Sanderson: Dale Sanderson, committee member.

Virginia Buccola: Virginia Buccola, committee member.

Alex Park: Alex Park, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Umang Patel: Umang Patel, pharmacist account manager for Magellan.

Ryan Pistorosi: Ryan Pistorosi, Health Care Authority.

Joey Zarate: Joey Zarate, Health Care Authority.

Dale Sanderson: Leta, has...

Leta Evaskus: Okay, first, and on the phone, can you introduce yourselves?

Ian Blazina: This is Ian Blazina with the Pacific Northwest EPC.

Jaymie Mai: Jaymie Mai from the Department of Labor and Industries.

Gerald Gartlehner: And Gerald Gartlehner from the RPI UNC EPC.

Leta Evaskus: Okay. Thank you. And this is Leta Evaskus. I just wanted to remind the committee members to get their conflict of interest forms to me by July 25<sup>th</sup>. I'm sorry, by June 25<sup>th</sup>.

Dale Sanderson: So, our first module, TIMs. Are we ready to receive that? Go ahead, please.

Gerald Gartlehner: Okay. So, good morning everyone. My presentation summarizes the sixth update of our TIMs report. The slides that you will see summarize the entire evidence that is presented in the report, but in the interest of time, I will focus on the new evidence that we added during this update. In the slides, new evidence is always highlighted with old writing. Next slide.

We addressed three key questions that follow standard [inaudible] and DERP format. Key question one addresses the comparative efficacy and effectiveness. Key question two, the comparative risk of harms and key question three addresses differences in benefits and harms in subgroups. Next slide.

The TIMs report now includes 21 different medications. For this update, we included four new drugs, brodalumab is an interleukin-17 receptor inhibitor that has been approved for moderate to severe plaque psoriasis in adults. Then ixekizumab also an interleukin-17 inhibitor that has been

approved for plaque psoriasis and psoriatic arthritis. Sarilumab is an interleukin-6 receptor inhibitor and has been approved for rheumatoid arthritis. And risankizumab is an interleukin [inaudible] 3 receptor inhibitor, which has not been approved by the FDA yet, as far as we know, but it is expected to be approved soon for the treatment of plaque psoriasis. Next slide.

In addition, we also included four biosimilars, two biosimilars for infliximab and one each for adalimumab and etanercept. Next slide.

Our inclusion criteria compared with the previous update, we did not make any changes to our eligibility criteria. We included head-to-head RCTs of at least 12 weeks' duration and head-to-head observational studies that included 1,000 patients or more. Next slide.

To summarize the strength of the evidence or the confidence that we have in these results, we used the approach of the agency for healthcare research and quality evidence based practice centers. And for your reference, the definitions are summarized on slides 6 and 7. Next slide, slide 8.

Literature search, we conducted the update searches through November 2017. We also received dossiers from eight pharmaceutical companies. They are listed here at the bottom of this slide. Next slide.

So, what are the results of our literature searches? Our update searches detected more than 2,500 new citations, of which 33 new studies met our inclusion criteria. Overall, the [inaudible] report is a very large report. It now includes 93 studies with 37 head-to-head trials and 56 head-to-head observational studies. Next slide.

So, let's get started with key question one, how do targeted immune modulators compare in the efficacy and long-term effectiveness? Next slide.

Let's get started with rheumatoid arthritis. Since the last update in 2016, one new drug has been approved for rheumatoid arthritis, sarilumab. And overall, for this update, we found five new head-to-head RCTs for

the treatment of rheumatoid arthritis. I will first present new evidence on the comparative effectiveness of TIMs as first-step treatment. And then, evidence on the comparative effectiveness as second-step treatment. So, second step treatment in patients who did not achieve adequate response with the first step targeted immune modulator. So, for first-step treatment, we added three new RCTs, a large trial compared adalimumab with certolizumab, [inaudible] the EXXELERATE study. This trial was conducted in patients who had prognostic factors for severe disease and at 12 weeks, the efficacy was similar between the two treatment groups. Next slide.

The second RCT compared adalimumab with sarilumab in 369 patients. At 24 weeks, patients with sarilumab had statistically significantly better ACR-50 response rates and significantly better reductions of the EAS28 scores than patients treated with adalimumab. The study was funded by the producer of sarilumab and ACR-50 responses, for example, were 46% for sarilumab and 38% for adalimumab. Next slide.

The third trial for first-step treatment compared adalimumab with tofacitinib. This study was funded by the producer of tofacitinib. And overall, we now have three studies with more than 2,200 patients for this comparison. The two larger trials show similar efficacy between adalimumab and tofacitinib. And with this new study that we added for this update, we upgraded the strength of evidence for this comparison to moderate. Next slide.

Combination strategies as first-step treatments, we did not find any new studies on combination strategies based on the two RCTs that we have. We still have moderate confidence that combining two treatments, two drugs, does not lead to better efficacy. Next slide.

Now, rheumatoid arthritis and second-step treatment, so for the comparative efficacy of TIMs as second-step treatments, we included two new RCTs. The first one compared abatacept with secukinumab in patients with moderate to high disease activity despite anti-TNF treatment. Secukinumab is currently not approved by the FDA for the treatment of rheumatoid arthritis, and this study assessed two doses of secukinumab, both doses were clearly less effective than abatacept.

They did not report any P-values for the comparisons, but when we calculated them, abatacept was significantly statistically significantly more efficacious than either of the two secukinumab doses. Next slide.

Earlier in the presentation, I reported on a new RCT comparing adalimumab with tocilizumab as a first-step treatment. This trial also has an open label path for second-step treatment. After 12 weeks, patients who had not responded were switched to the other drug. So, nonresponders to adalimumab were switched to certolizumab and vice versa. Response rates after switching then were similar, about 60% of patients who did not respond initially then responded when switched to the other drug. The last study that we included for second-step treatment for rheumatoid arthritis was a French effectiveness trial that compared anti-TNF drugs with abatacept or rituximab, or tocilizumab as second-step treatment. All of these patients had failed initial anti-TNF treatment. And in this study, the anti-TNF drugs had significantly lower effectiveness than the other drugs, as a class. Next slide.

Juvenile idiopathic arthritis, we did not find any new evidence for juvenile idiopathic arthritis. Next slide.

Ankylosing spondylitis, also no new head-to-head evidence for ankylosing spondylitis. Next slide.

Psoriatic arthritis, we included two new head-to-head trials for psoriatic arthritis. These trials compared adalimumab with ixekizumab and adalimumab with tofacitinib. Both tofacitinib and ixekizumab are two newly-approved drugs for psoriatic arthritis, but for both comparisons, the efficacy was similar. Next slide.

For Crohn's disease, we did not find any new studies. The strength of evidence is still insufficient. Next slide.

Ulcerative colitis also still no head-to-head evidence for ulcerative colitis. Next slide.

Plaque psoriasis, since the last update in 2016, ixekizumab and brodalumab have been approved for the treatment of plaque psoriasis.

For this update, we included seven new trials, a small trial compared apremilast, which is an oral targeted immunomodulator with brodalumab. And this study showed similar efficacy between the two treatments. We added two new good quality trials that compared brodalumab with ustekinumab. Each of these trials demonstrated that brodalumab was more efficacious than ustekinumab. The strength of evidence for this comparison is moderate. Next slide, slide 23.

Also new to the update, the comparisons of etanercept with infliximab, and etanercept with ixekizumab for the treatment of plaque psoriasis. The etanercept with an infliximab study was a small poor quality trial that found that infliximab was significantly more efficacious than etanercept. We rated the strength of evidence as insufficient. Etanercept and ixekizumab were compared in two well-conducted trials, the Uncover 2 and 3 trials. Both trials showed that both those regimens tested ixekizumab were significantly more efficacious than etanercept for the treatment of plaque psoriasis. Next slide.

We did not find any new evidence for etanercept versus secukinumab and etanercept versus tofacitinib for the treatment of plaque psoriasis. Next slide.

We found one new trial that compared ustekinumab with ixekizumab. In this... it was a relatively small trial. So, in this small trial, ixekizumab was more efficacious than ustekinumab. The PASI 90 response rates were 73% versus 42%. Next slide.

So, the last new trial for plaque psoriasis compared risankizumab with ustekinumab. Risankizumab is not currently approved by the FDA for plaque psoriasis, but it is expected to be approved soon. The trial indicated greater efficacy for risankizumab. It's a fairly small study, has a high risk of bias, because of lack of blinding and high attrition rates, and consequently, the strength of evidence was insufficient. The study comparing secukinumab with ustekinumab was already part of the last update for this update, as we have added the 25... the 52-week data, which showed superiority of secukinumab at the superiority of... that the superiority of secukinumab was shown at 16 weeks. We saw results were ultimately maintained at 52 weeks. Next slide.

We still do not have any comparative evidence on the efficacy and effectiveness of TIMs in children. Next slide.

Key question 2 on harms. So, for key question 2, we included new data from... so, we included altogether data from 17 head-to-head trials and 42 head-to-head observational studies. Next slide.

Most of the new RCTs that I presented during the efficacy part also contributed data on overall adverse events and most of the results did not show any significant differences in overall adverse events among the drugs. Next slide.

Discontinuation because of adverse events, we included several new studies for discontinuation because of adverse events; however, we can draw only two conclusions with moderate strength of evidence, and these are the infliximab consistently has higher risk of discontinuation than adalimumab and etanercept. And the second moderate conclusion is that adalimumab and tofacitinib have similar discontinuation rates. With some exceptions, most of the other comparisons showed no differences but often, this was based on single studies with few events, or based on results of individual studies that were contradicting in their results. So, we rated the strength of evidence of all of the other comparisons as low or insufficient. Next slide.

For serious adverse events, the evidence is mostly insufficient to draw conclusions with any certainty. Next slide.

Injection site and infusion reactions, we found several differences for injection site or infusion reactions. New evidence indicates that adalimumab has a lower risk for injection site reactions than ixekizumab, but all of these comparisons actually have serious limitations and rated as low strength of evidence. Next slide.

We found no new studies on mortality. The strength of evidence is still low. Next slide.

For serious infections, infliximab consistently had the highest risks than the comparator drugs. This is based on five large observational studies with more than 50,000 patients, and we rated the strength of evidence as moderate. Most of the other comparisons did not show any significant differences in serious infections, but the strength of evidence for all of the other comparisons is still low or insufficient. Next slide.

For the comparative risks of malignancies, we added one new Japanese observational study. We now have eight studies with data on more than 50,000 patients. And overall, these studies did not find significant differences among compared drugs. The strength of evidence was still low. Next slide.

Gastrointestinal perforations. We found two new observational studies that showed that [inaudible] has a significantly higher risk for lower GI perforations than TNF-inhibitors as a class. Next slide.

For many of the other specific adverse events that we were interested in, that are listed here on this slide, the evidence is simply insufficient to draw any conclusions. Next slide.

We did not find any new evidence on the harms of combination strategies. The strength of evidence is still high that combining two targeted immunomodulators, actually leads to substantially higher risks of serious adverse events. Next slide.

For harms in children, we found two new observational studies in children with juvenile idiopathic arthritis. They reported no differences in serious infections between adalimumab etanercept, but the strength of evidence is insufficient, simply because of the rare nature of serious adverse events. Next slide.

Key question 3. So, do the included drugs differ in effectiveness or harms in the subgroups? Unfortunately, for subgroups, we still do not have any new evidence. We still have one old RCT, which is summarized on slide 41. Next slide.



So, in summary, the data for the comparative efficacy are mostly limited to single randomized trials still. These studies show similar efficacy of targeted immunomodulators for rheumatoid arthritis, psoriatic arthritis, and Crohn's disease and, in most cases, however, there are some notable differences in efficacy for plaque psoriasis and rheumatoid arthritis. We still stated combination strategies do not provide additional benefits. And for many of these studies, funding bias could play a role. So, if there is... if studies show statistically significant differences, then usually, these studies are funded by the producer of the new drug that is apparently better. Next slide.

Data on harms are based on RCTs and large comparative observational studies. So, most of the comparisons are still of low or insufficient strength of evidence. As I said before, infliximab is associated with a greater risk for serious infections and greater risk for withdrawals due to adverse events than other TNF-inhibitors. Combination strategies lead to higher risks of harms and, unfortunately, the comparative evidence on harms in children and subgroups is still insufficient. And this slide concludes my presentation. Thank you, very much, for your attention. If you have any questions, please go ahead.

Dale Sanderson: Any questions from the committee for the speaker? I just have a brief question. So, the infliximab seems to separate itself significantly in terms of problems and discontinuation. Any... do you have any overall comments about that?

Gerald Gartlehner: Yes. It does. So, infliximab is probably one of... it is one of the drugs that has been on the market for a fairly long time now. So, now we do have large observational studies that appear to show that infliximab has a higher risk for adverse events and also a higher risk for discontinuation, because of adverse events. These studies are mostly based on the registry. So, they don't go into much detail. So, much of what we can say is really that, that the risk of harms appears to be higher for infliximab.

Dale Sanderson: Thank you. We have a number of stakeholders. We could start out with Tony Hasan. And then, Dr. McLean could be next in line. And we have a number of presenters. So, please, please hold your comments to three minutes. And if you could introduce yourself and who you are with.

Tony Hasan: Can you all hear me okay? Everybody on the phone? My name is Tony Hasan. I am with Eli Lilly and Company. I'm with Global Peace Outcomes in Real World Evidence. I'm here to talk about Taltz, or ixekizumab. It selectively targets IL-17A and is approved for the treatment of adults with moderate to severe plaque psoriasis. And it's for systemic therapy and phototherapy and for active psoriatic arthritis. In three large phase-3 studies, Taltz has demonstrated a significant improvement in patients with moderate to severe plaque psoriasis, with up to 90% of...

Leta Evaskus: I'm sorry. Could you hold on just a second? I'm not sure if your mic is on. Can you tap it? Okay. It does sound like it's on. Okay. Sorry.

Tony Hasan: I'll speak a little bit closer. Is that better?

Amber Figueroa: Can you clarify which drug you're talking about?

Tony Hasan: Taltz, ixekizumab. Sorry about that. Let's see. So, as I said, in patients with moderate to severe plaque psoriasis, up to 90% of patients achieved PASI 75 at week 12. And complete resolution is possible with ixekizumab with 35 to 42% achieving clear skin at week 12. Taltz is currently the only IL-17A with PASI 100 results in the U.S. package insert. At week 12, Taltz showed superiority in two head-to-head trials versus U.S. approved etanercept in patients achieving PASI 75 and sPGA 0 and 1. Of the patients treated with ixekizumab who responded to sPGA 0 or 1 at week 12, 75% maintained this response at week 60. Additionally, head-to-head data showed significantly higher response rates for Taltz compared to ustekinumab at 24 weeks. In three pivotal trials, examination of age, gender, race, body weight, and previous treatment with a biologic did not identify differences in outcomes or response to Taltz among these subgroups at week 12. In a network metaanalysis of biologics for the treatment of psoriasis, the number needed to treat per additional PASI 75, 90, and 100 response at week 12 versus placebo was lower for ixekizumab compared to secukinumab, ustekinumab, adalimumab, and etanercept. Ixekizumab is the first and only psoriasis treatment with genital psoriasis data in the label, providing rapid clearance of genital skin that was statistically significant as early as week one versus placebo. Regarding psoriatic arthritis in two randomized placebo double-blind

placebo-controlled studies, patients treated with Taltz demonstrated greater clinical response, including ACR-20, ACR-50, and ACR-70 compared to placebo at 24 weeks. Responses were seen regardless of prior anti-TNF alpha exposure. Ixekizumab inhibited the structural progression of joint damage compared to placebo at week 16 in these trials, as well. Taltz is available as an 80 mg/1 mL single dose prefilled auto injector or a single dose pre-filled syringe. The disposable one-time use pen comes premixed with no reconstitution required, and the pen controls the depth and injection... and the rate of injection. Taltz may increase the risk of serious infections, and serious infections have occurred with the most common adverse reactions being injection site reactions, upper respiratory tract infections, nausea, and tinea infections.

Dale Sanderson: If you could draw your, uh, conclusions, please.

Tony Hasan: Sure. So, in conclusion, Taltz is safe and efficacious for patients treated with... for moderate and severe plaque psoriasis, as well as psoriatic arthritis and demonstrated superiority to other biologics currently on the market. The easy to use device is simple for patients. They simply remove the base cap, press firmly against the injection site, unlock, and press the button. The patient simply waits for the second click, right there, letting them know the dose has been administered, never having to handle or actually touch the needle. Thank you. Happy to provide any answers to any questions that you have or any additional information that you may have. Great. Thank you, so much, for your time.

Dale Sanderson: Would Dr. McLean please, and then on board is Mr. Hager.

Gia McLean: Good morning, everyone. I'm Gia McLean. I'm a medical science liaison with Celgene. I want to thank you for listening to my comments today on apremilast, which is marketed under the trade name of Otezla. Now, for this talk, I'm going to refer to the product by its chemical name of apremilast. Now, I know you have a very full packet of information in front of you. So, I'm just going to highlight some key points about the product, and then I'll share four major updates with you.

Apremilast is a novel oral small molecule that was approved by the FDA in 2014 for the treatment of active psoriatic arthritis and also for

moderate to severe plaque psoriasis. As a reminder, apremilast is not a biologic. It's a novel oral small molecule that works intracellularly to inhibit phosphodiesterase 4. Now, apremilast restores the balance of multiple cytokines by modulating levels of antiinflammatory cytokines and proinflammatory cytokines, like TNF-alpha, IL-17, and IL-23, which, as you know, is different from how the biologics work in that they work extracellularly and usually only on a single cytokine. The recommended dose is 30 mg, given twice a day, and it can be given without regard to meals. In addition, it has a novel mechanism of action. It also does not require any prescreening for TB or any regular lab monitoring, as well. Now, the first update concerns apremilast addition to the GRAPPA treatment guidelines. GRAPPA is the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. This group published their second set of guideline in 2016. So, this is the first set of U.S. guidelines to include apremilast in an update, since its approval in 2014. These guidelines present specific treatment recommendations in six areas, six domains of psoriatic arthritis. Now, apremilast is included in all domains in at least the same level, as the biologics, with the exception of axial and skin disease. We don't have data in the axial area; however, for skin disease, apremilast is recommended before the biologics. And again, this is fully published information. My second update is regarding our long-term safety data. We now have data from pooled five-year studies looking at our two clinical trial programs for PSO and PSA. They are known as Esteem for psoriasis and Palace for psoriatic arthritis. And these data have been presented publically. They show no increased adverse events with continued exposure to apremilast and no new safety signals at five years out. Third update, apremilast a first in class oral treatment to receive a positive recommendation from NICE, which is the National Institute for Health and Care Excellence. Then, finally, we have fully published safety and efficacy data and difficult to treat aspects of psoriasis, including nail, scalp, palmar plantar psoriasis, and also pruritus, which is itch. Now, although we're talking about a very small body surface area, this accounts for a great level of functional disability in these patients, and it really has a significant impact on their quality of life. Also, this is something that is not captured in the PASI 75.

Dale Sanderson: If you could conclude your comments, please.

Gia McLean: So, in summary, I just want to review the warnings and precautions, diarrhea, nausea, vomiting, depression, those are on our website and in the package insert. And then, in summary, the important key takeaway is apremilast is not a biologic. It's an oral with a novel mechanism of action. It has no black box warnings or RIMS program requirements and Celgene respectfully asks for the committee to consider allowing your Medicaid members to receive Otezla unrestricted. Thanks for your time. Any questions?

Dale Sanderson: I see none. Mr. Hager. Then, on board is David Gross.

Anthony Hager: Hi, everyone. Thank you for this opportunity. My name is Anthony Hager. I'm with Bristol Meyers Squibb, innovative medicines, and I am here to provide testimony in support of Orencia, abatacept, on behalf of BMS. In adults, Orencia, abatacept, subQ or IV is indicated for the reduction of signs and symptoms inducing major clinical response, inhibiting the progression of structural damage, and improving physical function of moderate to severe RA, as mono or a combination therapy.

Orencia should not be administered concomitantly with TNF antagonists, and its use is not recommended concurrently with other biologic RA treatments, such as anakinra. Additionally, in children 6 or older for the IV formulation, and 2 and older for the subq formulation, Orencia is indicated for the reduction of signs and symptoms of moderate to severe polyarticular GIA. Orencia is also indicated for the treatment of adult patients with active psoriatic arthritis and may be administered as an IV infusion or subq injection with or without nonbiologic DMARDS. The safety profile in psoriatic arthritis is consistent with the safety profile in rheumatoid arthritis.

Abatacept is the only T-cell co-stimulation modulator among biologic therapies for RA. Orencia has a unique mechanism of action, therefore. Since it works upstream at the level of the T-cell, Orencia has been shown in clinical trials to reduce serum levels of TNF alpha, IL-6, soluble IL-2 receptor, rheumatoid factor, and acute phase reactant, such as CRP. In clinical trials, the most commonly reported adverse events included headache, URTI, nasopharyngitis, and nausea. And the most serious adverse effects in clinical trials with Orencia were serious infections and

malignancies. I'd like to draw the committee's attention to data relating to key question 3 from the DERP report, specifically whether there is a difference in effectiveness or harms in RA subgroups, especially in patients with early versus established disease. The AMPLE trial sets reference 38 in the DERP report is a phase 3 randomized two-year, multinational investigator blinded study that compared abatacept versus adalimumab on background methotrexate and biologic naïve adult RA patients who had an inadequate response to methotrexate. The mean disease duration for the study was 1.9 years for abatacept, 1.7 years for adalimumab. With respect to the primary endpoint, that's patients achieving ACR 20 response at one year, abatacept was noninferior to adalimumab. An exploratory analysis of this study, the AMPLE study, looking at efficacy based on baseline anti-CCP2 antibody status found that when assessing efficacy in anti-CCP positive patients by concentration cortile, patients in the abatacept cohort were the highest anti-CCP2 antibody concentration, so, that's cortile 4, had higher responses than patients with lower concentrations, and that's cortile 1 through 3. This association was not observed in the adalimumab cohort.

Dale Sanderson: If you could draw your conclusions, please.

Anthony Hager: Absolutely. In closing, I ask that you evaluate coverage policy in this class to allow for a non-TNF biologic treatment option by adding Orenzia, abatacept, to the Washington State preferred drug list. Thank you. I'll take any questions.

Dale Sanderson: I see none.

Anthony Hager: Thank you.

Dale Sanderson: David Gross, and Margaret Olmon is on board.

David Gross: Good morning. My name is Dave Gross, and I am with the medical affairs division with Pfizer Pharmaceuticals, and I am here to give a brief update on Xeljanz for your consideration for the PDL. Xeljanz or tofacitinib is indicated for the treatment of adult patients with rheumatoid arthritis who have had an inadequate response, or intolerance, to methotrexate. It is also indicated for the treatment of adult patients with active psoriatic

arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs. Most recently, Xeljanz was approved for the treatment of adults with moderately to severely active ulcerative colitis, and that is what I'll concentrate on today, as far as the clinical data. Dosage for RA is 5 mg twice daily, or 11 mg of the extended release formulation. It may be used as monotherapy or in combination with methotrexate or other nonbiologics. For psoriatic arthritis dosing is the same. And for ulcerative colitis, the recommended dosing is 10 mg twice daily for eight weeks. And then, 5 or 10 mg twice daily depending on the response of the patient. Xeljanz does include a box warning for serious infections and malignancy. Patients treated with Xeljanz are at increased risk of developing serious infections that may lead to hospitalization or death. Lymphoma and other malignancies have been observed in patients treated with Xeljanz and viral reactivation, including cases of herpes virus were observed in clinical trials.

As stated previously, Xeljanz was recently approved for patients with moderate to severely active ulcerative colitis. In the UC phase 3 clinical development program, there were two induction studies, which I'll review briefly, a maintenance study, and an open... one open label long-term extension study. In the two induction studies, a greater proportion of patients receiving Xeljanz 10 mg twice daily achieved clinical remission with absence of rectal bleeding, improvement of endoscopic appearance of mucosa, normalization of endoscopic appearance of the mucosa, and clinical response at week 8 compared to placebo. These studies included patients that have previously failed or were intolerant to TNF inhibitors, corticosteroids, and/or other immunosuppressants. In the maintenance trial of 52 weeks, a significantly greater portion of patients in both the Xeljanz 5 mg twice daily and 10 mg twice daily group versus placebo achieved remission and the other outcomes that I talked about previously.

In the open label extension study, nonresponders to Xeljanz, so people that did not respond in the induction study, continued another eight weeks after induction for a total of 16 weeks and 51.2% of these patients achieved clinical response.

Dale Sanderson: If you would conclude your remarks, please.

David Gross: In conclusion, to manage this disease effectively, we need an alternative disease-modifying agent available earlier in the formulary continuum. A medication with a novel mechanism of action and available for oral administration would offer this additional treatment for patients that are suffering from these three disease states, including ulcerative colitis in the state Medicaid population. Thank you for your time. And I'd be happy to answer any questions you may have.

Dale Sanderson: I see none.

David Gross: Thank you.

Dale Sanderson: Margaret Olmon, please. And a Mary Kemhus is on deck.

Margaret Olmon: Hello. My name is Dr. Margaret Olmon from medical affairs of Abbvie. I want to thank you for the chance to talk to you about Humira today, provide an important update, and answer any questions that you might have. First, I'd like to remind you of the 10 currently approved indications for Humira, and I'd like to focus your thoughts on the two treatments for children. Humira is approved in rheumatoid arthritis, in juvenile idiopathic arthritis, in psoriatic arthritis, in ankylosing spondylitis, Crohn's disease, in pediatric Crohn's disease, in ulcerative colitis, in plaque psoriasis, in hidradenitis suppurativa, and in the treatment of noninfectious intermediate posterior and panuveitis in adult patients.

Humira is now available for pediatric patients in a formulation without citrate buffers and will be available for adult patients later this year. Sodium citrate is known to cause pain. It, and other inactive ingredients, have been removed. Especially that pain of injection that you get with Humira, in patients with juvenile idiopathic arthritis, and those with pediatric Crohn's disease could lead those patients to discontinuation of treatment, and that would be poor outcomes, joint erosion in the rheumatoid arthritis patients, and in the Crohn's disease patients, they would have flares. That's why we focused on the patients that were children first, and adults will come soon.



Abbvie conducted a comprehensive development program to demonstrate that Humira without citrate buffers is comparable to the current Humira formulation. This program included both analytical and clinical studies that showed comparability of the safety, quality, and efficacy of both presentations. The same therapeutic amount of Humira will now be injected in half the volume with a thinner 29-gauge needle. The Humira pen has also been enhanced to include a larger viewing window and painted numbers. Further, the black needle cover is not made with natural rubber latex. Importantly, there is only one Humira. All presentations of Humira originate from this same master cell line with the same active ingredient that patients and physicians have depended on for over 15 years. With longstanding safety data, 71 global clinical trials, and over 1 million patients exposed, Humira has a well-defined published benefit to risk ratio. All TNF antagonists carry similar box warnings regarding serious infections, tuberculosis, and malignancies. Patients starting on any anti-TNF, including Humira, should be screened for TB and carefully monitored for serious events. Please see the full prescribing information at [www.rxabbvie.com](http://www.rxabbvie.com) for comprehensive safety and efficacy information.

In summary, 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 the preferred status of Humira to include the new citrate free formulation on the PDL for the people of Washington. I want to thank you, so much, and answer any questions you might have. And since I have...

Dale Sanderson: None that I see.

Margaret Olmon: ...half a second, I would like to thank our friend from OHSU for looking at risankizumab before the approval. As soon as it's approved, I'd be happy to provide more clinical information for you. Thank you.

Mary Kemhus: Hi, good morning. Can you hear me okay now? Okay. So, I think I might be your last one. So, I will hold to time. My name is Mary Kemhus. I'm a pharmacist with Novartis medical affairs. Today, I'd like to discuss secukinumab or Cosentyx. It's the only fully human IL-17a inhibitor approved to treat moderate to severe plaque psoriasis, psoriatic arthritis,

and ankylosing spondylitis. Novartis requests that the committee add Cosentyx as preferred to the Washington Medicaid, and I'm going to provide you with just a few reasons why. So, the DERP report highlighted some of the comparative data that's available for Cosentyx. It did not include the most recent Clarity trial, which was an additional head-to-head trial versus ustekinumab. Again, confirming the consistency of results that we see in PASI 90 and PASI 100 results in psoriasis. I'd like to actually move onto psoriatic arthritis and ankylosing spondylitis, though. There is a significant unmet need in managing that population. Currently, there's really only TNFs available specifically for ankylosing spondylitis and up to 40% of patients have an inadequate or no response to an anti-TNF therapy, such as Enbrel or Humira. Cosentyx does offer a treatment alternative with a mechanism that specifically targets the key cytokine involved in the development of the inflammation and the disease progression. Radiographic progression of disease can lead to mobility loss and disability, and Cosentyx has been shown to inhibit radiographic progression in both psoriatic arthritis and in ankylosing spondylitis. In fact, almost 80% of patients showed no radiographic progression in the spine in the ankylosing spondylitis studies at four years. So, for all indications, Cosentyx has demonstrated long-term sustained efficacy and a well-tolerated safety profile. Over 150,000 patients have been treated to date. The most common adverse events are those you would expect from a biologic, nasopharyngitis, diarrhea, upper respiratory tract infections, but I do want to highlight that immunogenicity remains very low, less than 1%, and injection site reactions are almost negligible with this product. So, in light of comparator data, long-term efficacy, safety across multiple indications, and improvements in radiographic progression, I would urge you to consider providing patients with Cosentyx in an unrestricted manner for the Washington PDL, providing a non-TNF inhibitor treatment option. I'm happy to address any questions that you may have. Thank you.

Dale Sanderson: Thank you for your timeliness. Any discussion amongst the committee as we prepare to give a motion here?

Alex Park: Can I ask a question? I thought that Alefacept was withdrawn from the market? And so, I'm wondering about continuing to include it in the category.

Ryan Pistorosi: Even though it may be removed from the market, it's still considered a drug to be reviewed, meaning that the evidence has been presented. It won't be eligible to be preferred or non-preferred if it's not available on the market, but in case it does come back to the market, then we would be able to add it back, but that's kind of just a bit of background why it's on there still.

Alex Park: Okay. Thanks for clarifying.

Dale Sanderson: Several of the presenters seem to imply that there were additional indications besides what's listed here in the motion. Is this a comprehensive list of FDA approvals for...?

Ryan Pistorosi: One of the suggestions could be to remove the list of indications and just leave it saying FDA approved indications, because it sounds like they keep adding.

Dale Sanderson: That would be great. Any other discussion? Would anyone like to entertain a motion? I'm wondering... so if we need to go down this laundry list of difficult to pronounce names, can we just refer to the list that is here?

Amber Figueroa: I'll take a stab at it, if everyone promises not to laugh.

Dale Sanderson: We promise not to laugh. And there's three additional ones that were not added before.

Leta Evaskus: I've put them in there.

Dale Sanderson: Okay. So, those are now in there. Alright. Amber, thank you very much and go ahead.

Amber Figueroa: Alright. Here we... here we go. 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...

Leta Evaskus: Excuse me, Amber. We switched it.

Amber Figueroa: ...oh, you switched it around? Oh, sorry.

Leta Evaskus: I'll blow it up.

Amber Figueroa: That's okay. After considering the evidence of safety, efficacy, effectiveness, and special populations for the use of targeted immune modulators for their FDA approved indications, I move that abatacept, adalimumab, alefacept, anakinra, apremilast, brodalumab, canakinumab, certolizumabpegol, etanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, sarilumab, 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.

Dale Sanderson: I'll second. Did we take out the FDA indications and just say...

Leta Evaskus: Do you want to do that in that second part, as well?

Ryan Pistorosi: Right. So, I guess on the second part is that the PDL must include a drug approved for these indications. Were you looking to add to this list?

Dale Sanderson: As long as it's a comprehensive list of everything that's been FDA approved, then I'm...

Donna Sullivan: If you do that, then every single drug that has a unique FDA indication would have to be preferred. So, I think what we typically do is if the drug is not preferred, but it has a unique indication, it will get approved for that indication, but it will be non-preferred for everything else. So, I would prefer you to just leave it as it is and let us continue to handle those unique drugs as we have in the past.

Dale Sanderson: I would suggest we defer to HCA's recommendations.

Leta Evaskus: This is Leta. You guys need to vote now.

Dale Sanderson: Okay. All in favor, please say aye.

Group: Aye.

Dale Sanderson: Opposed, same sign. It's approved. So, moving onto overactive bladder report.

Leta Evaskus: Ian, are you on the phone?

Ian Blazina: Yes, I am.

Leta Evaskus: Okay. You can go ahead.

Ian Blazina: Alright, I am going to present a report on drugs to treat overactive bladder from May of this year. Next slide.

As some background, overactive bladder is a common syndrome marked by urinary urgency often with frequency and nocturia in the absence of pathological factors. The AUA clinical practice guidelines from 2015 recommends behavioral therapy as first-line treatment, antimuscarinics, and beta-3 adrenoceptor agonists as second-line treatment, and Botox and nerve stimulation and some others as third-line treatment. The antimuscarinics have anticholinergic adverse effects, which contribute to low medication persistence, solifenacin and darifenacin have fewer adverse events, because they target receptor subtypes that are more prevalent in the bladder and mirabegron, adverse effects include increased blood pressure, dizziness, and urinary retention. Next slide.

So, we assessed the key questions, what is the evidence in comparative effectiveness and harms of the overactive bladder drugs? And is there evidence on whether effectiveness or harms vary by subgroup? Next slide.

On this slide, there is just a brief figure showing the methods. Our searches were through March of 2018. We were looking for head-to-

head trials in adults with overactive bladder, and the bottom three cells show the different categories of drugs. Next slide.

This is a table of the included evidence by drug. Since the last summary review, we identified 19 new head-to-head trials, and one new cohort study. Next slide.

This is another overview of the cumulative evidence. Overall, we included 45 RCTs, sample sizes ranged from 60 to 2,444, six trials rated poor quality. Most of the trials were eight to 12 weeks with one trial being a year long and almost all the trials were funded by the drug manufacturers. Next slide.

So, for the comparison of mirabegron 50 mg versus solifenacin 5 mg, there was no evidence in the prior report. There were six trials new to this update, although two were poor quality and not synthesized. At 12 weeks, there were no differences in incontinence episodes based on three trials with high strength of evidence. Also, no difference on adverse event withdrawals based on four trials, constipation based on three trials, both with moderate strength of evidence. And there were no differences in other anticholinergic harms, including blurred vision, dizziness, or arrhythmia. Mirabegron was superior to solifenacin in urgency episodes, but the absolute difference was very small at 0.54 fewer episodes per day. This was based on two trials with moderate certainty. There was also lower incidence of dry mouth with mirabegron. You can see that's 3.8% or 7.7% based on three trials. Next slide.

This slide is a forest plot of the pooled estimate for incontinence episodes for 24 hours. You can see that the overall binding is not significant, finding no difference. Next slide.

For the comparison of mirabegron 50 mg versus tolterodine extended release 4 mg, we found six RCTs, five are new this update. Mirabegron was slightly superior to tolterodine, with a greater reduction in incontinence episodes with absolute change of 0.15 fewer episodes. This is based on five trials with high strength of evidence and a lower incidence of dry mouth. There were no differences in urgency episodes, adverse event withdrawals, constipation, or other anticholinergic harms,

including dry mouth, dizziness, and arrhythmia. There was inconsistent evidence on micturition for 24 hours. The eight to 12-week trials found no difference, but with some statistical heterogeneity, the one-year trial had conflicting findings at 12 weeks and 12 months, and it was difficult to interpret. Next slide.

For the comparison of fesoterodine 8 mg versus tolterodine extended release or immediate release 4 mg, no new evidence. There are three trials from the prior report, finding that fesoterodine increased patient perception of improvement, resulted in fewer incontinent episodes, fewer urgency episodes, but anticholinergic harms were not reported, and the absolute differences in all of these outcomes were very small. Next slide.

So, the comparison of tolterodine 4 mg versus oxybutynin 5 to 10 mg oral or transdermal 3.9 mg. The prior report identified 14 trials, and we found two subsequent trials, although one was poor quality. There was no significant difference in incontinence episodes based on eight trials from the prior report, and we have moderate certainty in that finding. Withdrawals due to adverse events were lower with tolterodine based on nine trials, and the pooled relative risk is 0.43, and we have moderate certainty of that finding, as well. For anticholinergic harms, there was no difference in dry mouth, and the others were not reported. Next slide.

This is a slide, a forest plot, of the withdrawals due to adverse events. Tolterodine versus oxybutynin showing that there are fewer withdrawals with tolterodine by about half. Next slide.

For the comparison of solifenacin 5 mg versus tolterodine 4 mg, the prior report included five trials, and we identified one poor quality trial subsequent. Solifenacin was better than tolterodine in incontinence episodes and urgency episodes, although again, the absolute mean differences were very small at -0.3 and -0.43 episodes per day. This was based on four trials with moderate certainty. There were no differences found in harms or adverse event withdrawals based on five trials and specific anticholinergic harms were not reported. Next slide.

The comparison of solifenacin 5 mg versus oxybutynin immediate release 15 mg, there was no evidence in the prior report, and we found one study in this update. The strength of evidence would be low for all outcomes. There was no difference in urgency episodes. Fewer patients taking solifenacin withdrew due to adverse events by about half. There was lower incidence of dry mouth, 35% versus 83%. And there were no differences in constipation or other anticholinergic harms, including dizziness, somnolence, and confusion. Next slide.

For the other overactive bladder drugs, we found no studies for flavoxate, hydrochloride, and there was no evidence for multiple comparisons that are listed here, as well as the only poor quality evidence for a couple of other comparisons. Next slide.

So, in conclusion, we identified 45 studies of overactive bladder drugs cumulatively, 19 head-to-head trials, and one observational study were new to this update. Most of the evidence is for mirabegron and older evidence for the comparison of tolterodine versus oxybutynin. The mirabegron evidence is nine trials and found that mirabegron was statistically-superior to solifenacin and tolterodine on some benefit outcomes, but the opposite differences were very small. The reductions were on the order of half to one episode per day, while baseline rates were on the order of 2 to 12 episodes per day. The incidence of dry mouth was lower with mirabegron, but there were no differences in adverse event withdrawals or other anticholinergic adverse events. Next slide.

Other new evidence is limited to single studies for each comparison. There were some small differences in benefits, but they are not likely to be clinically meaningful. Most of the reductions were small, relative to baseline rates. However, both solifenacin and tolterodine resulted in significantly fewer withdrawals due to adverse events than oxybutynin. That's the end of this one. Are there questions?

Dale Sanderson: Are there any questions from the committee?

Alex Park: Thanks for that well-organized review. I have heard that darifenacin and trospium sometimes are thought to cross the blood brain barrier less



avidly. Did anything come up in your harms review on that being favorable for cognitive impairments and effects?

Ian Blazina: The cognitive stuff was very poorly reported. So, we did not find any of that. Trospium also had very few studies. In general, the anticholinergic adverse events were not super well reported.

Amber Figuero: I just wanted to say, I like all your tables and graphs. They break up the words. It looks nice.

Ian Blazina: Thank you.

Dale Sanderson: Any other discussion from the committee? Questions? So, there are no stakeholders for this. Would anyone like to make a motion?

Nancy Lee: After considering the evidence of safety, efficacy, and special populations for the treatment of overactive bladder, I move that darifenacin, fesoterodine fumarate, fluvoxate, mirabegron, oxybutynin, gel patch tab solution, 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 a once-daily formulation and vice-versa. A once-daily formulation must be included as a preferred drug on the Washington preferred drug list.

Catherine Brown: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. We can move onto the anticoagulant scan.

Ian Blazina: Alright. And that will be me again, as well as everything else from here on out, so that you could see. So, this is the preliminary update scan number two for direct acting oral anticoagulant drugs. Next slide.

The original report was May 2016, with searches through September 2015, and that was an original report. The last scan was scan number one in April of last year. And the current scan searches run through February of this year. Next slide.

This scan addressed the key questions looking at the treatment, effectiveness and harms of treatment of venous thromboembolic events in adults. Key question 2 is looking at the effectiveness and harms of extended treatment to prevent recurrence of events. Treatment 3 is looking at effectiveness and harms of prophylaxis to prevent events in people with atrial fibrillation or undergoing orthopedic surgery. And key question 4 is looking at the subgroups. Next slide.

So, we included people receiving treatment of deep vein thrombosis or pulmonary embolism, extension of treatment for DVT or PE to prevent recurrence, prophylaxis to prevent VTE in patients undergoing orthopedic surgery, and prophylaxis in patients with atrial fibrillation. Next slide.

This table lists the included interventions. Next slide.

Since the last scan, we identified one new drug, betrixaban, approved in 2017. No new box warnings and one potentially relevant comparative effectiveness review, which only covers part of the scope of the scan, only focusing on orthopedic surgery prophylaxis. Next slide.

Since the last scan, we identified 8 primary publications, 6 of the 8 are in atrial fibrillation populations and 4 of the 8 are evaluating dabigatran. We also identified 12 secondary analyses. Cumulatively, we have 11 primary publications. None are head-to-head and none are of the new drug, betrixaban, and 34 secondary analyses. Next slide.

In summary, since the last report, we identified one new drug, one new comparative effectiveness review that only covers part of our scope, and 11 primary trials, 8 new this scan, 34 secondary analyses, and 12 new to scan. That is actually the end of this presentation since the last slide pertaining to the DERP group. Are there questions?

Dale Sanderson: Do we have any questions, like, from the committee? I see none. Thank you. We have three stakeholders. Mr. Brent Wright is first. Chris Conner is on deck. Please hold your comments to three minutes, please.

Brent Wright: Thank you. I think I can beat three minutes. My name is Brent Wright. I'm with the HUR department of Boehringer Ingelheim. There's not a whole lot more I can tell you about Pradaxa. Just real quickly, Pradaxa was approved in 2010. Indications include nonvalvular a-fib, DVT, PE, DVT/PE prophylaxis, and DVT/PE in patients that have had total hip reconstruction. Just a reminder that we are still the only direct anticoagulant that has a reversal agent, Praxbind. It has been on the market, since 2015. That's it. If you have any questions, I'd love to answer them.

Dale Sanderson: Are there any questions from the committee? I see none. Thank you. Chris Conner. Mae Kwong is on deck.

Chris Conner: Good morning everybody. My name is Chris Conner, and I'm with Bristol-Myers Squibb, and I am here to make a brief statement in support of apixaban, or Eliquis, and its place on the Washington preferred drug list. So, I'm required to mention the FDA approved indications for Eliquis, or apixaban, and they are to reduce the risk of stroke or systemic embolism in patients with nonvalvular a-fib. It's to treat DVT and PE, and for the prevention of the recurrence of DVT and PE after initial treatment, and it's also indicated for the prophylaxis of DVT in patients with hip or knee replacement surgery. Similar to the other direct-acting oral anticoagulants, there's a black box warning for apixaban or Eliquis, and that warning is in regards to the increased risk of thromboembolic events in patients who prematurely discontinue. In addition, there is an increased risk of spinal hematoma in patients undergoing neuraxial anesthesia or spinal puncture. For a full listing of the safety warnings and precautions, adverse events, I will refer you to the package insert and the full product labeling. While there are no randomized head-to-head control trials comparing the direct-acting oral anticoagulants to one another, there are a number of observational studies that do exist that have looked at patients with nonvalvular a-fib and have attempted to compare these agents to one another. Now, these economic... these analyses have primarily focused on economic outcomes, such as all-cause

healthcare costs, healthcare costs associated with hospitalization, and also major bleed related hospitalization costs. In one such observational analysis, in a matched cohort of patients of adults with nonvalvular a-fib, who were naïve to oral anticoagulant therapy, researchers found that all-cause hospitalization costs and major bleed-related hospitalization costs were significantly higher for the rivaroxaban, Warfarin, and dabigatran matched cohorts relative to apixaban. In addition to the economic analyses that I just mentioned, there are similar nonindustry sponsored independent observational analyses that have compared the risks of stroke and systemic embolism and major bleed in cohorts of adults with nonvalvular a-fib taking these direct-acting oral anticoagulants. I'm required to state that these observational studies are designed to uncover associations and not causations, and they are not designed, or not meant to replace randomized control trials, which really are needed to establish comparative clinical efficacy and safety. That said, observational studies may serve as an important complement to the body of evidence that is built on randomized control trial evidence and can be an important tool for population health policy decision makers like yourselves more interested in trying to better understand how these medications work in clinical practice. In close, I would just like to ask for your continued support for apixaban, as a drug available on the Washington preferred drug list. Thank you. Any questions?

Dale Sanderson: None that I see. Thank you.

Mae Kwong: Good morning. My name is Mae Kwong, and I am a pharmacist with Janssen Scientific Affairs. Thank you for giving me the opportunity today to present to you on Xarelto, otherwise known as rivaroxaban, which is a direct oral anticoagulant. First, I would like to note the prescribing information for rivaroxaban. It has been updated to include a new indication, which is the reduction of risk of recurrence of DVT and/or PE in patients at continued risk after completion of initial treatment lasting six months, based on findings from the Einstein Choice study, in which Xarelto 10 mg daily resulted in a 74% reduction in venous thromboembolism versus aspirin with comparable rates of major bleeding. The label change now reflects a 10 mg dose for extended treatment versus previously it was a 20 mg dose that was recommended. In December, Janssen filed a supplemental NDA with the FDA for the

reduction in the risk of major cardiovascular events in patients with CAD and/or PAD, and to reduce the risk of acute lymphemia in patients with PAD based on a Compass clinical trial that enrolled more than 27,000 patients and was stopped a year early due to overwhelming efficacy in a group receiving rivaroxaban 2.5 mg twice daily in combination with aspirin, Xarelto reduced the risk of MACE events by 24% versus aspirin alone. This benefit was also seen on top of 90% of patients already on statins and 70% of patients on ACE inhibitors, ARBs, or beta-blockers. If approved, Xarelto will be the only direct oral anticoagulant indicated for patients with CAD and/or PAD. A breath of real-world evidence has demonstrated the consistent efficacy, as well as safety of rivaroxaban in nonvalvular a-fib patients consistent with our clinical trial. In recent studies, the FDA mini sentinel was actually published this year looking at over 30,000 patients compared to warfarin. This was a propensity score matched study. In this analysis, there was no increased risk of GI bleeding greater than what was seen coming out of our pivotal clinical trial, and more importantly, Xarelto was associated with significantly lower rate of ischemic stroke with a hazard ratio of 0.61. Xarelto is also being studied in phase-3 trials looking at VTE prophylaxis in medically ill patients and VTE treatment, as well as prophylaxis in cancer patients, as well as patients with CHF and CAD. So, in essence, in the next one to three years, there could be additional indications for Xarelto. As previously mentioned, although it's not marketed by Janssen, there is a reversal agent for rivaroxaban, as well as apixaban that has been approved now. So, dabigatran is not the only drug with a reversal agent. Thank you for your time. Are there any questions?

Dale Sanderson: None that I see. Thank you. So, this was a scan. So, we do need to approve the scan from the committee. And so, would anyone like to...

Amber Figueroa: I move that we accept the scan as adequate.

Dale Sanderson: Second?

Diane Schwilke: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. If we could move onto the motion for this, then?

Nancy Lee: This is Nancy. I'd like to propose a change in wording. Instead of newer anticoagulant drugs, to change it to direct-acting oral anticoagulants. And then a question of clarification regarding, I guess, at the time, who are the medically ill, 'cuz it says for the prevention of stroke or systemic embolism in patients who are medically ill, undergoing surgery, or with a-fib. So, I just wanted to know, just a clarification about that.

Amber Figueroa: I am wondering if we should pull out this list, 'cuz it sounds like... in the works, there are some other indications.

Donna Sullivan: Yes. That is typically what you have done in the past is when there gets to be too many indications or different indications for different drugs, you've changed it to say for their FDA labeled indication.

Diane Schwilke: Can you also add in the new drug into that list before we...

Leta Evaskus: This is a scan. So, the drug actually hasn't been reviewed. So, it's not available to be preferred.

Diane Schwilke: Oh, okay.

Dale Sanderson: Is there any other discussion before someone makes a motion here? The request for someone to make a motion.

Amber Figueroa: I'm just wondering what you guys think about, you know, if one, potentially two of them, having reversal agents and the other ones not, do you guys feel comfortable with having therapeutic interchange among them? Like, if you had somebody who was... I mean, I suppose if it's... they're so high risk you think you're going to have to reverse it, you probably shouldn't start it in the first place, but I'm just kind of... I don't have a feeling either way. I'm just thinking, clinically, if anybody has any thoughts on that?

Dale Sanderson: Comments from the committee?

Leta Evaskus: And one drug was left out of therapeutic interchange, the dabigatran. Could you speak into the mic?

Female: I think, because it has a little different mechanism, that's probably why it was left out.

Amber Figueroa: After considering the evidence of safety, efficacy, and special populations for direct-acting anticoagulant drugs for their FDA approved indications, I move that apixaban, dabigatran, edoxaban, and rivaroxaban are safe and efficacious for their approved indications. Apixaban, edoxaban, and rivaroxaban can be subject to therapeutic interchange in the Washington preferred drug list.

Alex Park: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. So, where...

Leta Evaskus: We have a 15-minute break.

Dale Sanderson: We have a 15-minute break. So, it's 10:25. So, back here at 10:40.

Leta Evaskus: Does everybody on the phone want to call back in, in 15, at 10:40? Alright.

Dale Sanderson: Let's please get started. Is Ian available?

Ian Blazina: Yes, I am.

Dale Sanderson: Please start.

Ian Blazina: Now, I'll be covering pharmacologic treatments for ADHD. This is preliminary update scan number three. Next slide.

The previous report was update five in July of 2015 with searches through April 2015. The last scan was update scan number two in June of last year. The current scan searches run through May of this year. Next slide.

The key questions look at the comparative evidence for pharmacologic treatments for attention deficit disorders. The second question looks at the harms of treatment. The third question looks at subgroups. Next slide.

We included pediatric and adult populations of outpatients with attention deficit disorder or attention deficit hyperactivity disorder, including inattentive hyperactive impulsive and combined subtypes. Next slide.

This slide shows a table in the included interventions. Next slide.

Since the last scan, there are several new drug formulations, one of mixed amphetamine salts and another extended release methylphenidate formulation. There were no new box warnings. There is one new potentially relevant comparative effectiveness review covering part of the scope, and that is looking at diagnosis and treatment in children and adolescents, though it would not cover adults. Next slide.

This scan, we identified 11 primary publications and no secondary analyses. Cumulatively, that means we've identified 14 primary publications, 4 studies of guanfacine, 2 compared to methylphenidate and 2 compared to dexmethylphenidate, and 10 studies of atomoxetine all compared to methylphenidate, as well as 3 secondary analyses, one trial each assessing response and remission, function, and sleep. Next slide. Next slide.

In summary, since the last report, we identified 2 new drug formulations, 1 new comparative effectiveness review covering part of the scope, and 14 primary trials, 11 new this scan, 3 secondary analyses, none new this scan, and there were no trials of the newly approved formulations. Are there questions?



Dale Sanderson: Questions from the committee? None that I see. Thank you, so much. This is a scan. So, we need...

Leta Evaskus: Dale, are there stakeholders?

Dale Sanderson: There are no stakeholders. Thank you. So, is there a motion to approve the scan as acceptable?

Diane Schwilke: I move to accept the scan, as adequate.

Alex Park: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. I think we can move on to antidepressants.

Leta Evaskus: You need to either reiterate the motion or make a new one. Nice try, Dale.

Dale Sanderson: Yeah. I did try. I'm trying to move us along a little faster than we should be here. Okay. So, any discussion on the motion?

Virginia Buccola: If there's no discussion I can move to make the motion. After considering the evidence of safety, efficacy, and special populations for the treatment of ADHD, I move that methylphenidate based and amphetamine based agents of both long- and short-acting formulations are safe and efficacious, a long- and short-acting formulation of each stimulant should be preferred drugs on the Washington State preferred drug list. No single stimulant medication is associated with fewer adverse events in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington preferred drug list. After considering the evidence of safety, efficacy, and special populations for the treatment of ADHD, I move that the nonstimulant atomoxetine is safe and efficacious and should be included as a preferred drug on the Washington State preferred drug list. After considering the evidence of safety, efficacy, and special populations for the treatment of ADHD, I

move that the alpha-agonist, clonidine and guanfacine, are safe and efficacious, and that both agents... both of these agents should be included as a preferred drug on the Washington State preferred drug list.

Dale Sanderson: Is there a second? I will second that. All in favor?

Group: Aye.

Dale Sanderson: All opposed, same sign. None that I see. Now, we can go on to the antidepressants. Thank you.

Ian Blazina: This is preliminary scan report number one on second-generation antidepressants. Next slide.

The previous full report was update number 5 in March of 2011 with searches through September of 2010, and that report included 12 drugs and multiple populations. Last year, April 2017, there was a targeted updated with searches through September 2016 looking at the new drugs, since the 2011 report, which is vortioxetine, levomilnacipran, and vilazodone compared with any of the second-generation antidepressants for only looking at major depressive disorder and generalized anxiety disorder. This is the first scan, since the targeted update. Next slide.

The key questions were the standard formulation of the first question looking at treatment for outpatients with major depressive disorder, generalized anxiety disorder. The second question looking at the harms. The third question looking at subgroups. Next slide.

We included adult outpatient populations with major depressive disorder, generalized anxiety disorder, diagnosed by a validated instrument. We excluded from this targeted updated, but included in the full report, the populations including dysthymia, seasonal affective disorder, OCD, PTSD, social anxiety, and premenstrual dysphoria. Next slide. Next slide.

We included interventions in this targeted update are listed here, these three drugs. Next slide.

Since the last scan, we identified no new drugs, box warnings, or comparative effectiveness reviews. Next slide.

In this scan, we identified 4 head-to-head trials, 2 compared vortioxetine to duloxetine and escitalopram, and 2 compared vilazodone to citalopram and paroxetine. There is one new secondary publication. Additional populations and drugs would add an estimate of more than 70 head-to-head trials. Next slide.

In summary, since the last targeted update, we identified no new drugs, comparative effectiveness reviews, or black box warnings, 4 new head-to-head trials, and 1 new secondary analysis.

The last slide is only relevant to the DERP group. So, that's the end. Are there questions?

Dale Sanderson: None that I see.

Nancy Lee: Just a clarification question on the 4 head-to-head studies. Can you just clarify when they were doing the head-to-head study of vortioxetine and vilazodone, the comparator group, they were on duloxetine and escitalopram, or escitalopram and paroxetine, or can you kind of comment on that?

Ian Blazina: Those were combination therapy groups.

Dale Sanderson: Other questions from the committee? So, we accept the scan now or wait...

Leta Evaskus: First, we'll do the Magellan presentation and then we'll do the motions, but Ian, we can let you go.

Ian Blazina: Okay. And I am sorry, actually, I misspoke. I just looked back into the scan, and that was actually multiple groups. So, the trials were vortioxetine versus duloxetine and vortioxetine versus escitalopram. And then vilazodone versus citalopram and vilazodone versus paroxetine.

Nancy Lee: Great. Thank you.

Dale Sanderson: Go ahead, please, with the rest of this.

Umang Patel: Okay. This is Umang Patel from Magellan. Just a quick review of how the presentation will work. It will be an overview of the disease state followed by the FDA approved indications, and then, the dosage and formulations that are available. Finally, we will wrap up with guideline updates. Next slide.

So, the first TCR we'll go over are the antidepressants, the other category. Next slide.

In terms of depression prevalence of 12-month and lifetime major depressive disorder is approximately 16.1 million American adults, or 6.7% of the U.S. population. The lifetime incidence of major depressive disorder in the U.S. is 12% in men and 20% in women. In addition, the incidence of depression has been reported to occur approximately in 12.5% of adolescents defined as ages 12-17 years. With appropriate treatment, 70-80% of patients experiencing major depressive disorder achieve response; however, as many as one-half of all patients do not experience sufficient symptom improvement with initial treatment. Among patients who remit, residual symptoms are common and associated with impaired psychosocial functioning and increased relapse rates. Until recently, known differences among antidepressant drugs were generally limited to safety and tolerability issues. However, over the past handful of years, a number of studies have emerged to evaluate possible differences among antidepressant classes in their ability to resolve specific symptoms of depression. Each of the groups of drugs in this class has a potential role in the treatment of major depressive disorder, primarily as a result of their heterogeneous spectrums of activity. As with many psychotropic drugs, patients failing to respond to one type of antidepressant may respond to a switch, augmentation of an antidepressant with another mechanism of action. Next slide.

We'll do a quick overview of the three different disease states. First, we went over MDD, but in addition to that, GAD, generalized anxiety disorder, it affects about 6.8 million adult Americans and about twice as many women as men. The disorder develops gradually and can begin

across a life cycle, though the risk is highest between childhood and middle age. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least six months, unable to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation, and physical symptoms that often accompany the anxiety can include things such as fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, and hot flashes. The second disease state, social anxiety disorder, SAD. In the U.S., SAD is the most common anxiety disorder affecting approximately 5.3 million per year. It is the third most common psychiatric disorder after depression and alcohol abuse characterized by marked and persistent fear of social or performance situations in which embarrassment may occur. Women and men are equally likely to develop the disorder, which usually begins in childhood or early adolescence. Social anxiety disorder is often accompanied by other anxiety disorders or depression, and substance abuse may develop if people try to self-medicate their anxiety. Lastly, we'll discuss panic disorder, which is a severe chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks. Incidence ranges between 3 to 6 million per year with one-half to two-thirds of those effected being female. Up to 15% of the generalized population, excuse me, general population experience isolated panic attacks, whereas up to 3.5% develop full panic disorders during their lifetime.

On the next slide, you'll see... over the next two slides, you'll see the various medications in this group. Whether or not they are available generic, and their various indications. Here, we do have Aplenizin, Forfivo XL, Wellbutrin XL, bupropion hydrochloride immediate release, Wellbutrin sustained release, desvenlafaxine ER base, Khedezla, Aptyrxol, Pristiq, Cymbalta, and Marplan on here. As you can tell, the majority of these are available in a generic form aside from Aplenizin, Forfivo, the desvenlafaxine ER base, the Aptyrxol, and the Marplan, as well. We also have whether... all of these here are indicated for major depressive disorder, where as some do have additional indications, as well, such as GAD or on the right-hand side, you can see diabetic peripheral neuropathy, fibromyalgia, or chronic musculoskeletal pain. Next slide.

Then, on here, we do have the additional medications in this class, Fetzima, we have Remeron, nefazodone, Nardil, Emsam, Parnate, trazodone, venlafaxine, Effexor ER, venlafaxine ER, Viibryd, and Trintellix. Just to give information, kind of a, take a step back and a broad step on this entire class, itself. Black box warning, antidepressants please note, have a black box warning regarding a risk of suicide. Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults compared to placebo in short-term studies of MDD and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. In terms of pediatrics, safety and efficacy in this pediatric population have not been established for nearly all products in this class, excluding selegiline, transdermal selegiline, or Emsam, is contraindicated at any dose in children under the age of 12. For pregnancy, based on animal data, the FDA classified all drugs in this category as category C; however, please note, Nardil and Parnate, the safety has not been established. The last two, the renal and hepatic impairment, in terms of renal impairment, bupropion, Pristiq, Fetzima, and Remeron, you must use with caution, and Cymbalta and isocarboxazid are not recommended for patients who have end-stage renal disease or renal impairment. Similar with hepatic impairment, dose reduction is recommended for bupropion in patients with moderate to severe hepatic impairment, and no dose adjustment is needed in desvenlafaxine, Marplan, Viibryd, and Trintellix. Next slide.

You'll see here, we have the dosing and availability. Note all medications on this slide are available in extended and sustained release, aside from bupropion hydrochloride, immediate release, for obvious reasons. Next slide.

Similar to the previous slide, all medications on this slide are available as tablets and capsules, with the exception of Emsam, which is a patch. Next slide.

Lastly, all medications here are available as tablets or capsules, as well. Next slide, please.

The American Psychiatric Association, 2010, recommend patients with MDD are recommended an SSRI, SNRI mirtazapine and bupropion as appropriate for initial treatment for most patients. Data showing superiority and efficacy of one or another class of drugs, such as MAOIs, TCAs, SSRIs, SNRIs, are not robust or clinically meaningful. They differ in their adverse event profile and safety characteristics that should be considered when choosing an initial therapy. Other factors to consider include drug/drug interactions, pharmacokinetics, patient preference, and historical patient response. The American College of Physicians in 2016, the guidelines on the nonpharmacologic and pharmacologic treatment of adult patients with MDD were released. After review of literature, they found that cognitive behavioral therapy, or CBT, and second generation antidepressants are similarly effective and have similar discontinuation rate. The ACP recommends treatment with either CBT or second generation antidepressants for MDD after discussing treatment effects, adverse effects, preferences, and accessibility with patients. They do not recommend one antidepressant over another, but note that bupropion is associated with a lower rate of sexual adverse effects, while venlafaxine has a higher rate of nausea and vomiting and discontinuation syndrome, such as flu-like symptoms. Please note that the next TCR we go over for SSRIs will have similar guidelines for obvious reasons. So, I will have these in the next TCR, but for SAD, the... please note that for both GAD, the ICGDA recommends SSRIs, SNRIs, TCAs, and CBT as firstline treatments. For SAD treatment, the ICGDA expert panel recommends SSRIs for firstline therapy. For panic disorders, the 2009 American Psychiatric Association treatment guidelines recommend SSRIs, SNRIs, and benzodiazepines for firstline pharmacotherapy.

Should I lump these together? So, I'll take questions at the very end of antidepressants. So, to go to the next topic, antidepressants of SSRIs. Next slide, please.

On this slide, you can see the various SSRIs available. We have Celexa, Lexapro, Prozac, Sarafem, Prozac weekly, fluvoxamine, fluvoxamine ER, Paxil, Paxil controlled release, Brisdelle, Pexeva, and Zoloft. Almost all are available as generic, aside from Sarafem and Pexeva. Please note Lexapro and Prozac are also FDA approved for MDD in peds. Aside from MDD, other indications here are also listed for their respective SSRIs,

including things such as GAD, SAD, panic disorder, OCD, PTSD, PMDD, bulimia nervosa, or VMS, which is moderate to severe vasomotor symptoms associated with menopause. The indications are for use in adults only unless additional ages are specifically specified. The mechanism of action for these SSRIs, just to give a little bit of clinical info, the selective serotonin reuptake inhibitors, or SSRIs, or antidepressants that block the reuptake of serotonin in the brain, compared to the older TCA, tricyclic antidepressants, SSRIs have less of an effect on histaminic and muscarinic receptors. The improved side effect profile leads to increased compliance with the SSRIs. Now, while there is no evidence that SSRIs are more effective than TCAs, their improved tolerability, as well as lower lethality and overdose, safety and cardiovascular disease, and lower incidence of weight gain, has resulted in the SSRIs becoming firstline agents for the treatment of depressive disorders. Next slide.

Here, we have all the SSRIs along with their dosage and their availability. Please note, majority are available as tablets or capsules, while Celexa, Lexapro, Prozac, Paxil, and Zoloft are also available as an oral solution. In terms of frequency, all SSRIs are taken once daily with the exception of fluvoxamine, greater than 100 mg, and the weekly dosage form of fluoxetine. In terms of pediatric, there are four main medications. Lexapro is indicated for the treatment of depression in patients greater than 12. Prozac is indicated for the treatment of depression in patients greater than 8 years of age, and treatment of OCD in patients greater than 7. Fluvoxamine is indicated for the treatment of OCD in pediatric patients ages 8 to 17. Lastly, Zoloft is indicated for the treatment of OCD in patients greater than 6 years of age. Just to echo the black box warning from the previous TCR, note that there is a black box warning regarding risk of suicide, antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults compared to placebo. Next slide.

In terms of guidelines, there are various governing bodies. We have the National Institute of Mental Health, 40 to 50% of patients responded to treatment with SSRIs, and that approximately one-third of depressed patients achieve remission within 12 weeks. While relapse rates are high, up to 30%, patients respond well to dose increases. The American College of Physicians in 2016, depression treatment guidelines for adults



recommend that clinicians should select either CBT or second generation antidepressants, including SSRIs, to treat patients with MDD. The American Psychiatric Association in 2010, MDD practice guidelines recommend SSRI, SNRI, mirtazapine, or bupropion, as appropriate, for initial treatment in most patients. Lastly, American Academy of Pediatrics, AAP, adolescent depression guidelines state that primary care clinicians should use evidence-based psychotherapy and pharmacologic treatment, such as SSRIs whenever possible. The treatment should be reassessed after 6 to 8 weeks, and if no improvement is noted, a consultation with a specialist may be needed. Next slide.

Just to touch on some of the additional indications we had seen. For bulimia nervosa, fluoxetine, Prozac, is the only SSRI medication approved by the FDA for the treatment of bulimia and has been shown to reduce the episodes of binge eating and purging behavior and their chances of relapse. Lastly, VMS, the vasomotor symptoms associated with menopause, the Endocrine Society believes SSRIs, SNRIs, gabapentin, and pregabalin for moderate to severe VMS in patients with contraindication to hormone therapy or choose not to use hormone therapy is indicated. Paroxetine mesylate or Brisdelle is the only SSRI approved to treat VMS. And just to echo with this, ACOG, the American College of Obstetricians and Gynecologists, also state SSRIs, SNRI's, clonidine, and gabapentin, and effective alternatives to hormone therapy should be used for VMS. Next slide.

Here, I did allude to this earlier, but for GAD, the ICGDA, International Consensus Group on Depression and Anxiety, recommend SSRI, SNRIs, TCAs, and CBT, as firstline. For the treatment of SAD, the ICGDA also recommend SSRIs. For panic disorders, again, 2009 APA treatment guidelines state SSRIs, SNRI's, TCAs, and benzos are roughly comparable in efficacy. SSRIs and SNRIs are frequently preferred as initial therapy due to their favorable safety and adverse effect profile, and the APA does not distinguish a particular SSRI among those that are approved by the FDA. For OCD, SSRIs are preferred, as firstline medication and all SSRIs that are indicated appear to be equally effective; however, individual patients may respond well to one over another. Lastly, for PTSD, SSRIs are recommended as the firstline medication for treatment. I will now open up for any questions.

Dale Sanderson: Any questions from the committee? I have a question. So, cognitive behavioral therapy, I know that's outside of the realm of what we're doing here, but it's... clearly it's, like, in conjunction with psychiatric medication and antidepressants and anxiety disorders and oftentimes it's actually effective instead of. Is that anything that we need to include or think about or is that... are we just assuming that other therapeutic measures have been taken here?

Donna Sullivan: I think that's kind of outside the scope of the P&T Committee, as far as clinical policies that might be a place to put in there, just, you know, a recommendation of those other cognitive therapies in addition to, or instead of, medication when appropriate, or something like that.

Dale Sanderson: So, have we accepted the scan?

Leta Evaskus: Not yet. Are there any stakeholders?

Dale Sanderson: There are no stakeholders.

Leta Evaskus: We will go back and first do the P&T motion.

Dale Sanderson: The first thing we need to do then is to accept the scan as adequate.

Nancy Lee: I move to accept the scan as adequate.

Dale Sanderson: Is there a second?

Virginia Buccola: I second.

Dale Sanderson: All in favor?

Group: Aye.

Dale Sanderson: All opposed, same sign. So, we have two motions. We have the P&T motion and we have the DUR motion. Any discussion on the P&T motion?

Amber Figuero: Again, I think the list of diagnoses is getting too long. I think we should just say for their FDA indications or something like that.

Dale Sanderson: Any other discussion? Would someone like to entertain a motion?

Diane Schwilke: I think there are no additions, correct? So, we can just reiterate? So, I move to reiterate the previous motion.

Donna Sullivan: Actually, I'm sorry. The motion has changed technically. So, you do need to read it so that...

Diane Schwilke: I guess I'll read it. That's okay. So, after considering the evidence of safety, efficacy, and special populations for their FDA approved indications, I move that bupropion, citalopram, duloxetine, escitalopram, fluoxetine, sertraline, fluvoxamine, levomilnacipran, mirtazapine, paroxetine, desvenlafaxine, venlafaxine, vortioxetine, and vilazodone are safe and efficacious for their approved indications. The Washington preferred drug list must include, as preferred, at least two SSRIs, one of which must have an indication for pediatric and adolescent use, at least one SNRIs or SSNRI, mirtazapine, and bupropion. The second generation antidepressants cannot be subject to therapeutic interchange in the Washington preferred drug list. Nefazodone is also efficacious for its approved indications, but does not have a higher risk of hepatic toxicity and... but does, excuse me, have a higher risk of hepatic toxicity, so should not be a preferred drug on the PDL. My last name has an H-, S-C-H.

Susan Flatebo: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. Okay. So, moving onto the DUR motion.

April Phillips: As she is pulling the slides up, I wanted to mention that there has been some updates to the slide, since the handouts were printed. They should be on the screen, but I'll try to point them out, as we go along.

So, this slide just kind of gives you a general picture of the amount paid versus the number of users, and it includes all antidepressants, the SSRIs and the others. It also includes both pay-for-service and the managed care plans. It also combines all strengths, dosage forms, and brands with the same generic ingredient. The current limitations for the antidepressant class include generics... the antidepressants are a refill protected class. The limitations include generics first, try and fail of two preferred before a nonpreferred, and at least one of those preferreds needs to be a generic. There are dose limits for duloxetine, citalopram, and escitalopram. Escitalopram was missed on the handout, but it's listed on the screen.

There is also an EA for both bupropion and duloxetine pertaining to their non mental health indications. Then, under the age of 18, a second opinion is required with Seattle Children's for an antidepressant duplication, more than one antidepressant, and when an antidepressant is included in a polypharmacy, which is defined as five or more mental health medications.

Our recommendation is to continue all current limitations, that all agents are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority, and a slight change to the third bullet, requires a trial of two preferred within the same subclass with the same indication and different active ingredients before a nonpreferred would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred. Are there any questions?

Dale Sanderson: Under the listed motion, I mean, the current limitations really... so, the motion should say slides 19 and 20?

Amber Figueroa: So, same subclass is what's not on here. So, is that referring to SNRIs, SSRI?

April Phillips: Yes. So, you'd have to try two preferred SSRIs before you can have a nonpreferred SSRI, or same with SNRIs or TCA, that type of...

Amber Figueroa: Okay.

Diane Schwilke: I don't know if this is exactly the most appropriate place to bring this up, but one thing that came up clinically, not related to this class, but it was in a class that has a small group of medications, I think we need to be a little careful in applying the blanket statement of two preferred before nonpreferred will be covered, especially when you're looking at a class that might only have three or four agents. This came up with like, GLP ones, for example. We had a case where Byetta and Bydureon were the preferred. Well, they're both the same active ingredient. So, that's not really appropriate to try them both if you had trouble with one. So, I know that's not the same class, but I think we need to, as a committee, to be a little careful with using that blanket statement, because I had to do a lot of work to try to...

Donna Sullivan: That was really a procedural error on our staff's part that they just weren't following the correct procedure. So, that shouldn't happen again.

Diane Schwilke: It wasn't even the one I was talking to you. It was actually when I worked with David on. So, that issue has caused a couple of problems for me, directly, as a prescribing provider. Again, not with antidepressants, but in classes that have fewer... so SSRIs have quite a few. I mean, maybe that's not a big deal, but when you look at SNRIs, there's fewer available. So, I think we have to be a little careful in putting that blanket statement on every single class.

Donna Sullivan: And that's why... so that's one of the reasons why we say with a different active ingredient, so that the two have to be different active ingredients, as well as we have the statement where you can't try and fail two if there's only one preferred. So, we're trying to get there, and any feedback you get, if they're not being, like, covered accordingly, just let us know. And we can make sure that we get the staff that are receiving those calls trained and using the policy appropriately.

Dale Sanderson: Any other discussion from the committee? Would someone like to entertain this motion?

Virginia Buccola: I move that the Apple Health Medicaid Program implement the limitations for the antidepressant agents listed on slides 19 and 20, as recommended.

Nancy Lee: I second that motion.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. Hearing none. That will adjourn the Pharmacy and Therapeutics Committee and convene the Drug Utilization Review Committee.

Umang Patel: The next class we'll discuss here are Alzheimer's agents.

Just to give a little bit of background, approximately 5.7 million Americans suffer from Alzheimer's disease, 5.5 million of which are aged 65 years of age and older. AD is the most common type of dementia, accounting for 60 to 80% of dementia disorders in the elderly and is the sixth leading cause of death in the U.S. Dementia is characterized by irreversible loss or decline in memory and other cognitive abilities. It is characterized by progressive cognitive decline associated with impairment of activities of daily living and behavioral disturbances. Other types of dementia include vascular dementia, dementia with Lewy bodies, mixed dementia, and frontotemporal dementia. It may also be associated with other disease states, such as HIV, normopressure hydrocephalus, Huntington's disease, Korsakoff's syndrome, and many that I've listed here. Many other conditions can cause dementia or delirium symptoms, such as thyroid disorder, vitamin deficiencies, but are reversible once the underlying condition is addressed. Patients with AD eventually lose all cognitive, analytical, and physical functioning. In addition, there are seven stages of AD over the course of the disease, and individuals will not experience the same symptoms or rate of disease progression.

Here, you'll see the medications in this class. We have Aricept, Razadyne, rivastigmine, Exelon patch, those are the acetylcholinesterase inhibitors.

Then, we have the NMDA receptor antagonists, which are Namenda and Namenda extended release. Then, we have the combination of both acetylcholinesterase inhibitors and NMDA receptor antagonists, which is Namzaric, donepezil and memantine ER.

Just to give a little bit of a clinical background, for mechanism of action, acetylcholinesterase inhibitors, so for donepezil, galantamine, rivastigmine, they exert their therapeutic effect by enhancing cholinergic effect. They increase the concentration of acetylcholine through reversible inhibition of its hydrolysis by the acetylcholinesterase enzyme. Centrally, the resulting increase in acetylcholine will improve cognition. Peripheral enhancement of acetylcholine causes the GI adverse effects that are noted with these acetylcholinesterase inhibitors. As the disease progresses, the therapeutic effect of the acetylcholinesterase inhibitors may lessen, as fewer cholinergic neurons remain functionally intact.

For NMDA, specifically memantine, it is an uncompetitive NMDA glutamate type receptor antagonist with low to moderate affinity that binds to the receptor. It allows the receptor to be activated during physiological memory formation, but blocks the receptor during pathological, and this demonstrates antagonistic at the serotonin and nicotinic receptors.

On the next slide here, you'll notice the different dosages and formulations over the next two slides. Here, we have the acetylcholinesterase inhibitors. There is a little bit more information here than historically in other TCRs. We have the starting doses, the minimum therapeutic dosage, the minimum time to reach it, the target dosage, and the minimum time to reach that, special consideration, and dosage forms. Please note on this slide, all are available as either tablets or capsules with the exception of the Exelon Patch, which is a patch. We also have Aricept, which is also available as orally disintegrating, the generic form.

Here, we have the NMDA receptor antagonists, memantine and the combination product. Here, again, they are available as tablets. We have memantine, which is available as tablets, dosepak, and oral solution. We have the ER form as extended release capsules and titration pack. Then,

the combination product is available as an extended release capsule and dosepak, as well.

Now, in terms of other populations, for pediatrics, there are no adequate or well-controlled trials documenting safety or efficacy of acetylcholinesterase inhibitors or NMDA receptor antagonist in children. So, it's not recommended. In terms of pregnancy, donepezil and galantamine are classified as category C, rivastigmine and memantine are classified as pregnancy category B.

For renal impairment, the galantamine dose should be dose adjusted for moderate renal impairment, and it is not recommended for severe. In terms of rivastigmine, a dose reduction is recommended for moderate to severe renal impairment.

Lastly, for hepatic impairment, galantamine has a dose reduction for moderate hepatic impairment, which is classified as Child-Pugh class score of B, and it is not recommended in severe hepatic impairment.

In terms of guidelines, the American Academy of Family Physicians in 2017 recommended management objectives for treatment of AD and PD related dementia, PD being Parkinson's include improving cognition and delaying disease progression, as well as promoting quality of life and social functioning. Decision to initiate a trial of therapy within acetylcholinesterase inhibitor, or memantine, should be based on individual assessment by a clinician, tolerability, adverse effect profile, ease of use, and costs should be considered when selecting treatment. Based on their literature review and evidence rating, they state that cholinesterase inhibitors should be considered for treatment of cognitive and functional decline in patients with mild to moderate AD. Dose ranges recommended include donepezil 5 to 10 mg per day, or at least 16 per day of galantamine, and 6 mg to 12 mg per day orally, or 9.5 per day transdermally of rivastigmine. Memantine, at a target dose of 20 mg per day, should be considered for treatment of cognitive and functional decline in patients with moderate to severe AD. In patients with moderate to severe AD or mixed dementia who are already receiving the cholinesterase inhibitor, memantine should be considered to treat cognitive and functional symptoms. They further recommend the use of



Vitamin E, a structured physical exercise program, and cognitive stimulation in the select populations.

On the next slide, the American Psychiatric Association, in 2007, and reaffirmed it in 2014, stated the available efficacy evidence remains modest for acetylcholinesterase inhibitors in mild to moderate Alzheimer's disease and memantine in moderate to severe AD. Based on the evidence available at publication, no increased benefit was seen with higher doses of donepezil, but higher doses of rivastigmine may increase benefit. Combination therapy, memantine with acetylcholinesterase inhibitors, may results in a slight benefit, but overall, clinical significance of this is unclear. Likewise, sustained benefit with either memantine or an acetylcholinesterase inhibitor is unclear. Lastly, efficacy data on the use of acetylcholinesterase inhibitors remains weak for the treatment of Parkinson's disease dementia with most evidence associated with rivastigmine. Any questions?

Dale Sanderson: Did you find any benefit behaviorally for these medications other than the cognitive benefit?

Umang Patel: Primary endpoints that they were looking more at where cognitive endpoints. So, I didn't see any for behavioral endpoints.

Dale Sanderson: We have no stakeholders. The motion is there. And I'm wondering if, again, we should include both pages 30 and 31.

April Phillips: There is an image, like the previous one, that kind of shows the amount paid versus the number of users. Current limitations that are already in place are for under the age of 18, they require a second opinion kind of Umang said. They're not recommended in children. Our previous DUR approval was a history of failure of all preferred products before a nonpreferred. So, our recommendation, this time around, is to continue the second opinion network consultation for 18 and under that all products were considered safe and efficacious and are eligible for preferred and grandfathering status at the discretion of the Health Care Authority. This time, we are going to change the trial of 2 preferred prior to a nonpreferred, unless contraindicated or not clinically appropriate, or there's only one that's a preferred product.

Dale Sanderson: Discussion for the committee? The motion is going to include slide 30 and 31? Any other discussion or questions?

Amber Figueroa: Slide 30 talks about the previous recommendations. So, I don't want to mucky the waters, but then slide 31 says continue all current limitations, except the.

Dale Sanderson: So, we don't need slide 30?

April Phillips: So, on the recommendation, I can remove continue all current limitations, since they're listed there with the changed.

Donna Sullivan: Do you wanna just do slide 31?

Amber Figueroa: I would. Yeah. I move that the Apple Health Medicaid program implement the limitations for the Alzheimer's agents listed on slide 31, as recommended.

Alex Park: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. Moving on to antimigraine agents.

Umang Patel: Next topic we'll go over are antimigraine agents, specifically... first we'll go over the triptans, and then we'll discuss the other.

Headache is one of the most common complaints by patients when presenting to a physician. About 64% of physician-diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bedrest due to their migraine symptoms. Migraines account for approximately 10 to 20% of all headaches in adults and affects over 38 million men, women, and children in the U.S. Approximately 85% of these patients with migraine headaches suffer less than 3 to 4 attacks per month. In addition, 18% of women, 6% of men, and 10% of children experience migraine and

epidemiologic profile that has remained stable over many years. The median frequency of migraine attacks among migraine sufferers is about 1.5 per month. The American Migraine Study 2 found that migraine caused decreased productivity and absenteeism from work for many patients, which obviously creates an economic impact.

On the next slide here, we'll look at the medications that are indicated. Here, we have Axert, Relpax, Frova, Amerge, Maxalt, Imitrex, Onzetra [Xsail], Sumavel [DosePro], Zembrace [SymTouch], Treximet, Migranow kit, Zomig, and Zomig ZMT. As you can see, all medications here are FDA indicated for the acute treatment of migraine attacks with or without aura and roughly half are available in generic formulation.

To give a little bit of a mechanism of action here. Migraine pain is believed to result from activity within the trigeminal vascular system. This activity results in a release of vasoactive neuropeptides with subsequent vasodilation, dural plasma extravasation, and perivascular inflammation. The therapeutic activity of triptans can be attributed to agonistic effects on the vascular and neuronal serotonin, so 5HT<sub>3</sub> receptors, and the relief of migraine headache may result, and this is what is hypothesized based on three different pathways first, intracranial vessel constriction via stimulation of the serotonin receptors. The second would be the inhibition of vasoactive neuropeptide release through stimulation of the serotonin receptors. Lastly, interruption of pain signal transmission within the brain stem through serotonin receptor stimulation. In addition to these, there aren't just triptans here. There are also combination products. So, naproxen is an NSAID that inhibits the synthesis of inflammatory mediators and has analgesic properties. So, you can see that with the Treximet combo. Lastly, camphor and menthol are topical analgesics, and the mechanisms of analgesia of these agents are not well-defined, but they are thought to be associated with antipruritic effect, a cooling sensation, and a counter irritant effect.

Here you can see all the medications, the available, single-dose, max dose, and the package size, as well. Please note that all are available as tablets. We do have Maxalt, which is a tablet and an orally disintegrating tablet. We also have Imitrex, which is a... it comes in a vial along with an injection kit. Sumavel...

[Recording: You are the only participant in the conference.]

That terrified me. So, okay. Holy smokes. Then, we have Sumavel DosePro, which is available as prefilled units in vials.

So, for pediatrics, on the previous slide in the indications, the ones that are pediatric approved were there, but I'll summarize, as well. Axert, Treximet, and Zomig are approved for adolescents 12 to 17 years of age. Maxalt carries an approval for pediatric patients 6 to 17 years of age whose attacks usually last four hours or more. And the other products in this class have not been approved for pediatric population, which is defined as less than 18 years of age. For pregnancy, all products in this review are pregnancy category C. Please note, products that contain NSAIDs should not be used in pregnant women, particularly during the third trimester. In terms of renal impairment, rizatriptan should be used in caution with patients who are on dialysis due to decrease in the clearance. Treximet and naratriptan are contraindicated in patients with a creatinine clearance of less than 30 and 15 respectively. Axert dose adjustments are recommended for patients with severe renal impairment.

Lastly, hepatic impairment, triptans should not be used in patients with severe hepatic impairment. Rizatriptan should be used with caution in patients with moderate hepatic insufficiency, and dosage adjustments are required for almotriptan, naratriptan, and sumatriptan in those who have mild to moderate impairment, and it is recommended for zolmitriptan in patients with moderate to severe hepatic impairment.

Just a continuation of the medications in this class, their availability, single dose, max dose, and package size.

In terms of guidelines, the U.S. headache consortium, the American Academy of Family Physicians, and the American College of Physicians recognize that triptans are effective agents for the acute treatment of migraine. Data reviewed for the guidelines did not demonstrate that any one triptan was superior. These groups indicated that therapy with any triptan for a patient with moderate to severe migraine pain in whom no

contraindications exist is appropriate. If a patient does not experience adequate relief or experiences intolerable adverse reactions with one triptan, treatment with another agent may be effective. Please note, multiple agents within this class were not available at the time of these publications. In terms of the American Academy of Neurology and the American Headache Society in 2012, and reaffirmed in 2015, they advise that antiepileptic drugs, such as divalproex sodium, sodium valproate, topiramate, and beta-blockers are effective in migraine prevention. All available triptans, along with dihydroergotamine, which we'll discuss in the next subtopic, acetaminophen, NSAID, select opioids, sumatriptan, naproxen, and acetaminophen/aspirin/caffeine combo are effective treatments, and they had no recommendations in terms of an advantage of one triptan over another.

I will go to the antimigraine agents, others, and then I'll open up for questions right after that. So, the next topic for antimigraine agents, others, here we only have just the indications available. So, we have for medications, we have Aimovig, which is a new medication that was recently approved. We have Cafergot, Cambia, dihydroergotamine mesylate, Migranal, ergotamine tartrate. We have Prodrin, which is a combination of isometheptene/caffeine/acetaminophen. We also have Midrin, which is isometheptene/dichloralphenazone and acetaminophen combo. Lastly, Migergot, which is an ergotamine tartrate and caffeine combination. Just to give you a little bit of information in terms of for this class, just the only black box warning is please note for NSAIDs, there is a black box warning with NSAIDs for an increased risk of CV thromboembolic events, including MI and stroke, and contraindicated in settings of coronary bypass graft surgery. For pregnancy, please note that many of these are Category X, Cafergot, dihydroergotamine mesylate, ergomar, Migergot, and Migranal. Anyone with an ergomar derivative. Cambia is a Category C prior to 30 weeks of gestation. And then afterwards, it's category D. Midrin is a Category C. Aimovig is a brand new recently-approved medication where there are no adequate data on developmental risk associated with pregnant women. So, there is no categorization at this time. I will now open... that ends the antimigraine, if there are any questions.

Dale Sanderson: Any questions from the committee? I have a question. So, do all of these agents have significant serotonin activity?

Umang Patel: For the others or for the triptans?

Dale Sanderson: Oh, the triptans, and, I mean, the triptans are all serotonin activity?

Umang Patel: It wasn't across all, because there are various subreceptor types. So, when I was going over the mechanism of action, there's a long subtype for each single mechanism of action. So, it's very specific on where it does work, but it's not, like, an SSRI where we think of an overall serotonin.

Dale Sanderson: So, it's, like, you know, the serotonin syndrome, which lots of people that are on SSRIs, they go on a triptan and... so are there certain triptans that would be safer?

Umang Patel: I didn't see a large incidence in terms of that as being something to worry about, but I can look into that, as well, and verify that.

Dale Sanderson: Any other discussion from the committee? We have one stakeholder. If you could limit your talk, please to three minutes.

Scott Budsberg: Hi. My name is Scott Budsberg, and I am a health outcomes and pharmacoeconomic specialist with Amgen. I appreciate the opportunity today to address the committee regarding Aimovig, also known as erenumab. As was stated earlier, Aimovig was approved recently, on May 17<sup>th</sup> of this year. It's the only fully human monoclonal antibody targeting the calcitonin gene-related peptide receptor. Aimovig is approved for the preventive treatment of migraine in adults. The recommended dose is 70 mg, self-injected subcutaneously once monthly. Some patients may benefit from 140 mg monthly, which is administered as two consecutive subcutaneous injections of a 70 mg syringe. The efficacy of Aimovig was assessed as a preventive treatment of episodic migraine and chronic migraine. The primary outcome in all three studies was reduction in the mean monthly migraine days comparing Aimovig to placebo. The two pivotal phase-3 studies of similar design were conducted in episodic migraine patients, or those patients that suffered

from 4 to 14 migraine days per month. Strive was a 6-month study. Monthly migraine days were reduced by 3.2 and 3.7 days in the 70 and 140 mg Aimovig arms respectively. Arise was a 3-month study where monthly migraine days were reduced by 2.9 days in the 70 mg arm and that was the only arm that was tested in that particular trial. One pivotal phase-2 placebo controlled study was conducted in chronic migraine patients. So, those patients with greater than or equal to 15 monthly headache days, of which at least 8 were migraine days. This three-month study conferred a reduction of 6.6 monthly migraine days in both the 70 and the 140 mg Aimovig arms. Aimovig is well tolerated. The most common adverse reactions in clinical trials occurring in at least 3% of patients and more often than placebo were injection site reactions and constipation. Antidrug antibodies occurred in 6.2% and 2.6% of the 70 and 140 mg doses respectively. With respect to availability, Aimovig is currently supplied as a 70 mg/mL single dose prefilled SureClick injector. Given that Aimovig is the only marketed CGRP receptor inhibitor for the preventive treatment of migraine and has demonstrated a statistically significant reduction in mean monthly migraine days with a low rate of adverse events, I am kindly requesting the committee make Aimovig available to patients. Thank you, very much, for your time, and I will take any questions.

Dale Sanderson: Any questions from the committee? Thank you for your time.

Umang Patel: Could I follow up with a question you asked me, in terms of the... could I follow up with your question about the serotonin syndrome?

Dale Sanderson: Yes.

Umang Patel: So, all of these triptans do have the warning that serotonin syndrome could be possible in patients with SSRIs, but there is no, I guess, clinical data to show one over the other being a better option.

Dale Sanderson: Thank you for that. We have a motion to entertain.

April Phillips: So, our first image is, one again, amount paid versus users. This includes both the triptans and the others. As you can see, sumatriptan is the largest, but it also includes all the formulations, the injections, the orals,

all of that. So, it makes sense that... so the next slide is not in your packet.

Virginia Buccola: I just had a question about the previous slide. I'm just wondering, could you explain the dihydroergotamine, the amount paid, but it doesn't... it's not visible that there's a number of users. I was just curious about that.

April Phillips: It's because it's a very low number.

Virginia Buccola: Okay. Thank you. So, this next slide is not actually in your packets. It is the current limitations that we have for the antimigraine agents, specifically the triptans. We have an average quantity limit, I believe, yeah, an average quantity limit for the triptans. It's based on an average of two doses per episode, which is usually in the labeling for most of the triptans. It can be listed as number of milligrams per 24-hour period. We took an average of four migraines per month and took package size into consideration, because if you did two doses and four migraines but only have eight doses per month, packages usually come in nine. So, we took that into consideration and would give a quantity limit of nine rather than eight. So, the next slide is our recommendation. Continue the monthly quantity limits, that all agents are considered safe and efficacious, and are eligible for preferred status and grandfathering at the discretion of Health Care Authority, and the third bullet has an update on it, a trial of two preferred products within the same subclass with the same indication and different active ingredients before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Dale Sanderson: Do we need to include the limitation slide in our motion?

April Phillips: Yes.

Dale Sanderson: So, call that slide number 42, and this one being slide number 43 then?

David Johnson: A clarification, the quantity limit in the drug file we received in our coding is not 9 universal.

April Phillips: It depends on the product.



David Johnson: Okay. As long as the... we make this clear.

April Phillips: It's the average quantity limit. I didn't call out specific ones, because it can vary on package size, and I didn't want to list out every product and every quantity limit for every dosage form. I kind of just gave a basic idea of where our dose limits were created, in case there's a new product that comes on. They know what basically our standard limit's gonna be.

Amber Figueroa: I don't... I'm not sure if this'll be covered, since it's a new medication anyway, but the Aimovig doesn't fit into the recommendations.

Donna Sullivan: So, Aimovig right now is not part of our migraine class, because it is so new. So, we will be developing a policy for it. So, right now, it's just considered not on the PDL. So, the plans will cover... it'll all be on PA and will eventually have a concise policy that we'll all use, but it'll be reviewed for medical necessity according to label from each individual plan. It's possible it will get reviewed in the fall... or no, the spring of next year. So, the migraine drugs are recontracted each spring. So, we might be revisiting this sometime next year, but we'll be bringing back the policy to you.

Dale Sanderson: Barring any further discussion, would someone like to entertain the motion?

Alex Park: I move that the Apple Health Medicaid program implement the limitations for the antimigraine agents listed on slides 42 to 43, as recommended and amended to include... I don't think we put any amendments, right?

Catherine Brown: I second.

Dale Sanderson: So, we have a motion. Can we have a second?

Catherine Brown: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign.

Umang Patel: Okay. The next class we'll discuss are the immunomodulators, specifically, topical immunomodulators. The two disease states we'll look at here are actinic keratosis, which is a premalignant condition of the skin that manifests as a small thick scaly patch. It is seen mostly in sun-exposed areas of the skin and should be treated, due to its potential to progress into squamous cell carcinoma, abbreviated SCC moving forward. For genital warts, according to the CDC, prior to HPV vaccines, about 360,000 people in the U.S. acquire genital warts each year. They are typically caused by HPV type 6 or 11 in 90% of occurrences. These are usually flat, papular, or pedunculated growths on the genital mucosa, and there is no evidence indicating that the presence of genital warts or their treatment is associated with the development of cervical cancer.

On the next slide here, we'll look at the two medications in this class. We have imiquimod, brand name Aldara. Then, there's also imiquimod, brand name Zyclara. Please note that Aldara is available in its generic form. This does have three indications, first clinically typical nonhyperkeratotic, nonhypertrophic actinic keratosis on the face or scalp in immunocompetent adults. We have biopsy-confirmed primary superficial basal cell carcinoma in immunocompetent adults, maximum tumor diameter of 2 cm on the trunk, neck, or extremities, including hands or feet. Only when surgical methods are medically less appropriate and patients' followup can be reasonably assured. The third and final indication is for external genital and perianal warts, condyloma acuminata in patients 12 years of age or older. For Zyclara, we have two indications, the first being clinically typical visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults. Secondly, the external genital and perianal warts, condyloma acuminata in patients 12 years of age or older.

You'll see the dosages for their respective indications and the availability of both our creams, due to this being a topical medication. Note that imiquimod is recommended to be applied as a thin layer once daily before bedtime to the affected area. It should be applied as a thin film to

the entire treatment area and rubbed in, until the cream is no longer visible. There are no contraindications listed for this. There are warnings not to use this medication with sun lamps, tanning beds, and other products, and to limit exposure to sunlight. In terms of pediatrics, the safety and efficacy for imiquimod in pediatric patients has not been established, and it is pregnancy Category C. There are no hepatic or renal dosage adjustments necessary.

Guidelines for actinic keratosis, there are no widely accepted guidelines for the treatment of actinic keratosis published in the United States. The British Association of Dermatologists in 2007, the treatment options below are listed, along with their associated strength of recommendation and quality of evidence rating. No therapy for mild actinic keratosis. Sunblock of SPF 16 applied twice daily for seven months, 5-fluorouracil applied twice daily for six weeks, topical diclofenac, Tretinoin cream, and imiquimod 5% cream. The International League of Dermatological Societies, European Dermatology Forum, recommend for single lesions, they suggest imiquimod 3.75% or 5%, and for multiple lesions, they recommend 3.75%, but they suggest you can use 2.5 or 5%, as well. In terms of genital warts, it should be guided by available resources, experience of the healthcare provider, and the preference of the patient. No definitive evidence suggests that any available treatments are superior to another, and no single treatment is ideal for all patients or all warts. Are there any questions?

Dale Sanderson: None that I see.

Donna Sullivan: Are there any stakeholders?

Dale Sanderson: There are no stakeholders.

April Phillips: As you can see, there is our utilization information. We have current limitations on it, but I do want to remove the second bullet on that slide, the try and fail criteria, since there is only actually one active ingredient. So, a recommendation is going to be that all topical immunomodulator products are considered safe and efficacious and are eligible for preferred status at the discretion of Health Care Authority.

Amber Figuero: I move that Apple Health Medicaid program implement the limitations on slide 51 for the topical immunomodulators, as recommended.

Dale Sanderson: Second. All in favor say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign.

Donna Sullivan: I just have to point out how perfectly timed this was.

Dale Sanderson: So, we are now going to adjourn for lunch. We have exactly one hour. Be back at 1:00. Thank you very much.

If we can convene the DUR meeting again. We have Dr. Robert Hilt with us to give a presentation. Please go ahead.

Robert Hilt: So, first of all, can everybody hear me. I'll just move it a little closer. Okay. So, I'm just here to give an update about antipsychotic reviews. Just as background, the state has been doing mandatory antipsychotic medication reviews, since about... sure. I will start there. That's maybe a little better. Thank you. I'm used to just launching. So, I'm a professor of psychiatry at the University of Washington. I run a partnership Axis line trauma and health consulate service for the state Health Care Authority in a collaboration with that, and one of the tasks that our consultants perform for the Health Care Authority is second opinion network medication reviews. So, For instance, last year, I think it was on the order of about 850 mandatory reviews we completed for the state in the previous year. Antipsychotics are one of the things that we review, ADHD medications above and beyond dose guidelines, polypharmacy of five or more concurrent psychotropics is flagged for review for children. Clonidine guanfacine at the alpha-2 adrenergic agonists outside of, again, state guidelines are things that we'll review. So, the antipsychotic guidelines were actually set initially back in 2009 by a child mental health group of experts of this state that had met and proposed some review triggers that then were brought to this drug utilization review board, were agreed upon, and we've been doing reviews about those guidelines ever since. 2009 is awhile ago. I said, we probably should do an update.

So, the Health Care Authority with Donna Sullivan's help and others got together, another group of experts primary care, child psychiatrists from around the state to talk about the review limits and come up with some recommendations of modifications, and I can say from the perspective of the review team, there were some things that were, like, we wished could be changed, and the group talked about some of those wishes, in addition to talking about what's been changed in FDA approvals and the new evidence since back in 2009. So, let's go to the next slide.

This is a busy slide. It'll be a little easier to read for you on the screen because of the highlights, as opposed in your book, the highlights don't show up in this printed form. So, on top is a list of the antipsychotics that are currently being triggered and named out as being triggered in the review system. There is mostly second-generation atypical antipsychotics, but a few first-generation agents, like haloperidol and Trilafon, or perphenazine. There are different breakdowns for some of those medications. There's a review always required if those medications are prescribed. Others, you can start at age 3 to 5 without a review, as long as it's below that dose for risperidone, if it's a dose below 2 mg a day, for olanzapine below 2.5 mg a day, and so on. So, at age 6 to 12, you can prescribe up to 20 mg of aripiprazole, for instance at age 13 to 17 up to 30 without a trigger for mandatory review. For those who don't know the process, because there's five Medicaid managed care plans, there's a process where the managed care plans are detecting that a script has arrived at a pharmacy. The Health Care Authority gets involved with sending a note to the doctor, did you mean that? Tell us why. Please send us a note. And as long as there isn't an error in the process, the Health Care Authority sends it to us. Then, we schedule a doc to doc discussion with the prescriber and try to do best practice coaching, but ultimately, we have to make a recommendation back to the Health Care Authority about pay for this, don't pay for this. Most of the time, we say pay for this, but we have a lot of care advice that we give otherwise. So, you know, it's somewhere around 15% or less of the time when we are flagged to do a review that we'll say we really... that really must be changed. Here's what we think it really has to be changed to. Usually, it's about coaching advice otherwise.

So, on the second set of guidelines is some recommendations that are new, and I'll walk through that. Aripiprazole, the first one on that first row there, aripiprazole and risperidone are the two medications that have been FDA approved for the treatment of irritability and agitation associated with autism spectrum disorder. The FDA approvals are actually at age 5 and 6. They're not in preschool age down to age 3:00 however, in clinical practice, the justifiable reason for the use of an antipsychotic in anybody in that age is really essentially the severe developmental disabilities, autism spectrum problems, and if risperidone is allowed in that age 3 to 5 range clinically to the group, they said we should have aripiprazole in the same cluster. We should be clinically considering them the same way. The previous 2009 set of recommendations in this 3 to 5 age range had allowed for olanzapine to be used at doses up to 2.5 mg a day. None of the experts thought that was a good idea anymore and thought that should be an always review these days, that the only two that are being recommended for allowance without review is a small dose of Abilify or risperidone. So, you can see 3 to 5, that's the only... those are the only two medications in the new set of recommendations. Before I go on to each individual one, I just want to be sure I pause. Is there any thoughts or questions in the rationale so far? Okay.

Dale Sanderson: Is there... the rationale for the olanzapine was because of the metabolics?

Robert Hilt: So, I'll go into, yes. So, there's no evidence to support olanzapine in very young children. So, it's not, like, research trial evidence that that original recommendation was based on. Back around 2008 or so, olanzapine had been fairly popular in terms of its degree of treatment effects; however, we learned over time just how significant the weight gain issues were with olanzapine relative even to the other atypical antipsychotics. It's led to a point of perspective that there is not really a justification for starting a young child off on olanzapine, if you really feel you need to use an atypical antipsychotic for treatment. So, yes. That's a long answer to your question, yes.

So, the next one down the list of recommended change from what had been approved before for a trigger was Clozaril, or clozapine. Clozaril is a

terrifically important atypical antipsychotic, in that it can be helpful, in some cases when none of the other antipsychotics have been helpful. However, it has a lot more side effects, requires very skillful monitoring, and the indications that really come up where it's appropriate in child mental health is an adolescent who has been through multiple scenarios of antipsychotics before. They have real deal schizophrenia, major bipolar, other things that are... everything is falling apart from... the group could see no justification for saying, go ahead and use it some, but in somebody age 12 years old or younger without a review. So, recommended changing to an always review for age 6 to 12, okay? They also changed the total mg a day limit down to be consistent with the FDA max. We just didn't think there was a justification for being 900. So, they brought it down to 700, and Dr. McLellan, for instance, one of our experts who was in the group who probably sees the most Clozaril prescribing work by running this child study treatment center in Tacoma said, yeah. It... make it 700. There should be a review if somebody wants to use more than that.

The next antipsychotic on the list that there is a change for is lurasidone. Lurasidone wasn't around back in 2009. It is available and on the market now, and there is an FDA approval for the use... for its use in young people, and the experts thought that was a very reasonable medication to add. We are always concerned about weight gain with this group of medicines. I think the jury is still out in totality with that particular medication, but some of the early reports have shown it looks a little bit better than some of the other choices that we have. So, of the group of antipsychotics, that would seem to be a great option to make available to our prescribers without necessarily requiring a review every time. So, the total daily dose, the 80 mg a day, is an adult FDA max. We said that would be the review trigger for an adolescent and half that amount for age 6 to 12.

Going down the list, quetiapine, previously, as you see above, the review triggers were 300 mg a day for age 6 to 12 and 600 mg a day for 13 to 17 years of age. The commonly accepted adult FDA max dose is 800 mg and the group could see no justification for saying, oh, you're an adolescent, you must need only 600 as a trigger. The general gestalt with the use of that medication over time is initial thought about dosages a decade ago

probably should have been migrated up a little bit. So, that's why we've suggested going up a little bit on the triggers, because it's to be consistent with relative potencies across categories; 600 mg a day in the past of quetiapine is not really equivalent in potency to 8 mg a day of risperidone. So, we were trying to adjust for what we really know about these medicines.

Then, the last one, the risperidone, the group had a feeling that the previous 8 mg a day maximum was overgenerous, and really 6 mg a day would be a more appropriate trigger point. There were a few medications on this list that are still listed as review required, for which there are actually FDA indications for use in adolescents, and I wanted to be sure I am pointing that out, what the group's recommendations were based on.

In yellow highlight, so there's... this table is arranged with two groups of two columns. The first two columns are about the ages, the youngest age allowed without a mandatory review per what we have proposed as a workgroup. The second column it says FDA youth age down to what age has it been FDA approved. For instance, for aripiprazole, the youngest age it's FDA approved is down to age 6. We've recommended age 3. Again, that age 3 to 5 category where aripiprazole and risperidone are both allowable without a review. Asenapine is one of those medications which does have an FDA indication for youth, but the group did not recommend having a use without review. Rationale for that stated by the members of the group were, asenapine is sort of a unique atypical antipsychotic. It's a tablet that you have to put under your tongue, let it dissolve in your mouth, causes numbness, paresthesias, and the like, has just as much weight gain, if not more than many of the other atypical antipsychotics, and the members of the group said, we can't think of an instance where we would recommend that for a young person. There's so many other choices that are more amenable. So, that was their basis by saying, let's make that an always review, essentially a check-step, are you sure, prescriber? Is there some rationale that makes sense? Clozaril, again, slight difference in age allowed. Our categories that we had arrived at, age 6 to 12, age 13 to 17, aren't exactly fitting whatever the FDA had thrown out there. So, there are some variations, like, age 13 and up allowed by us, age 10 and up allowed by the FDA. Haloperidol,



well I'll do a little aside. Haloperidol in all the other older antipsychotics, there's no data behind this. Thorazine, for instance, I think, is FDA approved down to age 2. I don't recommend it. There's no data behind that use. That was back, frankly, in the old days when people just picked an age and said, ah, down to here. So, I don't put clinically as much stock in some of these FDA approvals anyway. So, haloperidol, a difference in ages and a difference in total max dose. Believe it or not, 100 mg a day is the FDA max for haloperidol. No way would that be clinically appropriate for a youth. Lurasidone, we are going a little bit younger in age than the FDA, olanzapine a little bit younger than age. Paliperidone is another one of those agents that does have a youth FDA approval that the group did not say we should allow use without a mandatory review. The rationale for that was, I'll use a quote of one of the group members, it's just really expensive risperidone, but there is a clinical indication for it that's unique that if you had somebody who might need to be on a longacting injectable, say a once a month injectable, there's a nice formulation of paliperidone that's a once-a month injectable that we would, the group would say, yeah. We would switch somebody over to paliperidone if we wanted to use that, because the equivalent in risperidone is an every two week, and it's got more problems with its use. That's a small subset. So, the group had thought, let's just make an always review knowing that anybody that's gonna say any indication like that, yeah. That sounds great. Go for it. So, that was the recommendation.

Quetiapine, again, slightly different in age. Risperidone, slightly different in age. Ziprasidone, actually, is the one medication that's allowed without a mandatory review, but there is actually no youth FDA indication for. That isn't as common knowledge, frankly, among psychiatrists, because there's been a lot of years and a lot of experience with its use in youth. It had previously been allowed back in 2009 guidelines. The group did not feel it was necessary to change that. So, I just thought it was worth highlighting where the group's recommendation had diverged from what FDA approvals are and let you know what the rationale for that had been. So, I threw a lot of info for you. Thoughts and questions here?

- Nancy Lee: Will patients be grandfathered... I'm assuming patients who are... will be grandfathered in and don't have to go through this process, or, like, re-review who are already on agents?
- Robert Hilt: So, that gets into the triggering pathway. If somebody has been maintained on the medication, sort of its... that's a processing with the Health Care Authority in the plan. If it comes to us as a reviewer, and they've been on it, and they're stable on it, we're highly likely to say yes, continue that, unless there's a clear safety issue. We'll say Haldol. Let's say they were on 50 mg a day of Haldol and say, whoa. We got to make a plan to come back from that, but yes.
- Amber Figueroa: On the ziprasidone, it just feels weird if it's not FDA approved to be, like, yeah. You're 6. You can have it. Is there... I don't really know how the FDA works. Would they put... are they gonna go back and at some point say, yeah. It's okay. Everybody does it. So...
- Robert Hilt: I mean, the nature of getting an FDA approval is somebody has to sponsor it and spend a lot of money to go through the process and present at least two randomized control trials to the FDA, go through its process of approval, and frankly, a pharma company is only going to do that if they think they're gonna get a particular return on investment from going through that process. So, I don't expect there to become an FDA approval for youth, because it's just being used anyway, why would a... putting a pharmaceutical hat on, why would I make that investment?
- Dale Sanderson: Is there concern in terms of young exposure, especially to the more atypical agents, Haldol, as well as perphenazine, in terms of TD risk? Is that something that should be considered, you know? If you start somebody early on this, there's a time exposure factor here that... are you looking at someone now with TD in their 20s, late teens if they get started on this stuff at 5.
- Robert Hilt: It's extremely unusual for somebody to give a first generation antipsychotic to a very young child, typically when we've see that, it's been in adolescence. Your question about tardive dyskinesia risk with the first generation antipsychotics is broadly accepted to be significantly higher than the risk, significantly higher than this second generation or

atypical antipsychotics. What we don't actually know is, the numbers that we have of the frequency of tardive dyskinesia with the first generation agents, like, haloperidol, that was also frequency numbers of, I think, the risk is somewhere around 5% chance per year of use. That was also numbers that were done when we collectively, as a profession, psychiatry, would use pretty high doses, doses higher than would typically be used now. So, there is a debate really about what the rate of tardive dyskinesia would be with more appropriate, not snow you level dosing of the first generation agents. The cumulative risk of antipsychotics use in youth is 95% or higher of all antipsychotic prescriptions to kids are the atypical antipsychotics. They're not first generation. So, we're almost always talking about these other agents. And some kids are on them for a very long period of time. Does tardive dyskinesia happen? Yeah. It's low frequency, but I don't know the numbers, because nobody is really doing the data gathering about this, in terms of frequency. It is a concern, and it's something we always coach people about. Families have to know this if they're putting their kid on the agent and stay on it. It's medical necessity to notify them.

Nancy Lee: This is more, probably more of a question about the secondary review process, kind of in line with that, in terms of, like, longterm harms. Is there a review in place, like, you know, every 10 years just to reassess risk benefit?

Robert Hilt: Well, there's... for the medication review process, there is a... as I've had it explained to me, and those... my colleagues from the Health Care Authority can share, approvals are only Google for about a year. So, if somebody's on an out-of-guidelines dosage, even though we had recommended approval, a year later, we might get flagged to do this again. So, it does keep coming up, if you're out of these guidelines. Most of the prescribing that's done in this state is not outside of these guidelines. It's a... I said that 850, that's not all antipsychotic reviews. That's a bunch of things. So, the... I didn't add one other thing for context that I think is good food for thought, and I could have put this slide on here, too. I didn't think of that until today. We did actually publish with a Health Care Authority and with Donna's help, an article about what had happened to statewide Medicaid prescription of antipsychotics here, and we did a report showing over a course of several

years, with both the mandatory reviews that were happening, and we did lots of antipsychotic education to primary care providers via the PAL program, the elective consult calls. So, we put that all into the paper and showed there's about... it was a 49% reduction in statewide use of antipsychotics amongst youth, and that wasn't because we were saying no a whole lot. That was a relatively small number of no's, a whole lot of best practice education. So, we actually, I think, our state's pretty far out there in terms of... it's amazing how much this varies state to state, prescribing practices are quite regional. Our state, overall, doesn't have a problem anymore with antipsychotic use at large. We still have some providers in this state that are more generous with its use than others might be, but we don't, as a system, overall have this sky high rate of use.

April Phillips: I just want to clarify, when we receive an SON with a dose limit, even after a year, we will continue that authorization, unless, for some reason, it's exceeded or in the recommendation, yeah, they either didn't meet, or if it's only... they only say approve it for a year, then it'll go back to you.

Robert Hilt: And as reviewers, we, frankly, like, to minimize the churn, you know? I'd like it to be a good reason to talk to the provider rather than both of us saying, wait. Why are we doing this? So, anything the Health Care Authority can do to say, you know what, this really doesn't have to go to the review team. I'm behind it. And another effect of this, there is a fair number of lurasidone reviews that are happening right now, that I don't think really need to happen. I don't know how many less we'll end up doing, but we'll do a few less.

Dale Sanderson: So, a point of information, I'm sure you're aware of this, but ziprasidone and lurasidone have got to be taken with food, and I don't know how many times I've had people that wanted to increase the dose, and it turns out that they're not taking it with food. It's really how they're taking it more than the efficacy of the medication.

Robert Hilt: That's a great point, and you know, is it as common knowledge amongst all prescribers? No. It's getting a little sticker on the label of the prescription when people pick it up at the pharmacy. Frankly, I think that's a more effective and reliable way of making sure people know that – take with food. Oh, okay, 'cuz I don't know that all prescribers get that.

- Dale Sanderson: It's one of the banes of my practice is dealing with phone calls of people saying, the drug is not... it was working just fine, now it's not, and it turns out that they're now giving it on an empty stomach.
- Robert Hilt: Health plans and the Health Care Authority, I remember in years past, Dr. Thompson had done an analysis of saying how often there were significant gaps in therapy with something that you'd think somebody is motivated to take every single day, like, an antipsychotic, and it was a pretty high proportion of people that have, like, a more than 20-day gap that has happened in antipsychotic use over the course of a couple of months. So, just in terms of feel rates. So, across the board, the, oh it's not working, you have to have that thought, are you taking it. Not only are you taking it with food, but are you taking it.
- Dale Sanderson: Yeah. It's really hard for it to work if you're not taking it. Unless there's any other discussion, there are no stakeholders. I'll entertain a motion
- Susan Flatebo: My only question is, just because these are the dose limits by your recommendations, don't always agree with the FDA, do we need to say something in there about prescribed by a psychiatric specialist, or a psychiatric provider, or words to that effect?
- Virginia Buccola: I wonder if, I mean, that would be covered because of the PAL trigger for evaluation or for review, even if they're not a psychiatric specialist. I don't know?
- Robert Hilt: These reviews happen regardless of who the prescriber is. So, the reviewers get reviewed, too. Any... these guidelines that I say, any child psychiatrist doing great practice is going to have, in the course of a year, one or two kids who hit this, because there's always some outliers. You shouldn't have one every week, but, it's a universal... any prescriber gets reviewed.
- Virginia Buccola: To add to that, I would prefer not to use the term psychiatric specialist in this language, simply because it would limit, once a specialist has stabilized medication, it might limit transfer of that prescription to a primary care provider who felt comfortable continuing it.

Robert Hilt: And we have such a shortage of psychiatric prescribing specialists in this state, that there is an awful lot that has been done by primary care providers, which is why, in that report, I said, I counted how many times we've discussed and advised on antipsychotics when we're just talking to primary care. It's a pretty common occurrence.

Dale Sanderson: Anybody entertaining a motion here.

Virginia Buccola: I move that the Apple Health Medicaid Program implement the antipsychotic age and dose limits, as recommended.

Susan Flatebo: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. I hear none. With consent of everyone here, we're going to skip the break and go on to the idiopathic pulmonary fibrosis.

Umang Patel: Perfect. So, the next class we'll look at, idiopathic pulmonary fibrosis. Idiopathic pulmonary fibrosis is a chronic, progressing lung disease occurring primarily in middle-aged to older adults. It's characterized by progressive fibrosis resulting in decreased ventilation and gas exchange. In the U.S., the prevalence is estimated as 13 to 63 per 100,000, and incidence is estimated at 7 to 17 per 100,000. Researchers expect this number to rise due to improvement in accurate diagnosis and longer life expectancy, as disease understanding and management increase. The condition reduces exercise tolerability and quality of life and ultimately leads to death. Most patients live approximately three to five years after diagnosis. While the cause of IPF is unknown, a primary theory of pathogenesis is an inciting factor in a susceptible patient that may cause the initial alveolar damage provoking a response ultimately leading to the fibrosis. Potential risk factors for IPF include smoking, GERD, diabetes, viral infections, such as hepatitis C. Possible causes of pulmonary fibrosis include environmental toxins, medications, and genetic predisposition.

Most commonly, death is due to respiratory failure, but other causes include pulmonary hypertension, heart failure, pulmonary embolism, pneumonia, and lung cancer.

On the next slide here, we'll look at the two medications that make up this class. We have Ofev and Esbriet. Both are FDA approved for the treatment of idiopathic pulmonary fibrosis. Now, just to give a little bit of a background mechanism of action, just a broad overview, Ofev is a small TKI molecule. It specifically inhibits platelet derived growth factor receptors, PDGFR, alpha beta fibroblast growth factor receptors and vascular endothelial growth factor receptors among others, which have been associated in the IPF pathogenesis. The Esbriet mechanism of action is unknown. Its benefit may be due to the inhibition of the profibrotic cytokines, such as TGF beta that induces proliferation of fibroblast, which, in turn, is also a pathogenesis of IPF.

On the next slide here, we'll look at the dosages, additional comments, along with availability. Note that both of these are available as capsules, whereas Esbriet is also available as tablets. Just an FYI with this, smoking decreases the exposure of Ofev and Esbriet. Therefore, instruct patients to avoid smoking during treatment of these agents. In terms of pediatrics, safety and efficacy of either agent have not been established in patients less than 18 years of age. Ofev is pregnancy category D, whereas Esbriet is pregnancy category C. Pregnancy status must be verified prior to initiation in females of reproductive age should use adequate contraception during treatment and for at least three months after discontinuation of therapy. In terms of renal dose adjustment for Ofev, safety, efficacy, and pharmacokinetics have not been evaluated in patients with severe renal impairment, which is defined as creatinine clearance less than 30 or with end-stage renal disease. For Esbriet, use cautiously in patients with mild, moderate, or severe renal impairment, and if the patient is on end-stage renal disease or dialysis, the use of Esbriet is not recommended. In terms of hepatic impairment, Ofev dose adjustment is recommended if the patient has mild to moderate hepatic impairment, which is child Pugh class A and B. Medication is not recommended if the patient has moderate to severe hepatic impairment, child Pugh class B and C. Liver function testing should occur prior to initiating treatment of Ofev. In terms of Esbriet, if the patient does have

mild to moderate hepatic impairment, child Pugh class A and B use with caution and monitor for adverse effects. If the patient has severe hepatic impairment, it is not recommended, as its safety and efficacy have not been studied.

Consensus with the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin-American Thoracic Association in 2015 state the treatment of IPF is often symptomatic and preventative. Oxygen, smoking cessation, vaccinations, diet, and physical activity are amongst strategies employed to improve functional impairment that may lead to a better quality of life. No strong recommendations for a particular treatment; however, they recommend treatment with Ofev, Esbriet, and antacid therapy. In addition, recommendations for Ofev and Esbriet are based, primarily, on evidence in patients with mild to moderate impairment in PFTs. The guidelines strongly recommend against the use of anticoags, Gleevac, Letairis, and combination of prednisone, azathioprine, and acetylcysteine to treat IPF. PDE-5 inhibitors and dual endothelin receptor antagonists are also warned against using. Eventually, lung transplantation should be considered in patients with the risk of mortality within two years and note that at the time of the publication, this combination of governing bodies defer to recommendation regarding single versus bilateral lung transplantation. Any questions?

Dale Sanderson: So, N-acetylcysteine, Mucomyst, this came up with cystic fibrosis and the expert we had there basically said that N-acetylcysteine is no longer being used. Any comments on the use of N-acetylcysteine?

Umang Patel: For IPF?

Dale Sanderson: For IPF.

Umang Patel: I didn't look too much in detail in regard to that, but it seems that the data is showing that they're shying away, against that more towards these two drugs, and I'll have to see what the data... why the data states that.

Dale Sanderson: Thank you. Any other discussion? We have one presenter, speaker.



Brent Wright:

Hi, Brent Wright, Boehringer Ingelheim. I'll be covering Ofev today. Thank you from Magellan. You guys did a great job. I'll just cover a couple things looking at the studies and how we kind of came to efficacy and safety. To your question, you asked in the ATS guidelines, that's no longer there. It is still in some of the overseas guidelines, but in the ATS, it's no longer there. We'll start with that. Efficacy and safety data was derived from clinical studies, three of them covering 1231 patients. One was a phase-2 study and then two phase-3 studies known as study 2 and 3. They were randomized double-blind placebo control studies comparing treatment with 150 mg of Ofev twice daily versus placebo over 52 weeks. The primary endpoint for these studies was the rate of... annual rate of decline of FVC, which is the main marker in patients with idiopathic fibrosis. What they found in the first trial that was statistically significant of Ofev, 150 mg, in the annual rate of decline of FVC, the statistical significant difference was 130 mL. In the second trial, statistical significance was found at 125 mL, and in the third trial, statistical significant difference of 94 mL. The secondary endpoint of these trials was timed at first exacerbation for IPF. This is important, because we know in IPF patients, exacerbation can lead to worsening disease and death overall. Acute IPF exacerbation was defined as unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest x-ray, and/or new high resolution CT, [inaudible] abnormalities without pneumothorax or pleural effusion, and exclusion of alternative cases. Acute IPF exacerbations were adjudicated in both studies 2 and 3. What was found in those is, in study 1 and in study 3, the risk of first acute IPF exacerbation over 52 weeks was statistically significantly reduced in the patients on Ofev compared to placebo at a 16% relevant risk reduction at 20% relevant risk reduction respectively of those two studies. One last thing, just dosage administration, which you covered off on, but there's a couple things that are important. Recommended dose is 150 mg twice daily, approximately 12 hours apart with food. Recommended dose for patients with mild hepatic impairment, or child Pugh A is 100 mg twice daily with food. Consider temporary reduction to 100 mg in patients that have side effects of just diarrhea, and then they can return back to the 150 mg twice daily if those symptoms subside. And prior to initiation, like Magellan brought out very clearly, conduct a liver test, such as AST, ALT,

and bilirubin, and a pregnancy test need to be done on all women within pregnancy age. Then, obviously, there are a ton of safety considerations with these drugs that within three minutes wouldn't get through. So, any questions?

Dale Sanderson: None that I see. Thank you for your time.

April Phillips: On our utilization slide, you can see there is actually very little use of either product. So, on the next slide, we have no current limitations other than PA on these products. They're just PA to labeling. So, our recommendation is that all agents are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products with the same indication and different active ingredients before a nonpreferred product will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred. And I understand that sounds a little wonky, because there are only two products. It's stated that way in case there happens to be a new product that comes on the market, you know, next week.

Alex Park: Can I ask a question of Umang? Is there... did you encounter any data about combination therapy with the two agents?

Umang Patel: Combination with both of them together? No. I did not.

Dale Sanderson: Any other discussion from the committee? Barring none, I will entertain a motion.

Catherine Brown: I move that the Apple Health Medicaid program implement the limitations for the idiopathic pulmonary fibrosis agents listed on slide 58, as recommended.

Dale Sanderson: I'll second it. All in favor.

Group: Aye.

Dale Sanderson: All opposed, same sign. Alright. Okay. Next module, intranasal rhinitis agents.

Umang Patel:

Okay. So, the next three TCRs we'll go over, there is... it's very heavy slidewise. There's a lot of dosing information and things like that, but the good news is, clinically, it isn't as dense as it is up there. So, we may be going a little bit faster than you may have anticipated for the remainder.

So, this one here, the intranasal rhinitis agents. Allergic rhinitis is a constellation of symptoms affecting approximately 8% of adults and 10% of children in the United States in 2017. It's characterized by sneezing and itching of the eyes, nose, and palate, rhinorrhea, and nasal obstruction. It is often associated with postnasal drip, cough, irritability, and fatigue. Symptoms develop when patients inhale airborne antigens, to which they have previously been exposed and have made antibodies. Antibodies bind to the receptors on mast cells and respiratory mucosa and to basophils in the peripheral blood. Mast cells release preformed and granule-associated chemical mediators, and these cells generate other inflammatory mediators and cytokines, which lead to nasal inflammation and with continue allergen exposure, chronic symptoms. Perennial allergic rhinitis is an IGG mediated reaction to allergens with little or no seasonal variation, persistent chronic and generally less severe than seasonal allergic rhinitis. Vasomotor rhinitis, or irritant rhinitis, is a condition of unknown origin. It's aggravated by fumes, odors, temperatures, atmospheric changes, smoke, or other irritants. This form of rhinitis generally a condition diagnosed in adults causes year-round symptoms that include congestion and headache.

On the next three slides, we'll see the various medications in this class and their indications. Please note that, again, over the next three slides, this class is broken down into three subgroups. We have the nasal corticosteroids, which you see in front of you. We'll have the intranasal antihistamines. Then, we'll have the combination products of nasal corticosteroids and intranasal antihistamines.

So, on this slide, you can see that all indications vary slightly, but for the most part, as you can tell, it's for the treatment of intranasal rhinitis. We have beclomethasone, budesonide, ciclesonide, flunisolide, Flonase, fluticasone propionate, and we also have fluticasone propionate OTC. Note about half of these are available in generic form, as well. To take a

step back, clinically, the mechanism of action for these following topical administration, the corticosteroids produce an antiinflammatory and vasoconstrictor effect. They gain entry into the cell, and the receptor complex undergoes a conformational change. Direct effects may be a reduction in the cytokine induced production of the inflammatory mediators. Note that fluticasone propionate or Xhance, and mometasone, Sinuva, are specifically for the treatment of nasal polyps in adult patients; however, the exact mechanism of action for this is unknown.

This is just a continuation of nasal corticosteroids, as well, here. We have Ticanase, Xhance that I mentioned earlier, Nasonex, Sinuva, triamcinolone, and we have triamcinolone OTC, as well.

On the next slide here, now we have the second subcategory, the intranasal antihistamines, which is composed of azelastine, we have Astepro, and we also have Patanase. These three are all available in generic, as well.

Then, lastly, we have the combination of both intranasal corticosteroid and the antihistamine combinations. So, for that, we have Dymista, Ticalast kit, and then we have what are referred to as 'others.' We have Alzair, and we have ipratropium nasal spray, 0.03, and 0.06%. Again, to give a little bit of clinical background for these, for the intranasal antihistamines. So, Astepro Dymista, it's a fexofenadine derivative, which exhibits histamine receptor antagonistic activity. It demonstrates inhibitory effects on the release of inflammatory mediators from the mast cells. For Patanase, it's an antihistamine with selective H1 receptor antagonistic activity. For the Atrovent, it's an anticholinergic event that blocks cholinergic receptors and reflux mediated hypersecretion from the nasal glands. Lastly, Alzair is a particle that absorbs moisture from the nasal mucosa and swells to create a protective gel-like barrier in the nasal tract. This gel barrier prevents allergens from making contact with the mucosa. So, it stops cell degranulation and the release of histamines within the body.

So, the next five slides are going to be dosing and availability where it is broken down between the dosing for adults, which is characterized as

greater than 12 years of age, children less than 12 years of age, and availability. Please note, as one would expect, all the medications in the TCR are intranasal sprays, but just to reiterate. In terms of pregnancy, Astepro and Dymista, along with Patanase, are all of the intranasal corticosteroids, except for budesonide that are pregnancy category C. Data available for Xhance, which is fluticasone propionate, does not suggest there is an association to risk to the fetus or any adverse developmental outcomes. Atrovent and budesonide are pregnancy category B.

It is a continuation of the nasal corticosteroids for the dosing where we see the dosing and availability for Flonase, fluticasone propionate, and Ticanase.

Here, we have, I believe, the last slide for the nasal corticosteroids. For Flonase, Xhance, Nasonex, Sinuva, triamcinolone, and Nasacort Allergy 24-hour OTC. Keep in mind for pediatrics, with the exception of Sinuva and Xhance, which are approved for patients greater than or equal to 18 years of age, all other agents in this class are approved for pediatrics.

Here, we have the intranasal antihistamines for azelastine, Astepro, and Patanase. In terms of medications in this class that require hepatic dose adjustment, reduced liver function may affect the elimination of corticosteroids. The relevance of this finding to intranasal administration has not been established yet. So, there are no dose adjustment recommendations.

The last slide for the dosing and availability, here we have the combination products and the others where we look at Dymista, Ticalast, Alzair and ipratropium 0.03 and 0.06%.

In terms of guidelines, next slide please. The American Academy of Allergy, Asthma, and Immunology in 2017 state treatment of both adult and adolescent patients greater than or equal to 12 to 15 years of age, with allergic rhinitis, they recommend pharmacological therapy may include intranasal and oral antihistamine decongestants and corticosteroids. Other therapies include intranasal cromolyn, intranasal anticholinergics, and leukotriene receptor antagonists. When specific

monotherapy management is being considered, intranasal corticosteroids are more effective than LTRAs. If a patient is not adequately controlled on an intranasal corticosteroid or has moderate to severe symptoms, addition of an antihistamine may be considered, preferably an intranasal antihistamine agent versus an oral antihistamine product; however, the guidelines do not specify one agent over the other. Combination therapy with intranasal corticosteroids may provide an added benefit and rhinitis medication management frequently requires a step up approach if therapy is adequate or a step down approach if symptom relief is achieved and maximized with other approaches, including avoidance measures.

Lastly, the American Academy of Otolaryngology and the Head and Neck Surgery Clinical Practice Guidelines for Allergic Rhinitis in 2015 state intranasal steroids and oral antihistamines are the first line treatment for allergic rhinitis in adults and children over 2 years of age. The panel issued a strong recommendation for use of intranasal steroids in patients who qualify... whose quality of life is effected by allergic rhinitis, as well as for oral second-generation antihistamines for patients with sneezing and itching as their primary complaints. Clinicians may offer intranasal antihistamines as second line therapy for patients with seasonal, perennial, or episodic allergic rhinitis after failure of intranasal steroids or oral antihistamines. There may be specific patients in whom an intranasal antihistamine would be an appropriate firstline therapy. The guideline also recommends combination therapy in patients who have had an inadequate response to monotherapy. Lastly, the most effective addition to intranasal steroid therapy is an intranasal antihistamine. Any questions?

Dale Sanderson: There are no stakeholders.

April Phillips: On the image for the utilization, you can clearly see, fluticasone is the front runner on there. On the next slide, our recommendation is that all agents are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products within the same subclass, with the same indication, and with different active ingredients before a nonpreferred drug will be authorized, unless

contraindicated, not clinically appropriate, or only one product is preferred. You can see that this particular slide was updated to include within the same class, because nasal steroids versus antihistamines.

Amber Figueroa: I move that the Apple Health Medicaid program implement the limitations for the intranasal rhinitis agents listed on slide 73, as recommended.

Nancy Lee: I second that motion.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign.

Umang Patel: So, the next topic we'll discuss are leukotriene modifiers. On the next slide here, asthma in the United States affects approximately 25.7 million people. It is one of the most common chronic childhood diseases effecting approximately 7 million children. It's a chronic inflammatory disorder of the airways, in which many cells and cellular elements play a role. The inflammation also causes an increase in bronchial hyperresponsiveness to a variety of stimuli. In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. In terms of allergic rhinitis, to go back from previously in 2012, 17.6 million adults and 6.6 million children reported to have allergic rhinitis. Again, it's an inflammatory condition that presents with nasal congestion, rhinorrhea, sneezing, and/or itching.

On the next slide here, you'll see that we have four main medications, Singulair, Accolate, Zyflo, and Zyflo CR. Note, Zyflo and Zyflo CR are both FDA approved for the prophylaxis and chronic treatment of asthma in adults and children greater than or equal to 12 years of age. Accolate is FDA approved for the prophylaxis and chronic treatment of asthma in adults and children greater than or equal to five years of age. Singulair has multiple FDA indications, first prophylaxis and chronic treatment of

asthma in adults and children one year of age or older, the acute prevention of exercise-induced bronchoconstriction in patients six years of age or older, relief of symptoms of seasonal allergic rhinitis in patients two years of age or older, and lastly, relief of symptoms of perennial allergic rhinitis in patients six months of age and older. To give a little bit of background on the mechanism of action, leukotrienes are inflammatory mediators produced from a variety of inflammatory cells, including mast cells, eosinophils, basophils, and macrophages. They are the most potent bronchoconstrictors yet identified in humans. Leukotriene mediated effects include airway edema, smooth muscle contraction, mucus secretion, microvascular permeability, and altered cellular activity associated with the inflammatory process.

So, how these medications work, Singulair and Accolate are leukotriene receptor antagonists that work on the cysteinyl leukotriene receptor on the airway smooth muscle cells. This, in turn, will cause... include a mild bronchodilation, as well as reductions in the allergens, exercise, and sulfur dioxide induced bronchoconstriction. Zflo is an inhibitor of the five lipoxygenase and thus inhibits leukotriene on a different subreceptor but has the same overall pathway.

On the next slide, here we have all the dosing and availability for the medications. Please note that all are available as tablets and Singulair is also available as a chewable tablet and granule packets. In addition, when Singulair is used for asthma and allergic rhinitis, it should be given once daily in the evening. For different populations, for patients who are pregnant, note that montelukast and zafirlukast are category B, and Zflo and Zflo CR are category C. There is no dose adjustment for any patients who are renally impaired for any of these four medications. In terms of hepatic impairment, patients who... for Zflo and Zflo CR, it's contraindicated with patients who have active liver disease and patients with LFTs three times upper normal limit. In terms of zafirlukast, it's primarily metabolized in the liver, and it's contraindicated in patients with hepatic cirrhosis.

On the next slide here, we'll see, for asthma, the Global Initiative for Asthma in 2018 recommends a stepwise approach to asthma. Step one and two describe options for mild asthma with as-needed short-acting



beta-2 with or without low-dose inhaled corticosteroid. Step three includes a low-dose ICS and a LABA as the preferred controller option for moderate asthma. Step four for severe asthma recommends medium to high-dose ICS plus a LABA. The addition of sublingual immunotherapy or SLIT therapy may be considered in asthmatic adults with allergies to house dustmites, who exhibit allergic rhinitis, who have asthma exacerbations despite the treatment with an ICS. Lastly, step five advises consideration of a monoclonal antibody and other add-on therapies in select patients. Now, know, at each step, alternative controller options are described, including leukotriene receptor antagonist during step up and step down therapy. The National Asthma Education and Prevention Program and GINA both recommend ICS as the cornerstone for the treatment of asthma while leukotriene modifiers are included as potential alternatives or add-on therapy in some patients. GINA states that leukotriene modifiers are less effective than ICS but may be appropriate for initial controller treatment for patients who are unable or unwilling to use ICS, intolerant to ICS, or who have allergic rhinitis. Limited data exists to support the use of leukotriene modifiers in acute asthma.

This next slide, for allergic rhinitis, the AAAAI, the American College of Allergy, Asthma, and Immunology in 2017 published updated guidelines for the treatment of seasonal allergic rhinitis. For initial treatment of moderate to severe SAR in patients 15 years of age and older, the guidelines recommend monotherapy with an intranasal corticosteroid, given their demonstrated clinical benefit over the others. The authors note that Singulair is the only leukotriene modifier that is also approved for allergic rhinitis and can be considered for patients with comorbid asthma, another FDA approved use for it. The guidelines also recommend combination therapy with intranasal antihistamines when INCS monotherapy fails and acknowledged that many patients require multiple agents for relief from symptoms of allergic rhinitis. Any questions?

Dale Sanderson: None that I see, and there are no stakeholders.

April Phillips: You can see on our utilization slide that montelukast is the majority of our claims. Our recommendation is that all agents are considered safe

and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority, and all nonpreferred products require a trial of two preferred products with the same indication and different active ingredients before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Dale Sanderson: Discussion with the committee? I move that the Apple Health Medicaid program implement the limitations for the leukotriene modifiers listed on slide 81, as recommended.

Virginia Buccola: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign.

Umang Patel: The next topic we'll discuss are NSAIDs. Now, this topic has a lot of information in front of you, because of the various forms, the dosage. So, I want you to know, I'm not just flying through this, but a lot of the information is very repetitive. Alright. Next slide.

Alright. Just a quick overview. NSAIDs are nonsteroidal antiinflammatory drugs. They're commonly used to treat rheumatoid arthritis, osteoarthritis, and pain from various etiologies. NSAIDs are the most widely used drug in the United States with approximately 80 million prescriptions being filled yearly, which accounts for roughly 4.5% of all prescriptions. It is estimated that over the counter NSAIDs are used five to seven times more than the prescription NSAIDs. NSAIDs are associated with adverse effects, including GI bleeding, peptic ulcer disease, hypertension, edema, and renal disease. In addition, NSAIDs have been linked with an increased risk of myocardial infarction, which is reflected in the black box warning for all NSAIDs. In July 2015, the FDA issued a safety alert strengthening the existing warning on the increased risk of heart attack and stroke associated with NSAIDs.

On the next four slides, we'll have the various NSAIDs available and their indications. You can see that the medications in this therapeutic class are listed by their various indications, and there is a separate column for those unique ones that some of these contain. So, just to give you a little bit of background, OA is osteoarthritis. RA is rheumatoid arthritis. JIA is juvenile idiopathic arthritis or juvenile rheumatoid arthritis. AS is ankylosing spondylitis, and PD is primary dysmenorrhea.

On this slide here, we look at Celebrex, diclofenac potassium, Zipsor, Voltaren, Zorvolex, Diflunasil, Lodine, Nalfon, flurbiprofen, Motrin, Indocin, Tivorbex, ketoprofen IR, ketoprofen ER, ketorolac tromethamine. Just to give a little bit of background on them, both oral and topical NSAIDs inhibit the cyclooxygenase-1 or COX-1 and cyclooxygenase-2, or COX-2 enzymes that catalyze the synthesis of prostaglandins. These prostaglandins are partially responsible for the development of pain and inflammation associated with various medical conditions.

Again, just to continue on with the indications, here we have medications, meclofenamate, Ponstel, Mobic, Vivlodex, nabumetone, naproxen, Daypro, Feldene, sulindac, and tolmetin. Everything that I had read up until now were all single ingredient agents. The next subcategory are combinations. So, we have CapXib kit, Lidoxib kit, diclofenac sodium along with capsaicin, and we have diclofenac sodium with misoprostol.

Continuing the combination agents, we have the esomeprazole with naproxen combination, ibuprofen and famotidine combination, ibuprofen/capsaicin/menthol/methyl salicylate combo, meloxicam/capsaicin/menthol/methyl salicylate comb here, as well, and lastly naproxen/capsaicin/menthol/methyl salicylate.

The next slide for the indications are all nasal NSAIDs and topical NSAIDs. So, for nasal NSAIDs, we have Sprix, which is ketorolac tromethamine, and this is FDA indicated for pain along with for topical NSAIDs we have Flector, diclofenac sodium, keep in mind these are all topical. We have Voltaren gel, diclofenac sodium and capsaicin, diclofenac sodium/camphor/menthol/methyl salicylate, again topical, and diclofenac sodium and menthol.

On the next many slides, we'll go over dosing and availability. We'll briefly glance at the dosing and availability. As you can see on this Celebrex, Zipsor, Zorvolex are all available as capsules. The remainder are tablets. In terms of alternative populations for pediatrics, for oral NSAIDs, it is recommended to use with caution in patients with juvenile rheumatoid arthritis, due to the risk of intravascular coagulation. Celebrex is indicated for relief of juvenile rheumatoid arthritis in patients two years of age and older. Mobic is indicated in patients greater than two years of age. Vimovo is indicated for juvenile rheumatoid arthritis in adolescent patients 12 years of age or greater who weigh 38 kg or more who require symptomatic relief of arthritis and are at risk of developing NSAID-related gastric ulcers. Safety and efficacy for Indocin and Ponstel in children less than 14 years of age has not been established. The safety and efficacy in diflunisal in children 12 years of age or younger has not been established. The safety and efficacy for oxaprozin in patients less than 6 years of age has not been established. The safety and efficacy of tolmetin in patients less than 2 years of age has not been established. Lastly, for topical NSAIDs, the safety and efficacy for pediatrics has not been established.

For patients who are pregnant, all oral NSAIDs are in pregnancy category C prior to 30 weeks' gestation, as is ibuprofen famotidine combo, and naproxen esomeprazole. Note that diclofenac sodium and misoprostol is category X and has a black box warning because misoprostol may cause abortion in pregnant women. Diclofenac is category C.

The last two dose adjustments for renal impairment longterm administration of NSAIDs results in renal papillary necrosis, or renal injury. So, be wary of that. Lastly, hepatic impairment, a dose reduction of about 50% for celecoxib is recommended in patients who have moderate hepatic impairment.

Again, the recommended dosages for the various FDA indications, the maximum daily dose, and the availability. Please note, all the medications here are available as tablet or capsule, along with Motrin just ibuprofen is available in suspension form, as well.

Similar to the previous slide, all single ingredient agents here listed by their dosages for their FDA indications, and all available as capsules or tablets. Indocin is available as a suppository and a suspension, as well.

On the next slide here, again, these are the single agents continued and available as capsules or tablets with Mobic and Naprosyn available as suspension.

We have the ending of the single agents and the beginning of the combination agents, all by the dosages of their FDA approved indications. The remainder of the single agents are available in tablets or capsules. The combination agents have specific kits.

Here, we have, again, the combination agents continuing where they are all available as tablets, and the bottom agent, the naproxen/capsaicin/menthol/methyl salicylate combo also comes in a comfort gel.

Here, we see the nasal NSAIDs, which are very evidently available in the nasal spray, and topical NSAIDs here that are available as a patch for Inflector or a topical solution for the remaining three on this slide.

We have the topical NSAIDs continuing that are available as gel.

And the last slide for dosing and availability here, for the topical NSAIDs, show the various dosage and availability in gel form, as well. I'm sorry, in topical solution form.

On the next slide here, we see various governing bodies, first American College of Rheumatology state oral and topical NSAIDs are among pharmacologic therapies recommended for OA of the hand, knee, and hip. We have the American Association of Orthopedic Surgeons state treatment of osteoarthritis of the knee does not specify a specific NSAID or route of administration for osteoarthritis symptoms. If the risk of GI adverse events is increased, the topical route is preferred among other treatment strategies. The American Academy of Orthopedic Surgeons in 2017 state management of osteoarthritis of the hip does not specific NSAID. However, they do note strong evidence to support NSAIDs to

improve short-term pain, function, or both in patients with symptomatic osteoarthritis of the hip. Lastly, with the American College of Physicians in 2007, non-pharmacological therapy, such as heat, massage, acupuncture, spinal manipulation is the first line for acute or subacute low back pain lasting 12 weeks or more. For acute or subacute pain, NSAIDs or skeletal muscle relaxants may be used. For chronic pain lasting over 12 weeks, the firstline recommendation is non-drug therapy, such as exercise, multi-approach rehab, acupuncture, stress reduction; however, NSAIDs may be added, if needed, followed by tramadol or duloxetine. Opioids for chronic pain should only be considered if prior therapy fails and the potential benefit outweighs the risk. The gout guidelines in 2016 recommended corticosteroids, NSAIDs, and colchicine to treat patients with gout flares. In addition, NSAIDs for prophylactic therapy can also reduce the risk of gout flares in patients starting urate-lowering therapy. Any questions?

Dale Sanderson: None that I can see. We have no stakeholders.

April Phillips: On the utilization slide, it just includes single agents. So, I wanted to make that clear, that it doesn't include the combination agents, like Umang had talked about. Our current limitations are must try all preferred products before a nonpreferred product would be authorized. There are prior authorizations for Cambia, Flector patch, Pennsaid, Voltaren gel, Solaraze, and Rexaphenac, so basically all topical diclofenac require a prior authorization. So, it's limited to FDA labeling or compendia supported diagnosis and dosing limits. We have dose limits on Toradol, which per labeling, limits it to a maximum of five days or less. Then we have limits on Celebrex, mainly for dose maximum. You can have three tablets per day of the 200 mg or max, or 2 tablets of the other strength. Mainly, that's just a cost savings measure. If you need more than 2 of one strength, there's probably a good chance that you could move up to a higher strength, which would be just as cost-effective.

So, our recommendation is to continue all of the current limitations listed on the slide before. All NSAID products are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products with different active ingredients before a

nonpreferred product would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred. I want to call out that we did change the previous try and fail from all to only two.

Dale Sanderson: Discussion from the committee? I move that the Apple Health Medicaid program implement the limitations for the NSAIDs listed on slides 101 and 102, as recommended.

Alex Park: I second.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. Please go ahead with the proton pump inhibitors.

Umang Patel: Our last class for today are the proton pump inhibitors. Acid suppression is the mainstay of therapy for GERD. The American Gastroenterologic Society, the AGA, and the American College of Gastroenterology recommend proton pump inhibitors as firstline therapy for the treatment of severe GERD-related symptoms or erosive esophagitis. H2 blockers can be used in patients with mild symptoms or verified nonerosive disease. PPI's provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. The AGA also states that for healing esophagitis and symptomatic relief, PPI's are more effective than H2 blockers and H2 blockers are more effective than placebo. PPI's are used in conjunction with various antimicrobials for the eradication of H. pylori, the most common cause of peptic ulcer disease. Antisecretory therapy with either H2 blockers or PPI's accelerate ulcer healing and provide rapid symptomatic improvement. The mechanism of action for PPI's, they reduce gastric acid secretion by specifically inhibiting the proton pump, which is an H<sup>+</sup>/K<sup>+</sup> ATPase at the secretory surface of the gastric parietal cell. The PPI's are pro-drugs, which require activation in order to inhibit gastric acid secretion. So, after oral administration, PPI's are absorbed into the systemic circulation and ultimately enter actively secreting parietal cells at highly acidic pH. The agents are then activated and a profound longlasting antisecretory effect

is produced, capable of maintaining the gastric pH above 4, even during postprandial acid surges.

On the next two slides here, we'll look at the various PPI's that are available and their indications. On this slide, we have Dexilant, Nexium, Nexium 24-hour OTC, esomeprazole strontium, Prevacid, and Prevacid OTC. Note, Nexium and Prevacid are available as a generic form, and the indications here vary for duodenal ulcer for treatment or maintenance. We have pyrosis or AKA heartburn, H. pylori eradication, GERD, erosive esophagitis, both treatment and maintenance, pathological hypersecretory conditions, gastric ulcers, and lastly, NSAID induced gastric ulcers.

We have Prilosec, Prilosec OTC, omeprazole OTC, Zegerid, Zegerid OTC, Protonix, and Aciphex. Note that Prilosec, Prilosec OTC, Zegerid, and Protonix are available in generic form.

On the next slide here, we have the dosing and availability for the first three, Dexilant, Nexium, and Nexium OTC. In terms of for pediatric patients, Nexium is indicated for short-term treatment of GERD for patients aged 1 to 17 years, and the healing of erosive esophagitis, aged 1 to 11 years. Prilosec is indicated for children aged 1 to 16 years for the short-term treatment of GERD and the maintenance of healing erosive esophagitis. Aciphex is indicated for the short-term treatment of GERD in patients 12 years of age and older. Protonix is indicated in children 5 years of age and older for the short-term treatment up to eight weeks in the healing and symptomatic relief of erosive esophagitis. Lastly, Dexilant is indicated for the healing of erosive esophagitis, maintenance of healed erosive esophagitis, and relief of heartburn, and the treatment of nonerosive GERD for children 12 years of age or older.

On the next slide here, we have esomeprazole strontium and Prevacid, their various FDA indication and their respective doses, pediatric indication doses, and the oral availability. For patients who are pregnant, Prilosec, Zegerid, esomeprazole strontium and Protonix were categorized as class C. All other agents, including esomeprazole magnesium are rated pregnancy category B.



On the next slide here, we have lansoprazole, Prilosec, Prilosec OTC, and omeprazole OTC. All medications on this slide are available as tablets or capsules. In addition, Prilosec is also available as an oral suspension.

Next slide here, we have Zegerid, Zegerid OTC, and Protonix. For patients with renal or hepatic impairment, if there is hepatic impairment, the clearance of PPI's may be reduced in patients with advanced age and those who have mild to moderate liver disease. The decrease in clearance, however, does not necessitate a dose reduction. Dexilant requires a dose adjustment for hepatic... moderate hepatic impairment and is not recommended in severe hepatic impairment. Nexium requires a dose adjustment in moderate to severe hepatic impairment. Lastly, Protonix requires a dose adjustment in moderate hepatic impairment and has not been studied in patients with severe hepatic impairment.

Lastly, for renal impairment, dose reduction is not required in patients with renal impairment due to significant metabolism of PPI's by the liver. The only one thing to note is, the PK and safety of esomeprazole strontium has not been studied in patients with severe renal impairment. Therefore, it's not recommended.

On the next and final slide for dosing adjustment, here we have Aciphex with its various indications, adult and pediatric doses, along with oral availability.

The following slide, the ACG guidelines, the American College of Gastroenterology, for the diagnosis and treatment of gastroesophageal reflux disease in 2013 indicate that PPI's eliminate symptoms and heal esophagitis more frequently and more rapidly than other agents, including H2 blockers. Empiric medical therapy with a PPI is recommended with a presumptive diagnosis of GERD based on symptoms of heartburn and regurgitation. PPI therapy should be initiated, as a once-a-day dosing before the first meal of the day. In patients with partial response to PPI therapy, increasing the dose to twice a day therapy, or switching to a different PPI, may provide additional symptomatic relief. PPI's should be administered in the lowest effective dose, including on-demand or intermittent therapy for those who require longterm therapy. Patients who respond to short-term PPI should

subsequently attempt to stop or reduce the dose of the PPI, and for those who cannot reduce PPI's, they should consider ambulatory esophageal pH impedance monitoring before committing to lifelong PPI's to help distinguish GERD from a functional syndrome. The best candidate for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD, such as central obesity or large hiatal hernias.

The American Gastroenterological Association, AGA Institute, in 2008, state that PPI's are more effective than H2 blockers in healing esophagitis, symptomatic relief, and maintaining healing of esophagitis. A further review conducted in 2017 updated the guidelines to specify that longterm use of PPI's for the treatment of patients with symptomatic GERD and Barrett's Esophagus is recommended, and that consideration of longterm PPI treatment for patients with asymptomatic Barrett's Esophagus be made, as long as the dose is periodically reevaluated, so the lowest effective dose is used based on symptom control. Additionally, longterm PPI users should not routinely use probiotics to prevent infection, raise their intake of calcium, vitamin B12, or magnesium beyond the RDA and should not be routinely screened or monitored for bone mineral density, serum creatinine, magnesium, or B12. The 2015 ACG guidelines on Barrett's Esophagus recommend once daily PPI therapy and recommend against routine use of twice-daily regimens, unless needed for poor control of reflux symptoms or esophagitis. Lastly, the guidelines for the management of dyspepsia, in 2005, updated in 2017, in areas with H. pylori prevalence greater than 10%, patients should be tested and treated for H. pylori before an acid suppression trial. H. pylori negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for four to eight weeks is recommended as first line therapy. A short course of PPI therapy has demonstrated symptom control than therapy with H2 blockers in a meta-analysis of large studies, and for patients who respond to initial therapy, treatment should be stopped after four to eight weeks. Any questions?

Dale Sanderson: None that I see. There's additional pages in this. Is this a separate section or?

April Phillips: We are reviewing the PPI policy at the same time as this class.

Dale Sanderson: There are no stakeholders.

April Phillips: Our utilization slide and then on the next slide, we are going to start the policy. This policy was previously reviewed and approved by the DUR board February of 2017. It limits one capsule or tablet per day. The first two months are covered without prior authorization. Those two months are a rolling 12-month period. So, if they take one month and then three months later take another month that will still be approved without authorization. If they've taken two months and need an additional month to taper down to an H2RA, all the pharmacy has to do is call. They'll get the authorization to allow for a taper. It is covered through prior authorizations for certain concurrent medications or chronic medical conditions. It required a step through of all preferred products before a nonpreferred product will be authorized. The next few slides, we will go into more depth on that.

There is a list of concurrent medications. The last time this class... or this policy was reviewed, there was a request to add chronic corticosteroids to the list of concurrent medications, so that has been added. So, as long as there is a history of a claim within the last 30 days for those medications, it should automatically be authorized without a clinical policy... or clinical review. For low-dose aspirin, there is current pharmacy claim in history for the low-dose aspirin and then EGD within the last ten years showing a history of GI bleed.

Concurrent bisphosphonates, the policy is a current pharmacy claim and a previous trial of risedronate, which has been shown to have less issues with GERD than the other bisphosphonates.

The pancreatic enzyme therapy consultation notes from GI with the recommendation for use.

Concurrent chemotherapy, as long as there are notes from an oncologist or oncology specialist that are indicated that the PPI will help with the chemotherapy.

There is a list of gastrointestinal conditions for which a longterm PPI would be authorized, and the specific limits will follow. Consultation notes documenting pathological gastric acid hypersecretion will be approved. It's usually approved yearly, and it's just automatically renewed after that.

For Barrett's esophagitis, EGD within the last five years showing an impression of Barrett's and a pathology report with the histological confirmation.

For esophageal stenosis or strictures, just an EGD documenting the diagnosis.

For erosive or ulcerative esophagitis, an EGD within the last 12 months documenting the diagnosis. It will be authorized for up to 12 months and then if it needs additional refill or additional authorization, another EGD showing documentation of medical necessity to continue.

For duodenal ulcer, an EGD within the last 12 months. This will also be authorized for 12 months, and for re-authorization, it requires an EGD that documents continued medical necessity.

For gastric ulcers, an EGD within the last two months. It will be authorized for up to two months and re-authorization, once again, requires an EGD documenting medical necessity.

So, other chronic medical conditions listed there. So, for cystic fibrosis, just documentation from a pulmonologist or gastroenterologist or specialist documenting the diagnosis. Cerebral palsy, same thing, and a trial of ranitidine or difficulty with communication to tell, hey, this is what's going on.

So, our recommendation is to continue the PPI policy, as listed. All PPI products are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. We did change the third bullet a little bit. All nonpreferred products require a trial of only two preferred products before a nonpreferred product would be authorized, unless contraindicated not

clinically appropriate, or only one product is preferred. Are there any questions?

Dale Sanderson: Questions from the committee?

Diane Schwilke: Going back to the presentation, they don't have slide numbers, but basically the ACG guidelines are talking about in patients with partial response to PPI therapy, increasing to twice a day therapy or switching to a different agent is part of the recommendation, and twice a day therapy is never covered currently. So, I don't know if we want to look at that, because there is that limit of one unit per day. So, it doesn't allow for b.i.d. dosing in patients who respond better to that kind of dosing. It's slide 112.

Donna Sullivan: If they need twice a day dosing, then we just... they just need to provide documentation that that's required. It's just that one dose a day doesn't require prior authorization for that first two months. Then, after that, you would need a prior authorization to continue on with one of these conditions or if you needed b.i.d. dosing, they would just need to provide documentation for medical necessity for b.i.d. dosing.

Diane Schwilke: Okay.

Dale Sanderson: Do we need to include the limitation slide starting on slide 116? Are we fine just with the one slide there?

Amber Figueroa: I move that the Apple Health Medicaid program implement the recommendations for the PPI drug class listed on slide 133.

Dale Sanderson: I'll second. All in favor?

Group: Aye.

Dale Sanderson: All opposed? I think we're set. We'll adjourn the DUR meeting.