

Washington State Pharmacy and Therapeutics Committee
P&T Meeting Notes
April 19, 2017

Michael Johnson: It's 9:00 a.m. We're going to go ahead and get started. Welcome to the Pharmacy and Therapeutics Committee. At this point we'll do some brief introductions. So this meeting is taped. Throughout the meeting, please introduce yourself at the mike before you start speaking, but we'll go ahead and introduce yourself now starting to the left.

Julie Hartford: Julie Hartford, Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Charity Harris: Charity Harris, Health Care Authority.

Jaymie Mai: Jaymie Mai, Labor and Industries.

Doug Tuman: Doug Tuman, Labor and Industries.

Dale Sanderson: Dale Sanderson, committee member.

Jordan Storhaug: Jordan Storhaug, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Susan Fletebo: Susan Fletebo, committee member.

Michael Johnson: Michael Johnson, committee member.

Lisa Chew: Lisa Chew, committee member.

Catherine Brown: Catherine Brown, committee member.

Po Karczewski: Po Karczewski, committee member.

Nancy Lee: Nancy Lee, Committee member.

Diane Schwilke: Diane Schwilke, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Ryan Pistorresi: Ryan Pistorresi, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority and I'd like to take this moment to just welcome all the new members to the P&T Committee meeting, our first one this year. So welcome.

Michael Johnson: Thank you. I'd like to reiterate that. Thank you to all the new members. Some people may not be aware but this is a big commitment for no fame and glory. I think we start off with Donna.

Donna Sullivan: Because this is our first in-person P&T Committee meeting this year, it's actually our first P&T Committee meeting this year. I'm going to refresh your memories from the overview that we went over at the DUR Board meeting in January. So I just... I'm starting on slide 5 in your packet. It's under the tab called P&T Committee Overview or something like that. But the state gets its drug evidence-based reviews from the Drug Effectiveness Review Project and it's a collaborative of about 13 states. It is actually growing and some of these states have changed and there are others that are being added. But the states get together and we request OHSU, Oregon Health Sciences University, to do evidence-based reviews on drugs that are important to the states.

It's based on the Washington Prescription Drug Program, legislation that was passed in June 2003, and it really is a coordinated effort. The Prescription Drug Program is a coordinated effort between two agencies, which is the Health Care Authority, the Uniform Medical Plan for state employees, and the Medicaid program, as well as the Department of Labor and Industries, the Worker's Compensation Program. Our preferred drug list is really a subset of each program's overall formulary or drug list. We only have about 30 drug classes on our preferred drug list, the Washington preferred drug list at this time. And really the goal

was to, you know, create an evidence-based preferred drug list for all of the agencies to use. In addition to the preferred drug list the Prescription Drug Program also includes what is called the Therapeutic Interchange Program for endorsing practitioners. The legislation created this P&T Committee. It gave Health Care Authority the direction to create an evidence-based prescription drug program and then there is also legislation that created the Northwest Prescription Drug Consortium, which I'm not going to go into today.

So the Therapeutic Interchange Program it really means when you all select drugs to become preferred in one of these drug classes, if a physician has... or a prescriber has signed up to endorse our preferred drug list then if they write for a non-preferred drug the prescription will reject at the pharmacy and they will be asked to... the pharmacist will be asked to dispense the preferred drug instead. When the prescriber endorses the PDL the pharmacist is able to make that change without having to call the doctor to get a new prescription. That's what the law says. I don't know if that's what happens, but that's what the laws says that they can do. If that endorsing provider writes "dispensed as written" on the prescription then the prescription does not reject and it will be paid or it will be allowed to go through unless there is other clinical requirements or prior authorization that is required. So there are certain drug classes that are exempt from the therapeutic interchange and those are listed here. I'm not going to read through them all. And we have, at the last count, which is probably several years ago, about 7,200 endorsing practitioners and we really don't know what percent of all prescribers that is because there's so many licensed providers out there that aren't necessarily actively practicing in this state, but their licenses are active. So it's difficult to say how many of our providers are really endorsing. So the P&T Committee is made up of 10 members. Its membership is based on the federal rules that guide the composition of our Drug Utilization Review Board, which essentially says you can't have more than 50% doctors or 50% pharmacists on the committee. So that's why we have the four physicians, the four pharmacists, the nurse practitioner and the physician assistant.

The committee meets at least quarterly, but our schedule is for every other month. You all review the reports that come from the Drug

Effectiveness Review Project. You determine if the drugs are equally safe and effective, and then give us direction on whether or not you feel it is appropriate for the pharmacist to be able to do that therapeutic interchange that I had talked about.

Then your function as the Drug Utilization Review Board. It's established under the Social Security Act. It's an extension of the P&T Committee in an advisory role to the Medicaid program specifically and it guides the clinical criteria or utilization management piece of the drugs that Medicaid covers and then there are times when the Uniform Medical Plan or even Labor and Industries can, if they choose to, they may also follow those policies that you develop and that you approve.

I think that's pretty much it. The purpose of the DUR Board really is to make sure that the drugs that are being provided to the Medicaid clients are being used appropriately and safely and that when necessary that you would engage in a provider education program if you felt it was necessary. And we've done that at times past with... related to opiates and most of you probably were not here at the time, but I think it was in 2012 where we sent out a letter about opiate use and misuse in the state. So those are a type of educational program.

So the Washington PDL is just a list of drugs and it is really... the list right now is generated... the drug classes that are on the list are generated by the drug classes that are reviewed through the Drug Effectiveness Review Project. That is likely to change in the future and maybe even this year. And like I said there are about 30 drug classes on it and we have been using it since January of 2004.

The DERP reviews, there's many different kinds of reports that you guys all look at and depending on what kind of report it is, it makes a difference on whether a drug can be... is eligible to be preferred or not preferred. So when a drug... when we have a brand new report the Evidence-Based Practice Center will gather all of the evidence on all of the drug classes that are identified by the program and they will do a review on the entire class of drugs. Those usually get updated every maybe 18 months to two years depending on the governing board of DERP and what they want to be included. So what happens is when new

drugs come into... or get approved, they haven't been reviewed. So we've gone through and made some different types of reports that can incorporate some of those new drugs into... so that they can be eligible to be preferred and those are the expanded scans in the single-drug addendums. So you'll hear these terms or see them on the agenda that it's a new drug report. It's an updated report meaning that the EPC has gone back and searched for new evidence and has incorporated that into the existing report. An expanded scan will... is really just looking at the studies on the new drugs and giving just a brief kind of overview and weighting of the evidence and then a single drug addendum is basically just an evidence-based review on a single drug.

The other kinds of reports are scans. So each year the Drug Effectiveness Review Project will scan for literature and new studies on all of these drug classes and they will tell us that, okay there's two new drugs or there's new indications or there's now four new head-to-head trials and they'll bring that to the DERP Governance Board and they'll decide, okay does that merit doing an update of the class? So the scan doesn't really involve any evaluation of the evidence. It's just telling you that there is new evidence out there or that there is new drugs out there. So it doesn't really give you any information about the new drugs. So that's why in a scan if a new drug is identified we've determined that those drugs aren't eligible to be preferred because they haven't really been compared to what else is out there. So that's just kind of an overview of how the different reports work and if you have any questions as you're going through the process feel free to ask and we'll clarify those.

So the category of drugs on the PDL there's the preferred drugs on the PDL. By definition because they are preferred therapeutic interchange doesn't apply because there's... you don't stop it because it's not preferred. They might have other restrictions – prior authorization, quantity limits, step edits, things like that that you have approved. And then non-preferred drugs on the PDL are subject to therapeutic interchange when it has actually reviewed by the P&T Committee and that the P&T Committee has allowed interchange. And then substitution is allowed when the endorsing practitioner signs “may substitute” and DAW applies. So there's other times when a drug... those new drugs that I was mentioning earlier that have not been reviewed, those drugs are

considered to be in the class of drugs, but they are not reviewed. So those drugs... therapeutic interchange doesn't apply. The DAW doesn't apply and they are covered according to the program benefit design. So each Medicaid and Uniform Medical Plan, Labor and Industries. They can determine how... where they want to position those drugs on their own formulary. And then drug classes not on the PDL are also covered according to the program's formulary. And drug classes that you guys don't review, the therapeutic interchange doesn't apply to them. So if you don't see a lot of therapeutic interchange requests it's because it is only those classes that are on what we call the Washington PDL are subject to interchange.

We also have archived some classes and typically classes that get archived are classes that have been around for a long time. There are mostly generic products are on the list. Examples would be like the beta blockers, the ACE inhibitors where there's really not a lot of new evidence coming out on those particular drugs. So we're going to archive them and it's really just more of a cost savings initiative where we're not paying for those reports through the Drug Effective Review Project and we're not paying an actuary to do the cost analysis, which is another piece of the whole PDL process. So when we have a class to archive the committee will review the final scan, you'll vote whether or not it's appropriate to archive the class, you'll determine whether therapeutic interchange should or should not continue and then you can allow the agencies to prefer or change the preferred status on the drugs as long as it follows your last motion. So if you say, you know, only three of the drugs need to be preferred, we don't care which, then that would allow the agency to change to preferred status if they are equally effective. If you have said they are equally effective and maybe there is price changes that go along the way where one generic was more expensive at one point in time, but now its price has come down so we're going to change—either add it or we're going to swap it out.

And then the committee or the agencies can ask for a class to be unarchived, reactivated at any time. This is just really the PDL selection process. A meeting announcement goes out 37 days before the meeting and we're asking for supplemental rebates for the Medicaid program at that time. Those supplemental rebate bids are due seven days prior to

the meeting. Then the committee meets, you make your recommendations on preferred or not preferred on the drugs, the agency conducts a cost analysis, and the prescription drug program workgroup, which is the staff around the table we review the cost analysis and we make recommendations to the agency directories based on the results of that analysis, and then we send out notices of the PDL updates and then we implement the PDL. Usually that process... ideally it would take about 90 days, but it's been taking somewhere between 90 days and sometimes up to six months or longer, but that's the process that we go through. Questions? Amber?

Amber Figueroa: Can you clarify what supplemental rebates means?

Donna Sullivan: So supplemental rebates are specific to the Medicaid program and how rebates work for the Medicaid program is... there was a law passed in 1990 that created the Medicaid Federal Rebate Program and what that really means is that manufacturers that have a... or a federal rebate agreement with Medicaid or CMS then Medicaid has to cover those drugs. So those are federal rebates. In addition to those federal rebates the Medicaid programs can negotiate additional rebates on top of that and those are what we call supplemental rebates. So that's been the term that was created when that program was approved by CMS. So those are rebates above and beyond the federally-mandated rebate that the manufacturer has to provide to us. Any other questions? Great.

Michael Johnson: We'll go ahead and move on to anti-depressants.

Leta Evaskus: Our presenter is not on the phone. I can call her.

Michael Johnson: Okay.

Leta Evaskus: Oh, no I can't. This person is calling in from Austria. We may have to take a 10-minute break. I'm not calling long distance.

Gerald Gartlehner: Hi. This is Gerald.

Michael Johnson: We have your first slide up. Go ahead and start when you're ready.

Gerald Gartlehner: Oh wonderful. That is quick. Yeah, so my presentation today summarizes a targeted report on second generation antidepressants with a focus on three new antidepressants, levomilnacipran, vilazodone, and vortioxetine. Next slide.

Our report addressed three key questions – key question one is the comparative efficacy and effectiveness. Key question for outpatients with major depressive disorder or generalized anxiety disorder to levomilnacipran, vilazodone or vortioxetine differ in efficacy or effectiveness compared with one another or other second-generation antidepressants. Key question two – do these drugs differ in harms compared with one another or other second generation antidepressants? And key question three is the subgroup question – are there subgroups of patients based on demographics, other medications, or comorbidities for which one drug is more effective or associated with fewer adverse events than another. Next slide.

Overall for this report we included 16 second-generation antidepressants that are listed on this slide. The focus however, as mentioned before, was on the comparative effectiveness and risk of harms of levomilnacipran, vilazodone and vortioxetine. So levomilnacipran is one of the three new drugs. It is a new serotonin or epinephrine reuptake inhibitor. Vilazodone and vortioxetine are mostly SSRIs. Both also act as five hydroxyl tryptamine, one agonist and vortioxetine is also a 5HT3 antagonist. All three drugs are administered once daily and are currently approved for major depressive disorder only. Next slide.

For efficacy and effectiveness we were interested in head-to-head randomized controlled trials of at least six weeks treatment. We also conducted network meta-analyses and for network meta-analyses we also included placebo-controlled randomized trials of at least six weeks of treatment. For harms, in addition to the head-to-head randomized controlled trials we would have also included head-to-head observational studies. We did not find any. But we did not include non-comparative observational studies. We also did not include small comparative observational studies and systematic reviews. Next slide.

To summarize the strength of the evidence. So the confidence in the findings that we have we used the approach that you are probably used to, the approach of the HRQ, evidence-based practice centers. It incorporates four domains, risk of bias, consistency, directness and precision. Next slide.

The strength of evidence approach uses four categories to grade the strength of the evidence – high, moderate, low and insufficient. High means that we are very confident that the estimate of effect that we see in the studies lies close to the true effect and we are very confident that future studies would not change this effect much anymore. Insufficient is sort of from the other side of the spectrum. We either have no evidence or we are unable to estimate an effect or we have no confidence in the effects that we see and insufficient also means that future studies will have a major impact on the effect that we see. Moderate and low and sort of in between these two. Next slide.

For this report we conducted a comprehensive search of the literature in electronic databases. You see them listed here on this slide. Our search dates for this report were through September 2016. We also searched clinical trials [inaudible] and the WHO clinical trials registry, the FDA Center for Drug Evaluation and Research website and we searched the websites of the relevant pharmaceutical companies for unpublished studies. As always, for DERP reports we invited the pharmaceutical industry to submit dossiers. We received only one from Takeda Pharmaceuticals and they are the producers of [inaudible]. Next slide.

On this slide you can see the results of our literature search. We screened 4,744 titles in abstract of which we included 325 full text articles for further assessment. Overall we included 21 trials and these were 7 head-to-head RCTs and 14 placebo or active-controlled trials which we included for the network meta-analyses. This network meta-analyses built on a database of a prior systematic review on second generation antidepressants that we conducted for HRQ about three years ago. Next slide.

So on this slide you can just see a graphical display of the network of second generation antidepressants that we used for these network meta-

analyses. Overall the network includes 119 randomized controlled trials of which 98 are a fair or good quality. The outcome for this network is response to treatment on the Hamilton Depression Rating Scale, which is defined as an improvement of symptoms of at least 50%. Next slide.

So the seven head-to-head trials that I mentioned before of those six were in populations with major depressive disorder. Four of them compared vortioxetine with duloxetine. One vortioxetine with citalopram and one vortioxetine with venlafaxine extended release. Two of the trials that compared vortioxetine with duloxetine included vortioxetine doses that were outside the FDA approved dosing ranges so we sent them in a table in the report, but we did not include them in any of our analyses or we do not present them as findings into the slides here. For generalized anxiety disorder we included one randomized control trial, which compared vortioxetine with duloxetine. Next slide.

For harms we combined the adequately dosed depression and anxiety trials. As I mentioned before we did not find any eligible observational studies for the assessment of harms. Next slide.

So let's start with the results for key question 1 on the comparative efficacy and effectiveness. Next slide.

And let's start with major depressive disorder. Next slide.

So as mentioned in the beginning our focus was on three new antidepressants, levomilnacipran, vilazodone and vortioxetine. We did not find any studies directly comparing levomilnacipran with any of the other second generation antidepressants. So our results are limited to the meta-analysis which indicate singular response rates for levomilnacipran and all of the other second generation antidepressants. For vilazodone we found one head-to-head trial comparing vilazodone with citalopram and this trial and also results from the network meta-analysis indicate singular efficacy between vilazodone and citalopram. And network meta-analysis also shows similar efficacy between vilazodone and the other second generation antidepressants. Next slide.

So here on this slide, this slide summarizes results of the network meta-analysis comparing levomilnacipran with other second generation antidepressants. The outcome here is response to treatment after 6 to 12 weeks and as you can see in the [inaudible] plot there are not statistically significant differences for any comparisons except at the very bottom levomilnacipran compared with placebo. Next slide.

This slide presents the results of the network meta-analysis of vilazodone compared with other second generation antidepressants. It's a singular picture so levomilnacipran no statistically significant differences with any of the second generation antidepressants. The only statistically significant difference, again, is with placebo at the very bottom of the plot. Next slide.

We had two trials that compared vortioxetine with duloxetine. Overall these trials showed singular efficacy between the two drugs or response if you are to take the network meta-analysis into consideration and also for remission and functional capacity. Next slide.

The third direct comparisons between vortioxetine was with venlafaxine extended release and this trial and also the network meta-analysis showed singular efficacy between vortioxetine and venlafaxine extended release for response or for remission. Next slide.

On this slide you can see the network meta-analysis comparing vortioxetine with other second generation antidepressants. Again, the outcome is response to treatment. And here for most comparisons network meta-analysis found no statistically significant differences. However, there are two exceptions and these exceptions... you should see them circled in red. If not, please click twice on the slide then it is a little animated. So these exceptions are the comparisons of bupropion and fluoxetine for which vortioxetine yielded statistically significantly higher response rates than these two comparators. As for any meta-analysis we explored the robustness of these findings and we conducted various sensitivity analysis and it turned out that the statistically significant differences here were really dependent on one single study, which reported substantially higher response rates for patients on vortioxetine than on placebo. So this was in the network meta-analysis

model. When we removed the study from the model the statistical significance was lost and response rates between vortioxetine and bupropion and vortioxetine and fluoxetine were not statistically significant anymore and were similar again. Next slide.

So because of this lack of robustness that we had from the network meta-analysis without any direct head-to-head trials we rated these two comparisons as insufficient evidence. The other comparisons of vortioxetine with second generation antidepressants all showed similar efficacy and results were also stable during the sensitivity analysis. So we rated all of these other comparisons as low strength of evidence. Low because of the indirect nature of the network meta-analysis. Next slide.

Generalized anxiety disorder. Next slide.

Again, for generalized anxiety disorder we did not find any studies directly comparing levomilnacipran or vilazodone with other second generation antidepressants. We found only one eligible RCT that compared vortioxetine with duloxetine and it has to be noted that vortioxetine is currently not approved for the treatment of generalized anxiety disorder. So in this study patients treated with vortioxetine had numerically lower response and remission rates than patients on duloxetine. So for example 20% of patients on vortioxetine achieved remission compared to 28% of patients on duloxetine. The differences, however, did not reach statistical significance which probably is because of the small number of patients in this study. Next slide.

Key question 2 comparative risk for harms. Next slide.

For outcomes of interest for key question 2 were the overall rates of adverse events, discontinuation because of adverse events, serious adverse events, and then various specific adverse events and specifically suicidal ideas and behavior. So as mentioned in the beginning for harms we combined depression trials with the [inaudible] generalized anxiety disorder trial simply based on the assumption that the [inaudible] profile probably would be very similar regardless of the underlying condition. Next slide.

The overall rates of adverse events were similar for the drugs for which we had direct head-to-head evidence – vilazodone versus citalopram, vortioxetine versus duloxetine and vortioxetine versus venlafaxine extended release. In each group, in each treatment arm more than 70% of patients experienced at least one adverse event. Next slide.

Likewise discontinuation rates because of adverse events were similar between vortioxetine and duloxetine. Both were around 7%. By contrast discontinuation rates because of adverse events were substantially higher in patients treated with venlafaxine extended release than vortioxetine. So this was 14% versus 7%. Again, the difference did not reach statistical significance. Next slide.

Serious adverse events – patients in all of these studies experienced few serious adverse events overall. Risks appeared to be singular, but our confidence in results was low because of few events. So we rated them as insufficient or low. Next slide.

A similar situation for suicidal ideas and behavior. The study showed singular risks. The evidence however was really too weak to draw any firm conclusions. Next slide.

Studies showed some differences in specific adverse events. So for example vilazodone had statistically significantly higher risks for diarrhea and vomiting than citalopram. Next slide.

Dry mouth and sexual dysfunction and [inaudible] on the other hand were significantly less common in vortioxetine than the duloxetine treatment groups. Next slide.

And this slide just summarizes the adverse events outcomes comparing vortioxetine and duloxetine for which we were able to conduct meta-analysis. As you can see, except for dry mouth here there were no statistically significant differences. Next slide.

Key question 3 differences in effectiveness or risk of harms in subgroups. Next slide.

Unfortunately, we did not find a single eligible study that addressed differences in subgroups. Next slide.

So summary and conclusions. In summary for major depressive disorder we did not find any eligible RCTs for most comparisons based on the few head-to-head trials that we had and based on the network meta-analysis our conclusion is that response rates are similar between levomilnacipran, duloxetine, vortioxetine with one another and with other second generation antidepressants. For some outcomes of interest such as quality of life or hospitalizations, time to onset of efficacy, and also prevention of relapse and recurrence we did not find any evidence for generalized anxiety disorder. A single trial indicates lower response and remission rates for patients on vortioxetine than duloxetine, but then again vortioxetine is not approved for the treatment of generalized anxiety disorder. Next slide.

Summary for harms. Except for a few specific adverse events, risks were similar between vilazodone and citalopram, vortioxetine and duloxetine, as well as vortioxetine and venlafaxine extended release. And this slide also concludes my presentation. So if you have any questions, please go ahead.

Nancy Lee: I had a question about clarification regarding the [inaudible] study. Can you clarify? Did this study have a high risk of bias?

Gerald Gartlehner: No, it didn't. We rated it as small risk of bias. It just had an unusually high response rate for vortioxetine compared with placebo, which probably could just be a chance finding, but it really messed up our network meta-analysis model.

Nancy Lee: I also had a follow-up question regarding your sensitivity analysis. When you conducted the sensitivity analysis did you remove studies with high risk of bias?

Gerald Gartlehner: Um, yes. So we removed high risk of bias studies. We put them back in and that really didn't change much. Then we started exploring the stability of the statistically significant results in the vortioxetine network meta-analysis and that's when we started to remove single studies and

that's when we saw the statistical significance really was dependent on this one single trial.

Nancy Lee: I guess the point of confusion that I had reading your report was on page 16 where you said that when you explored the robustness you added high risk of bias studies to the network meta-analysis model. So I wasn't sure if you added them or removed them.

Gerald Gartlehner: Uh huh. You're right. We added them. So the numbers that we present are based on low or moderate risk of bias studies. We added them in and that didn't change anything, or not much. But the numbers that you have in the report are the ones from low and moderate risk of bias studies. That is correct.

Amber Figueroa: On slide 9 is there an X and Y axis to that or is that just a really cool graphic?

Gerald Gartlehner: That's the network meta-analysis? Yes. That is a really cool graphic. No, there is no X and Y axis. It is a new state of commands that we are very proud of.

Michael Johnson: Any other questions from the committee? There are no stakeholders. So I think... are we done with Gerald? Thank you Gerald.

Gerald Gartlehner: Okay. Thank you. Bye.

Michael Johnson: All right. So we'll turn to committee business at this time. I think what we did last time is we had two different proposals. If you look at page 2 we selected out nefazodone where it's higher incidence of hepatic toxicity. Let's keep it unless there are any discussions. I don't see a lot of new evidence that would distinguish one product from another in any populations. So I would propose that we would reiterate the prior motions with the addition of the new agents.

Donna Sullivan: But you do need to reread it.

Michael Johnson: At this time?

Donna Sullivan: Yes, please.

Michael Johnson: Okay. Unless there is any other discussion before I read this. Okay. I'll read the screen. So after consideration... or after considering the evidence of safety, efficacy and special populations for the treatment of major depressive disorder, dysthymia, seasonal affective disorder, subsyndromal depression, premenstrual dysphoric disorder, generalized anxiety, disorder, obsessive compulsive disorder, panic disorder, and post-traumatic stress disorder in adults as well as major depressive disorder in the pediatric population 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 SNRI or SSNRI, mirtazapine, and bupropion. The second generation antidepressants cannot be subject to therapeutic interchange in the Washington Preferred Drug list.

Is this all one motion or these are... I'll do it all as one. Okay.

So nefazodone is also efficacious for its approved indications but does have a higher risk of hepatic toxicity and so should not be a preferred drug on the PDL.

Amber Figueroa: I second that.

Michael Johnson: All approved say aye.

Group: Aye.

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

Donna Sullivan: Michael, we've called the next presenter but it doesn't sound like she's called in yet. We can just hang for a minute and try and reach her again.

Rebecca Holmes: Hello, this is Rebecca.

Michael Johnson: I think we are ready. We have your first slide up. Thank you for joining us.

Rebecca Holmes: I just want to double check that you have version 2 of this set of files.

Leta Evaskus: Yes, we do.

Rebecca Holmes: Great. So this is an expanded scan on statins. Again, we focused on new drugs since the last report and provide a bit more information than in a typical update scan. Next slide.

So the last report was in November of 2009. We did do a single drug addendum on pitavastatin in 2013 and we did a previous expanded scan on this topic in January 2016. Next slide.

So the inclusion criteria are broad including acute coronary syndrome or revascularization. Next slide.

Slide number 4 there are some changes here. Pitavastatin was new since the last report, approved in 2009. In the table there's combinations. Three of those four have been discontinued. The atorvastatin ezetimibe combination in 2015 and the two niacin combinations in 2016. Next slide.

We can skip over the outcomes, but we did make a change in the timing criteria to try to limit the scope a little bit. We now include only trials that are 12 weeks or more in duration. Next slide.

So for expanded scans, again we focused on head-to-head trials of drugs that are new since the last report. We did some quality assessment and data abstraction including authors' conclusions. We also added some dose comparison for this version of the scan. Next slide.

We pretty much covered this. There's the new pitavastatin in 2009. There's also a new formulation of simvastatin and the discontinued drugs as well. Next slide.

No new serious harms since the last report. There are two large good quality systematic reviews, but those are less helpful here because they pool results across statins. Next slide.

This is the tally of new trials since the last update report. There have been 46 head-to-head trials, 7 of those are new this scan, 16 secondary analyses and 57 placebo-controlled trials. Focusing on the trials of pitavastatin 8 of those were fair or good quality and 2 more were rated poor quality. Next slide.

Some additional details on the next two slides on the 8 pitavastatin trials. There's one comparison to rosuvastatin and several [inaudible] to pravastatin or atorvastatin. We also include some dose information here, which I'll talk more about later. Basically one star is lower dose and more stars are the higher dose. Next slide.

These are the last 4 of the 8 pitavastatin trials. The ones that are shaded are new this scan. There's a total of four new ones. Next slide.

So these are the dose comparisons that we've added. The pitavastatin doses in the 8 trials range from 1 to 4 mg per day, which is the same as the FDA approved dose range. The rosuvastatin trial had a dose of 2.5 mg per day compared to an improved range of 5 to 40 so less than that range. For atorvastatin the doses were at the low end of the approved range, 10 to 20 mg per day compared to 10 to 80. For pravastatin all of the doses were at the low end or below 10 to 40 compared to 40 to 80. And in all eight of the trials we're reporting here the pitavastatin was higher in relative terms than the comparator dose. Next slide.

So keeping those dose issues in mind here are the author's conclusions on the trials. Again, pitavastatin dose is higher than comparator doses. The low dose rosuvastatin actually improved lipids more than pitavastatin in one trial. For the comparison of pitavastatin and atorvastatin there was no difference in the effect on lipids. And for pitavastatin compared to pravastatin, pitavastatin improved lipid profiles more, again, at a higher dose. Harms were either not reported or infrequent so they were hard to compare. One trial did report overall adverse events, which were

more frequent and were similar for pitavastatin and pravastatin. Next slide.

So in summary we have two new drugs, but one has been discontinued since the report. Two fixed dose combinations with niacin were also discontinued. We have 46 new head-to-head trials. Next slide.

Focusing on the evidence for the eight pitavastatin trials authors conclusions were that low dose rosuvastatin improved lipids more than pitavastatin. Higher dose pitavastatin was more effective than pravastatin in three trials and there were no differences in effectiveness between higher dose pitavastatin and atorvastatin also had three trials and adverse events were difficult to compare. One other note is that there weren't any clinical outcomes in any of these trials. There was one trial of atorvastatin and ezetimibe that reported cardiovascular events, but we deleted that since the drug was no longer available. So that's what I have. I can take any questions.

Michael Johnson: I don't see any questions and there are no stakeholders. Thank you, Rebecca. I think we are done with you. Thank you.

Rebecca Holmes: Thank you.

Lisa Chew: I move to accept the scan.

Michael Johnson: I'll second. All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The scan is accepted as adequate.

Amber Figueroa: I think the question at this pose is the dosing as to whether or not it should be considered in the mind as a low dose as a high dose since it was being compared with not comparative doses. I don't see in our previous motion that we specify as an organization which one is high or low. There's... as far as therapeutic interchange. So do you want to speak to that, Donna? Any statin can be interchanged for any other statin? You guys don't specify low, high...

Donna Sullivan: So at this point in time I think that we distinguish them between a low potency and a high potency, but not based on dose. I mean a low... like low dose rosuvastatin would be interchangeable with, you know, a moderate dose of like simvastatin, but we wouldn't... a high dose of rosuvastatin wouldn't be something that you would switch with like lovastatin or simvastatin. We don't distinguish between that.

Amber Figueroa: We wouldn't need to categorize this new drug into any of those?

Donna Sullivan: No, I don't think so.

Amber Figueroa: Okay.

Michael Johnson: Any other comments or discussion?

Lisa Chew: I would like to reiterate the prior motion.

Donna Sullivan: Since we have new drugs we will have to reread it with the new drugs. Sorry.

Lisa Chew: After considering the evidence of safety, efficacy and special populations, I move that the following statins are safe and efficacious: pitavastatin, atorvastatin, fluvastatin, fluvastatin ER, lovastatin, lovastatin ER, pravastatin, rosuvastatin and simvastatin all forms and can be subjected to therapeutic interchange in the Washington Preferred Drug List. The PDL must include at least one high potency option (atorvastatin and/or rosuvastatin) and the PDL must include pravastatin as an alternative with minimal cytochrome P450 drug interactions. I move not to include the combination products as part of the statin drug class on the PDL.

Amber Figueroa: The niacin ones shouldn't be in there, should they, because they are no longer on the market?

Donna Sullivan: That's correct. They should be removed because they have been discontinued. I actually think they are in a separate motion, maybe. Did we do the combinations separately? I don't think the niacin products are listed in there.

Michael Johnson: I'm going to go ahead and second the motion. So all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The motion carries.

Amber Figueroa: Leta, can you take the niacin off of there?

Leta Evaskus: Oh this one here. Okay, gotcha. Thank you.

Michael Johnson: We'll take a 15-minute break. It's seven after. We'll be back at 10:25. Thanks.

Welcome back from break. I think our next topic is the PCSK9 inhibitors and I think Marian is on the phone. Are you ready?

Marian McDonagh: I sure am.

Michael Johnson: All right. We have your first slide up.

Marian McDonagh: Okay. Let's go. So this is the expanded scan on the PCSK9 inhibitors. So if we go to the next slide.

We did do an original full report on this topic back in July of 2015 and then we did a regular preliminary update scan last month and there was some new evidence on there. So we're doing a little more of an expanded look at that evidence here. Next slide.

The populations that are included are listed there on the slide. They are people with heterozygous or homozygous familial hypercholesterolemia. Patients who are unable to take statins intolerance to statins, and the people who are at increased cardiovascular risk, but haven't achieved their LDL goals of less than 100 or less than 70 depending on what their level of baseline risk is for cardiovascular events and that population would be excluding the familial hypercholesterolemia group. There are two drugs in the class and there are still only two. As I have here the searches ended in March of 2017 and we did find a total of 10 trials, two

of those are new for evolocumab and eight for alirocumab, which evens out the evidence base between the drugs a lot more than what we had found in the previous full report. Next slide.

What I'm going to do is walk through the characteristics of the studies first and it is by drug and by population and then we'll go through what the results are by population after that. So this slide is looking at the three new trials of alirocumab in patients who do have a risk for cardiovascular events and have LDL-Cs greater than 70. You can see the first two studies there are in patients at very high risk and these studies were filling some what you might call gaps or concerns in the evidence from the last report. Previously we had highlighted that many of the studies did not... really the patients entering the studies were not really on the highest or best dose of statin that they could have been on and you wouldn't call it intensive statin therapy. So these two studies are trying to resolve that. Trying to look at doubling the dose for either atorvastatin or rosuvastatin or switching from atorvastatin or rosuvastatin as one of the arms of the comparison here. And then the last study on the slide is a study of patients with moderate cardiovascular risk. And this is new to the report. It is monotherapy. So only alirocumab or only ezetimibe in those patients. Next slide.

So the first study on this slide is the first study of patients with statin intolerance in alirocumab. This is looking at... it includes atorvastatin 20 mg re-challenge arm. So the inclusion criteria for statin intolerance is much better here than it was previously. The previous studies we had for evolocumab had kind of loose criteria for how you got into the trial for statin intolerance. So this one is certainly better. The second study on the slide is a mixed population. It is a study that was done only in Japan and it includes a variety of different kinds of patients and looked at add-on therapy as alirocumab or placebo. Next slide.

We have three new studies, four including the bottom study there. It's the multi-population study from Japan. So really three new studies of alirocumab in patients with heterozygous familial hypercholesterolemia. So the first study was in patients who had very high LDL-Cs even on a good dose of statin. It was not a really large study and they had a very high discontinuation rate, 36% of patients did not finish the study. So

there's a lot of missing data. And they had some problems with randomization in that 19% in one group and 34% in the other were taking ezetimibe as well as a statin. So we rated that study poor quality because it had some real concerns with fairness of the data, let's say. Not that they did it intentionally, but that's how it worked out. And then the next two studies, Odyssey FH1 and FH2 are identical studies published in the same paper, but they were separately randomized. These are studies that are longer in duration than the previous studies of alirocumab in this population. So these are both 24 weeks, previous studies were 12 weeks. And also the sample sizes are much larger. The previous studies were less than 100 patients, certainly less than... even less than 80. So these are much larger and longer. And then there's also that study from Japan that also includes patients with heterozygous familial hypercholesterolemia. Next slide.

This is looking at the two new studies we have for evolocumab and again just looking at the characteristics of the study trials at first. So the first one is the four-year study in patients who had cardiovascular risk and they actually had cardiovascular disease at baseline. This is one you may have heard of in the news because this is the first study of the PCSK9 inhibitor to report cardiovascular events. So it was 26 months in duration and we'll get to talk about that one on the next slide. We'll get into all the results of that one. There is also a new study of patients with statin intolerance for evolocumab and this one does resolve the issues that we had previously about the types of patients that were included considered statin-intolerant or unable to or just not wanting to take a statin. This one is much better in terms of the criteria. Previously the other study was also only 12 weeks long. So this one is much longer. Next slide.

So this is the results from the four-year study. This is looking at patients with cardiovascular risk at baseline and LDL-Cs greater than 70. So that's the general patient population. This was patients with clinically-evident atherosclerotic CVD at baseline who were taking at least 20 mg of atorvastatin a day and still had LDL greater than 70. So the findings are that compared to placebo evolocumab did have better composite outcomes for cardiovascular events. So both the primary and the secondary outcome in this study were composite outcomes. So for example the primary outcome included any of the following:

cardiovascular death, MI, stroke, hospitalization for acute coronary syndrome, or coronary revascularization. For that one you can see that the hazard ratio is .85 and it was significant, significantly lower in the evolocumab group. But the absolute difference is pretty small – 11.3% versus 9.8%. So 1.5% risk difference there and that translates to a number needed to treat of 66. Similarly the secondary end point is quite similar in terms of the differences in the statistical significance. And so also then this study did look at individual events and didn't find a difference, a statistically significant difference for cardiovascular death alone. So a little bit more about this population that was in the trial – about 80% of them had a history of MI and that was how they qualified for the study and most patients, 75 to 90% were on some or multiple other treatments at baseline such as antiplatelet therapy, beta blockers, ACE inhibitors, and so on, but only about 70% were on a high intensity statin. That still leaves 30% who were not. So those were the first findings for cardiovascular events. Next slide.

This is looking at patients who were in a similar population, higher cardiovascular risk and still LDL-Cs greater than 70 when they were on a statin, but these are just looking at lipid outcomes. So here we have those two studies that we talked about a minute ago that... used arms where patients were having double their atorvastatin or rosuvastatin dose or switching from atorvastatin to rosuvastatin. So these studies confirmed the findings of the previous studies where we were concerned that the control groups didn't have really the best dose of statin going on so it might be contributing to the findings, but these studies confirm the findings that alirocumab does reduce LDL-C more than a statin alone. And you will see on the second study though, option 2, the bottom line there shows the P value of 0.1177. That is for the comparison of alirocumab plus a statin versus ezetimibe plus a statin. And so they... in that one it did not reach statistical significance although you can see that the difference in the proportions of patients achieving the goal is pretty big at 14.5%. And then the bottom study is the new monotherapy study alirocumab alone versus ezetimibe alone. And here the alirocumab arm did have lower cholesterol levels, LDL cholesterol levels as well. So a pretty big difference there. And then if we move to the next slide this is looking at the population of patients who have... truly have statin intolerance and as I said there are two new trials here. For alirocumab

this is a new study. We didn't have a study in this population before and alirocumab was superior to ezetimibe. And then the second study is evolocumab, which was tightening up the criteria for getting into the study and evolocumab was superior to ezetimibe and that confirms the previous findings with a broader criteria. So the criteria... for example, they had a run-in period where they had patients randomized through atorvastatin or placebo and then looked at their muscle symptoms... who had muscle symptoms. 17% did not have symptoms while they were on the atorvastatin re-challenge, but 26% did have symptoms while on placebo and 10% had symptoms on both. So that's interesting information for getting into the study. Next slide.

This is looking at the population of patients who have heterozygous familial hypercholesterolemia and all of these studies are in alirocumab. And alirocumab was superior to placebo when added to a statin in all of the studies and confirms the previous findings. Again, these were studies that were longer and larger and... next slide.

This shows you the actual results from those three studies and then the fourth study in Japan that had that mixed population. These studies all confirm previous findings. Next slide.

These next two slides are just reiterating what we just went over and we're trying to summarize it all. We have 9 fair and good quality studies of over 30,000 patients. They range in duration from 24 weeks to 26 months. In the first study reporting cardiovascular end points evolocumab treatment was statistically significantly superior to placebo in reducing composite end points. But cardiovascular death alone was not significantly reduced. And the absolute differences are not large. The second conclusion on this slide is that alirocumab is effective in lowering LDL levels as monotherapy, which is a new finding or add on therapy compared to ezetimibe or intensified statin therapy. And this is in patients with moderate all the way up to very high risk of cardiovascular events. Other than the monotherapy these results do confirm previous findings. Next slide.

The final slide then the summary statement here the first one is for statin intolerance that both alirocumab and evolocumab now have evidence for

lowering LDL-C in patients with statin intolerance compared with ezetimibe. Then the last point is that new evidence in larger and longer studies confirms the findings of alirocumab in reducing LDL-C significantly in patients with heterozygous familial hypercholesterolemia. It just strengthens that evidence. All right. That's the conclusion. I'll take any questions.

Michael Johnson: Any questions from the board? I don't think there are any questions from the board. At this time we have one stakeholder. Marian, if you could just hold on the line here shortly. We have Dr. Sylvia Churchill. Come up to the mike and you'll have three minutes. You can just introduce yourself and who you represent.

Sylvia Churchill: Is this working? It is. Hi. My name is Sylvia Churchill. I'm a pharmacist here in Washington State and I work for Amgen as a health outcomes and pharmacoeconomics specialist. Thank you for the opportunity to talk about evolocumab. A very good overview already of the [inaudible] trial. I just wanted to basically emphasize that evolocumab is indicated to be given on top of maximally tolerated statin therapy and it is for those patients who, when they're on maximally tolerated statin therapy can't achieve the LDL levels that they need. So it's important to note that in the [inaudible] study prior to randomization patient statin therapy was optimized and stabilized over a period of up to 16 weeks and during that period of time when patients first entered the trial it was a... 60% of the patients were on high intensity statin, 40% were on moderate intensity statin. By the end of that lipid optimization period they were able to increase that to 69% of patients on high intensity statin therapy and 30% on moderate intensity statin therapy. So it is important to note that you do want to increase that level up to the maximum ability, but that not all patients can tolerate above the moderate intensity statin. That's important because you do want to make sure that you maximize the benefit of your statin before you add a PCSK9. The [inaudible] results show that adding evolocumab resulted in a relative risk reduction of 15% for the primary end point, and 20% for the composite of heart attack, stroke or cardiovascular death. The benefits were driven by a reduction in MI by 27%, in stroke by 21% and a reduction in coronary revascularization procedures by 22%, but no significant difference in CV mortality. Of note, getting a difference in CV mortality is very difficult in

these trials. If you look at all of the 26 lipid lowering trials in the CTTC only two were able to show a cardiovascular mortality benefit and that was the 4S and the Lipid Trial, but in those trials both of those were placebo-controlled. They had very high baseline LDLs to start and their studies were five and six years long. We need to remember that the [inaudible] study was only 26 months or 2.2 years long.

At this point are there any questions I can answer about the study or help clarify about evolocumab? No. Okay. Well, please refer to the PI for complete information and thanks for your time.

Michael Johnson: Thank you. Any other questions for Marian before we let her go? All right. Thank you, Marian.

Marian McDonagh: Okay. Thanks.

Michael Johnson: I'm going to propose that we accept the scan as adequate.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The motion passes. So we can look at the previous proposals.

Amber Figueroa: I move that we keep the same motion. I don't think I have to say it since there's no new drugs.

Donna Sullivan: That is correct.

Amber Figueroa: Yay! I reiterate the prior motion I believe is the correct wording.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. That passes. I think our next topic is hormone replacement therapy. I'll give you a second to catch up. Are you there Brittany?

Brittany Lazur: Yes, this is Brittany. I'm ready when you are.

Michael Johnson: I think we have your first slide up so you can take it from here.

Brittany Lazur: Great. Thank you. So is the seventh preliminary update scan in the series for hormone therapy for postmenopausal women or women in the menopausal transition stage and this scan was conducted in September of last year. Next slide, please.

So the last update was update number 3, which was conducted in October 2007 with searches through March 2007. The last scan on this topic was scan 6 in September 2015 and the date of searches for this scan were July 2015 through August 2016. Next slide, please.

Populations for this scan included women experiencing menopause, natural or surgical, and also women transitioning through menopause in the perimenopause stage. We included a number of hormone therapy interventions such as the following that are listed on this slide. Next slide, please.

Listed here are the effectiveness, efficacy and harms outcomes of interest for this scan. Next slide, please.

So for new drugs or formulations in this scan we did not identify any new drugs or formulations, but in prior scans we identified three new drugs and two new formulations that are listed on this slide. In terms of new populations we did not identify any new populations in the current or prior scans. Next slide, please.

We've identified a number of warnings and revisions to boxed warnings, which are listed here. However, none of which were identified in this current scan. Next slide, please.

In terms of new comparative effectiveness reviews we did not find any relevant reviews in this scan, but in prior scans we identified one review conducted by the Agency for Healthcare Research and Quality. This was pretty comprehensive covering the entirety of the scope of this scan. It relates to comparative effectiveness of therapies for menopausal symptoms. It was completed in March 2015. We also identified five reviews that could answer pieces of an update report on this topic and these reviews are detailed more in the scan report itself. Next slide, please.

So for new evidence we identified, since the last report, 10 new potentially relevant head-to-head trials, one which is found in this scan and 38 new potentially relevant placebo-controlled trials, three trials and two publications that were identified in this scan. Next slide, please.

On this slide we have the characteristics of the head-to-head trials that we've identified since the last report and the trial that was identified in this scan is shaded. Next slide, please.

So since the last update report we've identified three new drugs and two new formulations, four new serious harms or boxed warnings or revisions to these boxed warnings, one new comparative effectiveness review that covers the entire scope of this scan, and five new comparative effectiveness reviews that could answer pieces of an update report on this topic. We've also identified 10 new head-to-head trials, one in this scan and 38 new placebo-controlled trials, three in this scan. Are there any questions?

Michael Johnson: I don't see any questions from the board. We're just waiting to see if there are stakeholders. So there are no stakeholders. So if you could just bear with us a moment, Brittany, because I think you do the insomnia next. So give us a second.

I'm going to propose that we accept this scan as adequate.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. I think... I didn't see any evidence where they discussed that would change our previous motion. So I make a motion that we would reiterate that. I'll read it if there is no further discussion.

Ryan Pistorosi: This is just a scan so none of the products that are new are being evaluated. So it is just the same products that were reviewed.

Michael Johnson: Okay. So we'll just reiterate the prior motion?

Ryan Pistorosi: That is correct.

Amber Figueroa: I second that.

Michael Johnson: So all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. Thank you. All right, Brittany. I think we have your first slide up. So you can start whenever you are ready.

Brittany Lazur: Great. Thank you. So this is the sixth preliminary update scan in the series for newer insomnia drugs and this scan was conducted in February of this year. Next slide, please.

So the last update report was update number 2, which was completed in October 2008 with searches through January of that year. The last scan was conducted in July 2015 and the date of searches for this scan were May 2015 through January 2017. Next slide, please.

So we included adults and children with insomnia including primary insomnia, breathing-related sleep disorder, insomnia related to another mental disorder, substance-induced sleep disorder, and sleep disorder due to general medical conditions. And for a full list of the outcomes that

we included in this scan, please refer to the full scan report document. Next slide, please.

On this slide we have the interventions that were included in this scan. Next slide, please.

So in this scan we did not identify any new drugs or formulations, but in previous scans we've identified three new drugs and three new formulations primarily zolpidem. Next slide, please.

In this scan we also did not identify any new serious harms, but in prior scans we identified one new harm that relates to next day impairment of driving and other activities that require alertness with eszopiclone-containing sleep aids. Next slide, please.

So since the last update report we've identified one new potentially relevant comparative effectiveness review. This is also an AHRQ review of management of insomnia disorder. This was conducted or completed in December of 2015. You can find the abstract in the appendix of our full scan report. This review included a broad range of drugs and non-drug treatments and assessed measures of sleep and daytime functioning associated with sleep parameters and harms. And some findings that were relevant to this scan included low to moderate strength that eszopiclone, zolpidem and suvorexant improved short-term global and sleep outcomes in general adult populations. However, the absolute mean effect was small. In addition, the evidence on adverse effects from trial data was generally insufficient or low strength. Next slide, please.

Since the last update report we've identified three new potentially relevant head-to-head trials, none in this scan, and 40 new potentially relevant placebo-controlled trials, five trials in four publications and additionally one secondary analysis was identified in this scan. Next slide, please.

Here we have the characteristics of the three head-to-head trials we've identified since the last update report. They all compare zolpidem with another insomnia drug and these trials are pretty small in terms of the number of participants they included. Next slide, please.

Here we have an accounting of the placebo-controlled trials we've identified since the last update report and you can see the majority of placebo-controlled trials that we've identified are of eszopiclone, zolpidem, or remelteon. Next slide, please.

So since the last update report we've identified three newly approved drugs and three newly approved formulations. However, none were new this scan. We found one new serious harm for eszopiclone in a prior scan, one new review from AHRQ on the management of insomnia and in terms of new evidence, three new head-to-head trials, none this scan, and 40 new placebo-controlled trials, five found this scan. Are there any questions?

Dale Sanderson: I have a quick question. In terms of safety in individuals with untreated sleep apnea, is there any comments on findings there?

Brittany Lazur: Since the last report it doesn't look like we found anything specific to that, but I can double check the scan report and also my colleagues and definitely refer any answers back to you.

Dale Sanderson: Thank you.

Michael Johnson: Any other questions from the committee? There are no stakeholders. So I think we are done with you, Brittany, unless you'd like to stay. Thank you.

Brittany Lazur: Great. Thanks so much.

Man: I will move to accept the scan.

Man: I'll second that motion.

Michael Johnson: All in favor say aye.

Group: Aye.

- Michael Johnson: All opposed same sign. Okay. The motion passes. Now we'll look at the next piece. Where Dale was going with the question, if you have sleep apnea, would being on a sleeping agent be safe, but I don't think any of the scans really addressed that. I think from a clinical standpoint...
- Amber Figueroa: On slide 3 it does say breathing-related sleep disorders, including obstructive sleep apnea is included in the population, but it doesn't say if it was treated or not.
- Nancy Lee: I have a question. I don't have the information regarding whether or not expansion of the scan to address the question about looking at the patient population for those with underlying sleep apnea and whether or not that might provide more information to addressing the question.
- Donna Sullivan: You can ask us to do that. I don't know if the DERP program would approve. The other states would have to vote on paying for that type of report. I'm not sure it would get reviewed, but if you give us the specific questions that you want answered we can take it to the program and see if they are able to do something for us.
- Nancy Lee: A follow-up question is, can we take a look at the previous... the last scan to see if that patient population was addressed since we don't have that information here?
- Ryan Pistori: So you might best find that information in the last actual report, but that previous report was done a number of years ago, back in 2008. So we haven't updated this class with a full report for a while. And so any evidence that's been published since then would not have been reported in that, but it looks like it was included in that original report so there would be some evidence available in there.
- Dale Sanderson: Can I briefly clarify what my concerns are in terms of sleep apnea. I have a large population of patients that have untreated sleep apnea. They cannot tolerate a C-PAP system and yet have significant insomnia issues and trying to treat them with something that will not worsen their sleep apnea symptoms is a real challenge. I sent them to sleep specialists and so the Belsomra, the suvorexant seems to be, from the sleep specialists that I've dealt with, seems to have been one agent that they have

recommended. I'm just pointing this out as a point of clinical significance.

Michael Johnson: I don't recall ever looking at a study that was done looking at sleep agents in an untreated sleep apnea population. I don't know that you would find that.

Donna Sullivan: I don't know if you would either. The question would be, what is the appropriate use of sedative hypnotics in patients with sleep apnea? My understanding is sleep apnea and the physicians can probably speak to it better, but is it really insomnia or that they are just not getting the rest that they need? They keep waking up and they feel tired throughout the day, which I think is a symptom of the sleep apnea. So the question is... it's not so much that they can't fall asleep, it's that they are stopping breathing and waking up and then falling back asleep and going through that cycle, which is causing the tiredness during the day. I think we can ask if the DERP program, through the various avenues that we have, if we can look into sleep apnea, but I'm not exactly sure when that would be.

Man: A sleep specialist on a couple of patients that I've had have actually done sleep studies to verify the impact of the agent on the obstructive symptoms and, again, is that sleep apnea symptoms or is it primary insomnia? That's the question.

Michael Johnson: Did that answer your question, Nancy? Did that help?

Nancy Lee: Yes.

Michael Johnson: My question from the board is do we think that we would need to have something like that? I mean my feeling is if you could find it... I mean I don't think you're going to find at least a moderate study that would be looking at this population. I think you might see some case reports and you might see a subpopulation, but those people that fell between the cracks that ended up on these agents... sometimes that's how you unmask untreated sleep apnea is you put them on a sleep agent or you treat them for some other condition and you find out they have untreated sleep apnea. I don't know if it's... is it worth asking? I guess that's my question.

- Donna Sullivan: I think that you should treat... look at treating sleep apnea is separate from primary insomnia, because they are two different clinical conditions and so we can... I'm not even sure that it is appropriate to address sleep apnea in this particular class. So it would really be looking at what do you do when you have sleep apnea where patients are intolerant to C-PAP. What are the alternatives? That's really the clinical question that you're asking. It may or may not be just these drugs. It could be other things that would be recommended instead of these types of medications to improve the patients' daytime wakefulness.
- Jordan Storhaug: I guess the question I have with that is, it's included in the inclusion criteria, which kind of surprises me that it would be included in the inclusion criteria because it's not necessarily something that I would expect to be associated with these drugs. But the fact that it is included in the inclusion criteria does seem to suggest that there is some reasonable relationship between these drugs and that treatment of which I'm not aware of any evidence to suggest that.
- Ryan Pistori: Right. I think having it be one of the inclusion criteria doesn't mean it was in their search strategy. It doesn't necessarily mean that there is sufficient evidence out there and unfortunately since this is just a scan, and the purpose of a scan is just to say here's the new evidence that's out there without really going into the evidence. I don't know if we can really say that there is sufficient evidence for use of these drugs in, you know, breathing-related sleep disorders, at least until we go back and look at the report or go to DERP and get those questions answered for you.
- Michael Johnson: Any other further discussion?
- Donna Sullivan: I mean if you'd like I can try to pull up the report, but again it's from 2008 so I don't know how much credit you want to give to the data.
- Michael Johnson: Two things – think we can look at entertaining a motion, but I think for the purpose of the board since it was in the inclusion criteria, I think it would appropriate to ask the DERP. When they did their search did they find, you know, what did they find that would... under that search

strategy that might be useful? Was there enough information that we would want an updated scan? You know, like a full review. So that's what I would ask. Did they find significant information that would change our decision in the future? Is that reasonable for the board? Do I need to propose we do that?

Donna Sullivan: You can ask us to do it now. I'm looking at the scan here and there's three new head-to-head trials and I'm assuming that none of those were in sleep apnea. We'll take it back to the board or to the DERP program and see if we can get some more information on sleep apnea.

Michael Johnson: Okay. Let's go ahead and look at entertaining a motion.

Amber Figueroa: Should we... are we able to table this until we find out if there is more information?

Donna Sullivan: You could do that.

Lisa Chew: Then does that mean that the scan... we're not accepting the scan as adequate?

Donna Sullivan: Yes, that is what you could say is that you don't accept the scan as adequate and that you ask us to find more information on sleep apnea.

Michael Johnson: I will change the previous motion to say that we are not accepting the scan as adequate given this issue of untreated sleep apnea and the use of sleep agents.

Man: Second.

Michael Johnson: On that new motion all in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. Thank you.

Amber Figueroa: Do you want to take away the Sanderson Storhaug underneath the scan accepted? You've got motions and seconds in two places. There you go.

Donna Sullivan: It looks like we are through the P&T Committee agenda and we're not quite ready for lunch yet. So if you like we can move into the DUR section and start before lunch.

Michael Johnson: I think that's good. We're going to adjourn the Pharmacy and Therapeutics Committee. At this time we'll convene the Drug Utilization Review Board. I think first topic we have antidepressants for Ryan.

Donna Sullivan: It's gonna be me. Sorry.

Michael Johnson: Oh, we're going to go in a different order. Okay.

Donna Sullivan: I'll be doing all of the DUR except for the Emflaza policy. So we just didn't get the agenda updated.

I'm going to talk about the Drug Utilization Review policies on the drug classes that you just reviewed as the P&T Committee. So the first class is the second generation antidepressants. I'm just going to go through... not going to go through all of these, but this is just the listing of their preferred status as of... prior to any changes that were made today. So this is not what is... will be going forward. This is the current PDL as it exists today. I just wanted to look at some utilization and this is new. We haven't looked at utilization in quite a while. With the antidepressant utilization duloxetine the agency, and this includes the managed care data, is the... duloxetine is the drug that we spend the most money on in the antidepressant class and as you can see towards the right it is not the drug that has the most users. So fluoxetine still continues to have the most users and is about mid-range as far as the money that we spend.

On the next slide our current limitations are the continuation of therapy is required under the statute. We also have a generics first program and the... we require that a person try and fail two preferred products prior to a non-preferred drug being authorized. The dose limits that we have in place are duloxetine there's a maximum of 60 mg per day. Citalopram has a maximum of 40 mg per day. There's an expedited authorization code for bupropion to verify that it is not being used for smoking cessation. Smoking cessation use is funded separately so we require that

EA code so that in our reporting to CMS and how it gets reimbursed for us that we can distinguish the difference between patients using bupropion for smoking cessation versus depression or other mental health-related indications. Duloxetine we have an expedited authorization code for diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. Any user under the age of 18 antidepressant duplications of two or more antidepressants does require a second opinion through our current program. Our recommendation is to require patients to step through all the preferred antidepressant products before a non-preferred will be authorized and then continue all of the other limitations. I'm not sure if there are any stakeholder comments.

Michael Johnson: There are no stakeholders.

Donna Sullivan: Okay. Any questions that you have?

Amber Figueroa: So when we go back to this list on slide 2 you're saying that everything that says generic preferred they would have to go through all of that before they got approved for the second generation?

Donna Sullivan: That is what we're saying. Not the second generation, for something that is listed as non-preferred.

Jordan Storhaug: Just to further clarify, so they would have to try nine different drugs before they would ever be able to take duloxetine?

Donna Sullivan: Yes. Essentially that is what that is saying. That's the current... this is the current PDL too. The process that would happen is that we'll do a cost analysis and looking at the recommendations that you made as the P&T Committee where we have to have, you know, the two SSRIs, the one SNRI, or SSNRI plus mirtazapine and bupropion and then, you know, depending on the price of duloxetine if it has come down it will be... more likely to be a preferred drug. I'm not exactly sure off the top of my head what its price looks like, but this is based on its current status. If duloxetine became preferred then obviously you wouldn't have to step through all of those.

Amber Figueroa: Clarifying again. So the expedited authorization criteria for duloxetine would mean that they would not have to try those nine drugs?

Donna Sullivan: Correct.

Amber Figueroa: Okay. But depression not being one of those diagnoses?

Donna Sullivan: Correct.

Po Karczewski: I'm confused. On slide 4 it says try and fail two preferred products prior to a non-preferred being authorized.

Donna Sullivan: That's our current limitation. We're recommending that... or to change it that they try all.

Po Karczewski: Okay.

Donna Sullivan: You can say... you can leave it at two, you can say four, you can say five, you can say all. This is just what we were recommending.

Po Karczewski: Just in my experience and I'm sure... the effect of these antidepressants is quite radically different depending upon what you're trying to achieve and so I think that two would be much more reasonable to go in through what, in my practice experience, and what I think my peers would support would be that some of these are activating and some of them are not. I would think that having to go through more than two to get to a non-preferred would not be a reasonable expectation.

Dale Sanderson: I would agree with that. I know that we went through this with the antipsychotics as well and it seems like two is a reasonable number.

Donna Sullivan: I think we landed on five with the antipsychotics.

Dale Sanderson: Five of the antipsychotics?

Donna Sullivan: Yes.

Amber Figueroa: I understand the concern with such a small amount of users and yet that being the number one cost. I'm not opposed to increasing it to maybe three or four, but I think having to jump through nine meds is not fair to the patient. I agree with Po that these all act somewhat differently and they also effect people differently. So I think it's unrealistic to ask them to jump through nine meds.

Lisa Chew: I have a question about the utilization data. Of the users for duloxetine what proportion of them actually have a concurrent, chronic pain condition?

Donna Sullivan: I don't know. I don't have that number in front of me, but that is a very good question because those people that were taking it for diabetic neuropathy, fibromyalgia, they are included in that utilization that I showed you. So we didn't pull out the utilization by diagnosis.

Lisa Chew: I guess another question I have was regarding the recommendation. Do you have any expectation regarding monotherapy versus combination therapy when you have to go through all the different products?

Donna Sullivan: At this point in time duplicate therapy is only... we look at it in children only. In adults we don't prevent duplicate therapy. We don't encourage duplicate therapy and April you might be able to answer that a little bit better and I'll put you on the stop.

April Phillips: I believe it was last fall, August or October we removed the adult duplication in the antidepressants.

Nancy Lee: When you're talking about duplication are you talking about with... from... two medications from each... from a specific drug class or like a bupropion plus an SSRI?

Donna Sullivan: I think it's either. We don't prevent duplication. At this point in time we allow two or more antidepressants to be prescribed. So we're not specific to which type of class it is. So the question, you know, the question would be is do you have to try bupropion plus fluoxetine before you can have duloxetine? Is that where you're going? We don't have that type of edit in place right now.

Michael Johnson: If we think two is not enough and nine is too many do we have a proposal for how many we think is reasonable to try before...

Po Karczewski: I think two is good the way it is.

Dale Sanderson: I would agree.

Amber Figueroa: I suspect that if there were a way to extract out those three criteria for expedited authorization that I bet a large majority of... what I'm trying to say is those people, whether we changed it to three or nine for duloxetine, the majority of them or probably at least half are taking it because of one of those three reasons. So I don't know cost wise if it's going to make a huge difference if we increase the number of meds that they have to go through to use it for depression. I agree with two. I would be okay with three also.

Michael Johnson: I think two or three is reasonable. Do you want to make a proposal?

Po Karczewski: So you're suggesting a proposal for two or three or two?

Michael Johnson: Let's state one so then we can all vote on it.

Po Karczewski: I would move that we leave the existing dose... the existing policy in place where you have to fail two preferred products prior to a non-preferred.

Michael Johnson: We also continue the other current limitations?

Donna Sullivan: Correct. So I've changed the recommendation now to continue all limitations as currently listed.

Michael Johnson: Sounds good.

Donna Sullivan: So if you want to make a motion then to approve that that would be great.

Michael Johnson: I'm going to second what Po just said, continue the current restrictions exactly like they are with two drugs. You want me to read that?

Donna Sullivan: Yeah.

Michael Johnson: So I move that the Medicaid Fee-for-Service Program continue the current limitations for the second generation antidepressant drug class.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. Pass.

Lisa Chew: Looking at the cost I do think it is worth breaking out those patients on duloxetine who maybe do not have pain and looking whether that it is a high proportion and if it is then looking at readdressing whether or not two is the right number.

Donna Sullivan: We can do that. This does also include the managed care utilization and so it would be interesting to look at their policies and see whether or not they're covering it for those indications and where they are steering. Thank you.

The next drug class newer sedative hypnotics. The preferred products right now are the generic zaleplon, generic zolpidem.

The next slide shows the sedative hypnotic utilization. The majority of our utilization and the majority of the drug zolpidem. Our current limitations are when prescribed for patients under the age of 18 that requires a second opinion for age 18 and older there is just a maximum daily dose of one tablet per day. Any requests for more than one tablet per day would require prior authorization and again they must... in this class they currently must try all the preferred drugs with the same indication before a non-preferred drug would be authorized unless it's contraindicated or not clinically appropriate. So we're just recommending to continue as we are.

Amber Figueroa: On the graph maybe you can explain it better. Maybe I'm not reading it right. When you look at the number of users from eszopiclone and remelteon, remelteon is preferred based on the previous and the other one is not and fewer people are using it and it still is costing the same.

Donna Sullivan: The generic zaleplon is preferred.

Amber Figueroa: Looking at the second and the third on the graph.

Donna Sullivan: Again, it includes managed care data. So the managed care plans most likely have... are preferring generics. So they may or may not have all restrictions. So this is the entire population and I apologize when I first pulled the data I did not realize that it included managed care.

To your question, what this would mean is that if you look at eszopiclone it is really expensive compared to how many people are using it because...

Amber Figueroa: Even fewer people are using the remelteon.

Donna Sullivan: Right, which tells you that it is even more expensive than the eszopiclone.

Amber Figueroa: But it's on our preferred?

Donna Sullivan: It is on our preferred.

Amber Figueroa: Okay.

Donna Sullivan: I forget in the motion, but I believe that you requested that it be preferred or be available. Any other questions?

Lisa Chew: I move the Medicaid Fee-for-Service Program implement the limitations for the new sedative hypnotic drug class listed on slide 8 as recommended.

Jordan Storhaug: I second that.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. It passes.

Donna Sullivan: Were there no stakeholders for the record?

Michael Johnson: Sorry. For the record there were no stakeholders for the insomnia policy.

Donna Sullivan: Thank you. So the next class is the PCSK9 inhibitors. This is the... Praluent is not preferred. The Repatha is currently preferred and that was the drug that you heard most of the information about today. It's not that... the reason why you didn't hear much about Praluent today was that there was no additional data that was available.

The next slide shows utilization and this is when I realized that managed care utilization was in our data because there's more use of Praluent than Repatha so I went and looked and realized that it included managed care and it's the managed care utilization... actually, all of this utilization is in the managed care plans. There wasn't any fee-for-service utilization during this time period. It doesn't tell you a whole lot about the fee-for-service program, but for the entire Medicaid program this is the utilization for these particular drugs. There really are not a lot of patients. You can see it is only about... just over 20, you know, somewhere within 20 to 25 patients that are taking this... one of these drugs.

The current limitations are that they must be prescribed by or in consultation with a cardiologist or endocrinologist. They have to have the diagnosis of the homozygous or heterozygous familial hypercholesterolemia or they have atherosclerotic disease and are statin intolerant. They must be using concomitant statin therapy. Statin intolerant patients must be on other lipid-lowering therapies such as ezetimibe or LDL apheresis and our recommendation is to continue all current limitations. Before we go to the motions I wanted to go through how we're defining statin intolerance.

So the statin intolerance is documentation of trial and failure of at least two statins after ruling out hypothyroidism, changes in physical activity and exercise, and potential for drug-drug interactions, due to pre-specified intolerance symptoms that began or increased during statin therapy and stopped when statin therapy was discontinued. So we're really just making sure that there's not something else causing, you know, muscle aches and pains or symptoms that might mimic statin side effects. Rhabdomyolysis caused statin, after ruling out other causes would be considered as a contraindication to statins so we would not make them be re-challenged with a statin.

Pre-specified intolerant symptoms are defined as myopathy, myalgia, muscle pain, ache, weakness without CK elevation. Myositis was like muscle symptoms that do increase CK levels. And then these are just the lowest starting daily doses of statins and we would require them to at least try, you know, the highest tolerated... preferably the maximum dose, but at least the highest tolerated dose before they... while they are still taking a PCSK9 inhibitor.

Michael Johnson: We have one stakeholder.

Donna Sullivan: Okay.

Sylvia Churchill: It's me again. I'm not going to bother walking all the way up there.

Donna Sullivan: Actually we do need you to walk up there so that it can get recorded. Thank you.

Sylvia Churchill: Okay.

Michael Johnson: And once again just because we are recording it if you could introduce yourself again for the recording.

Sylvia Churchill: Hello again. Sylvia Churchill. Pharmacist here from Amgen. I have nothing really to add at this point. I think those recommendations look clinically adequate. Thank you.

Michael Johnson: Thank you. Now we'll go to the motion.

Lisa Chew: I have a question. There's a lot of discussion about ensuring that people are taking statins with these inhibitors and I'm curious what process do we have in place to make sure patients are actually filling those medications and taking them?

Donna Sullivan: At this point in time I don't know if we have any edits in the system that would reject the PCSK9 inhibitor if they did not continue to take their statin, but that is something that we could do. The question then is, you know, if they continue taking their statin they would have to go through the authorization process over again because their prescription would get denied. So that could cause disruption in treatment. Potentially if it was appropriate for the patient to continue the statin I mean if you want us to do that we could, but that's just not... that's not something we set the system up to do. But the managed care plans may have, but I'm not sure if they have or not.

Ryan Pistorosi: I believe when we proposed the original policy back in December 2015 we did talk about it at that time, but since we haven't had any really request for utilization of it we don't really have experience, you know, seeing if there is that edit or what that process is like. But we can make sure that we can have that system in place, you know, going forward.

Michael Johnson: If there are no comments I will make the motion that I move that the Medicaid Fee-for-Service Program implement limitations for the PCSK9 inhibitor drug class listed on slide 14 as recommended.

Dale Sanderson: I'll second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay.

Amber Figueroa: It's not slide 14, it's 12.

Michael Johnson: It's 12. Oh, thank you. It is 12.

Donna Sullivan: Thank you for that clarification.

Amber Figueroa: I'm playing editor today.

Donna Sullivan: You're doing a good job.

Michael Johnson: Hormone replacement therapy. Is that...

Donna Sullivan: It will come up here in just a second. Okay. So... I think this might be spread across more than one slide. I'm going to page down. Nope. Okay. The drugs listed here are the current preferred status of the estrogens and the oral products. It looks like this is just the estrogens, not the combination products and I apologize. They are further down. So this is just focusing on the single estrogen products. Again, here is the utilization, estradiol is the obvious most commonly prescribed estrogen. This includes all of the formulations of estrogens or estradiol so the tablets, patches, anything like that it's all lumped into the one line.

The combination therapy is listed on slide 18.

And then the utilization, again, the estradiol and norethindrone combination or the conjugated estrogens and medroxyprogesterone are the most commonly prescribed in this population.

So the current limitations are there's an expedited diagnosis... expedited authorization for diagnosis of gender dysphoria. And they must try and fail one preferred drug according to formulation before a non-preferred drug will be authorized and that means if they want a patch they have to try one of the preferred patches before they can get a non-preferred patch. We're recommending that they try all of the preferred drugs according to their formulation before a non-preferred drug would be authorized unless contraindicated or not clinically appropriate. And then there is an expedited authorization code and those should be up above that... for the labial adhesions for children 0-5 and then for diagnosis of gender dysphoria we're recommending that we continue those, as well.

Michael Johnson: No stakeholders.

Donna Sullivan: Okay. Questions?

Michael Johnson: Any discussion?

Amber Figueroa: I move the Medicaid Fee-for-Service Program implement the limitations for the hormone therapy drug class listed on slide 20 as recommended.

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

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. I think the next topic is statins and there are no stakeholders for this topic, as well.

Donna Sullivan: Okay. Thank you. So right now most, if not all of the generic statins are preferred. I'm just scanning through here and it looks like they are all preferred. So the only non-preferred agent is the brand name products including Livalo. In our statin utilization the majority of patients... the majority of the utilization is atorvastatin followed by simvastatin. In our current limitations as we have generics first that they must try generic atorvastatin at the highest tolerated dose before a non-preferred generic or brand will be authorized. Dose limits – simvastatin is limited to 80 mg per day unless the patient was already taking 80 mg prior to the FDA change and labeling and then rosuvastatin there's a maximum of 40 mg per day and we just recommend that they continue all current limitations.

Michael Johnson: Any discussion on this? This is what we are currently doing?

Donna Sullivan: Yes, that is correct.

Michael Johnson: And so I'm going to motion that I move that the Medicaid Fee-for-Service Program implement the limitations for the statin drug class listed on slide 24 as recommended.

Lisa Chew: I second.

Amber Figueroa: I just had a question. I find it interesting to see that the atorvastatin use increased so much in 2016 compared to 2015. Does anybody have ideas about that?

Donna Sullivan: My thought is the managed care plans made a change because if you look at the rosuvastatin utilization was, I think, actually... well, it slightly decreased so that is my only possibility is something happened in managed care.

Amber Figueroa: Somehow it became easier to get atorvastatin and harder to get...

Donna Sullivan: Or it became harder to get rosuvastatin. Rosuvastatin is significantly more expensive than atorvastatin right now. It's possible that the managed care plans, you know, started preferring atorvastatin over rosuvastatin. We've had atorvastatin preferred for years. Other than there being an increase in prescribing it that would be the only... in increase of people being screened and trying to have lower levels of cholesterol, that could be a possibility, as well.

Woman: The other possibility is that there are some patients that transitioned from simvastatin to atorvastatin, as well.

Donna Sullivan: That's true because you can see the decrease in utilization across that drug as well.

Diane Schwilke: Yeah. I think all three you're kind of seeing a push towards a more higher potency use in general so all of those kind of moved into atorvastatin.

Donna Sullivan: Okay. A vote?

Michael Johnson: So a motion on the table? All in favor say aye?

Group: Aye.

Michael Johnson: All opposed same sign. All right. It passes. Okay.

Donna Sullivan: The next class is the NSAIDs and it will appear momentarily.

Woman: Shall we do lunch? It was supposed to start after lunch.

Donna Sullivan: It is close to 12. Do we want to keep going or do you want to stop and take your lunch? Lunches are here.

Woman: Let's stop and take lunch because you have more NSAIDs.

Michael Johnson: This is a good time for lunch.

Donna Sullivan: What time do we come back?

Michael Johnson: Let's do an hour. So we'll re-adjourn at 12:45. Thank you.

We're going to reconvene the Drug Utilization Review Board. I think we are... are we at NSAIDs?

Donna Sullivan: We are at NSAIDs.

Michael Johnson: And there are no stakeholders for NSAIDs.

Donna Sullivan: No stakeholders. Thank you. Again, we're looking at the NSAIDs, so the preferred products that are NSAIDs and...

Man: [inaudible]

Donna Sullivan: Say that again. It is an archived class just to let you know. The utilization on slide 27 ibuprofen obviously is the most utilized product followed by naproxen and it looks like meloxicam. I'm going to remind all of you that it does include managed care utilization.

Our current limitations is that they must try two preferred products before a non-preferred product will be authorized. We have a prior authorization for Cambia, Flector patch, Pennsaid, Voltaren gel, Solaraze gel and the Rexaphenac cream according to the FDA approved indications and I have those listed below. And so one of the reasons why we're doing this is that we were seeing patients that were... or prescribers that were prescribing it to be used in areas of the body that were not... that had not been studied. So we don't allow it for those indications.

There are dose limits on Toradol or ketorolac. They can have a maximum of a 5-day supply at a time and I think that's every 30 days. The Celebrex or celecoxib we have a maximum of three capsules or tablets per day for the 200 mg strength and then two per day for all of the other strengths and I think the 200 mg strength is the one that has the indication or the dosing schedule for prevention. That's why it is different. The recommendation is to continue the current prior authorization criteria in dose limits, but require that they try all the preferred drugs with the same indication before a non-preferred drug would be authorized unless it is contraindicated or not clinically appropriate. Questions from the committee? Comments?

Jordan Storhaug: Again, I have concerns about trying all the preferred drugs. It's a very long list, 20 different medications of preferred drugs. I'm sure not all those indications are... but it seems like an unreasonable barrier to me for a provider to have to try to figure out what all the possible drugs are before they be able to try a non-preferred drug.

Donna Sullivan: Is there a particular drug that you're concerned about? Because most of these are generic and I believe most of them are preferred already. Other than the celecoxib at this point in time.

Jordan Storhaug: Yeah, I guess that probably would be the only one on there. In general I think that is probably a principle. There's probably not a large benefit from it. But for people who might benefit from Celebrex to do 20 seems like an awful lot to try.

Donna Sullivan: Is there a particular... just to kind of push back is there a particular indication, because we can do an expedited authorization like if there is a... is there a particular clinical situation where you would rather them have celecoxib than one of the others that we could make a criteria around that versus opening it up to everyone?

Jordan Storhaug: I guess...

Donna Sullivan: Because the other... and this is how it would work is that you wouldn't have to... if you tried two and it didn't work and you wanted to go to

Celebrex or celecoxib you could request an authorization for it and if you have a clinical justification of why you need this one as opposed to all of these others, if you can establish why this one is the best next step then that would be considered for coverage. It's not just an automatic.

Jordan Storhaug: The explanation then is that they would just have to go through the expedited... I guess the corollary to that would be... would 10 medications... trying 10 preferred medications be enough from the committee that you feel like that is enough to try to go to something different?

Donna Sullivan: That's up to the committee.

Nancy Lee: I just had a follow-up question about... will be authorized unless contraindicated or not clinically appropriate. Is there some criteria for how you are defining not clinically appropriate?

Donna Sullivan: Um...

Woman: That is previous terminology that had been agreed upon. So that is just...

Donna Sullivan: It's pretty much just the standard language that we put in there. I mean it would be... if you really needed a selective... a COX2 and you're... and using a non-selective product would be not appropriate. It's not necessarily contraindicated, but it's not necessarily appropriate in that particular patient or there could be a drug interaction.

Michael Johnson: Just kind of a clarification. With the generics first policy, would that supersede non-preferred brands? I mean like if... so if Celebrex stated non-preferred there are other generics you'd have to try. Don't we always have to try all the preferred generics?

Donna Sullivan: The statute, I believe how it reads, is that for the first course of therapy they can try... we can require a generic before a non-preferred brand with the same indication. Other than the topical products all of the products are generic. I think the issue is, is that the generic celecoxib is still significantly more expensive than the ibuprofen, naproxen.

Jordan Storhaug: So tell me if I'm wrong, but this is a change in policy in that right now they only have to try two medications before they are able to use a non-preferred and we would be changing it so that they would need to go from two to all?

Donna Sullivan: That is correct.

Lisa Chew: My sense is that I think there's a lot of choices in the generic preferred for providers and that if there is a process with the expedited authorization for celecoxib for those... for a unique condition or unique circumstances where a patient needs that. I'm actually comfortable with this recommendation. I guess my sense is, you know, where I see a lot of the barriers to prescribing is the Voltaren gel where we try to use non-opiate medications for pain and maybe the patient isn't a good candidate for an oral NSAID either for renal function or GI bleeding, but it sounds like if they had contraindications to an oral NSAID that you could get the Voltaren gel through some prior authorization process.

Donna Sullivan: Yes. And if you were going to have a clinical situation where celecoxib would be most appropriate I would look to you to point out what those clinical situations are, because I'm not sure, you know, if it's more effective or safer than diclofenac or even meloxicam and [inaudible] that are also the semi-selective products, as well, that are preferred. We can call something out specific for celecoxib if you want to have a specific limitation that, you know, celecoxib you must try, you know, diclofenac, nabumetone, meloxicam or something of that nature—the other... the semi-selective products.

Michael Johnson: It looks like there is a really small use of celecoxib.

Donna Sullivan: And that's because it's not preferred.

Michael Johnson: Exactly. And so do you have any idea, numbers wise, how many in a year you get, or a month maybe? Ten people? Five people? Like a small number?

Donna Sullivan: April is shaking her head. Less than that.

April Phillips: We get very few requests.

Michael Johnson: Okay.

April Phillips: I don't know how many our system catches that they previously had... or previously had two preferred products and then it allows it to go through, but when it comes to prior authorization reviews we get very few.

Michael Johnson: So right now we're just... after two they are just automatically getting it.

Donna Sullivan: Right. I mean we can say four or five. It's up to you or you can leave it at two.

Michael Johnson: I mean I kind of agree with Lisa. I mean if there's a way to get it if you really need it, but there are so many other choices that it's hard to believe Celebrex is the best.

Donna Sullivan: With Medicaid there's always a way to get it.

Michael Johnson: I kind of tend to agree with Lisa that... I mean I'm okay with saying you should try all of our preferred before you get a non-preferred unless... unless you clinically think you need it. Then there's a process. I think that's reasonable.

Donna Sullivan: Uh huh.

Jordan Storhaug: I'm fine with that. The only question I have is we're putting up the barrier, but it doesn't sound like there's going to be much benefit in either way to be able to do this. It doesn't sound like we're probably moving that many people... gonna be moving that many people away with this process either and so I guess I kind of feel like it is a barrier without much benefit, but without much harm either. So I will support it in either direction.

Michael Johnson: Any other comments? Discussion? You okay with the new proposal or what are you...

Jordan Storhaug: I am fine with the new proposal.

Michael Johnson: Okay. Do you want to read it?

Jordan Storhaug: Sure. I can do that. I move the Medicaid Fee-for-Service Program implement the limitations for the NSAID drug class listed on slide 29 as recommended.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. Okay. The motion carries.

Ray Hanley: Michael, if I could just remind the folks to identify themselves before they talk for the prescriber. I'd really appreciate it. Thank you.

Michael Johnson: Ready for colchicine?

Donna Sullivan: Yes. Now the colchicine policy. So our current limitations for colchicine for acute gout is that they have tried and failed an NSAID, or prednisone, or they have a history of GI bleed or ulcer, or they have renal disease. For chronic hyperuricemia/gout prophylaxis that they have tried and failed allopurinol, probenecid, or probenecid with colchicine combination, or the history of renal disease and there's a maximum dose of 1.2 mg per day. The familial Mediterranean fever there is a maximum dose of 2.4 mg per day.

This is our utilization and most of the utilization is in the generic colchicine. There's a new product called Mitigare that has recently been approved and the Colcrys that has been around for several years once the FDA required that they go back through the approval process. So what I'm looking at here is just the... I'll show you the cost of these drugs and the reason why I'm making this recommendation because this isn't a PDL class I need the DUR Board to tell us to prefer one product over another. But we're looking at almost a dollar per tablet difference in the colchicine tablets and capsules compared to the Colcrys and the Mitigare

products. I'm recommending that we remove the PA criteria. The reason being is that we're approving almost 99% of these requests and that Colcrys and Mitigare would remain on prior authorization for use after the less-costly... because there are less costly alternatives that are the exact same drug. And then we're recommending just setting a maximum daily supply regardless of diagnosis at 2.4 mg per day. So it would average about... the average utilization is about 1-1/2 tablets per day right now.

Were there any stakeholders?

Michael Johnson: No stakeholders.

Donna Sullivan: Okay. So that is what's being recommended for the colchicine.

Michael Johnson: I mean these are the exact same chemical structure.

Donna Sullivan: Yeah. They are all colchicine. I believe that the Mitigare is just another brand that has come out. I don't remember if it went through the NDA process or the abbreviated New Drug Application process, but they are exactly... the colchicine capsules, I believe, are the generic for the Mitigare where the colchicine tablets are the generic tablets for Colcrys and it's the same product that has been around for a thousand years.

Lisa Chew: Just for my knowledge I'm just curious what the abbreviation on the columns stand for the AWP, NADAC.

Donna Sullivan: Oh, average wholesale price and then the national average drug acquisition cost. CMS does a survey because Medicaid is required to pay the pharmacies their acquisition cost plus a dispensing fee. So CMS has been doing a survey of retail pharmacies on a NDC by NDC basis, product by product basis asking pharmacies to report what their acquisition cost is and so this is just the average of all of those pharmacies that replied in the country. And then WAC is wholesale acquisition cost, not to be confused when I say WAC, Washington Administrative Code. So you need to know which WAC I mean. I try very hard not to talk in acronyms. So call me out when you don't understand what I'm talking about, please.

Michael Johnson: I'd be willing to bet 10 years ago this was pennies per tablet.

Donna Sullivan: I know, it was.

Michael Johnson: But having said that...

Donna Sullivan: I remember the phone calls.

Michael Johnson: It's like other medications that are generic that have been around for years. So I would... I'm willing to entertain the motion here unless there is other discussion. We could talk all day about how long old drugs have cost more over the past few years. I move that the Medicaid Fee-for-Service Program implement the limitations for colchicine listed on slide 33 as recommended.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Man: Is that slide 33 or 31?

Michael Johnson: Actually 31.

Amber Figueroa: No, we're doing new ones.

Michael Johnson: Sorry. It's 33, yeah. We got it right. I think the next topic is cyclobenzaprine and there are no stakeholders.

Donna Sullivan: Okay. So we're looking specifically at cyclobenzaprine, but I thought I'd give you the array of preferred products for skeletal muscle relaxants in general, which are displayed on that slide. Here is our utilization. Most of it is in cyclobenzaprine and methocarbamol. So what... with the skeletal muscle relaxant class itself we have generics first that we must try one preferred product before a non-preferred will be authorized.

Carisoprodol requires prior authorization. The P&T Committee for many years and the most recent one is in June of last year has recommended that carisoprodol not be covered because of abuse concerns and it is only indicated for acute treatment and for us to even consider covering it they must try all other skeletal muscle relaxants. That was your recommendation and that's been that way for many, many years. I don't think we have any utilization of it. Or if any very little. Our recommendation, again, we're moving towards, you know, stepping through all the preferred products before a non-preferred product will be authorized unless contraindicated or not clinically appropriate.

Specific to cyclobenzaprine there's a 7.5 mg tablet that is the generic for one of the other cyclobenzaprine follow along products that came out that cost \$3.70 per tablet compared to the 5 and 10 mg tablets that are pennies per tablet. So we're recommending to place the cyclobenzaprine basically on a prior authorization and not cover it unless there is some reason why a patient couldn't take the 5 mg or 10 mg or some combination of 1-1/2 tablets or whatever in order to get to a 7.5 mg dose. We're not really sure how significant that 2.5 mg difference is either up or down from the other strengths. So our policy is to recommend... is recommending this cyclobenzaprine, as well as the recommendation on 37. And I'll go back to the preferred products if you want to look to see what's preferred.

So right now baclofen is preferred, as well as Robaxin, and cyclobenzaprine and tizanidine.

Amber Figueroa: When you look at the use of cyclobenzaprine 150,000 people using it, I don't think that makes good sense of our resources to have to approve those. I mean as a prescriber that's my first go-to. Can we not just do prior auth or whatever for the 7.5 mg?

Donna Sullivan: That's what we're recommending. That the second... only the 7.5 mg strength will be on prior authorization.

Amber Figueroa: Okay. Thank you.

Donna Sullivan: So not the 5 and 10s. No, we would never do that to ourselves.

Amber Figueroa: Okay, okay, okay.

Donna Sullivan: I'm sorry I didn't make that more clear. I don't know how many patients we have on the 7.5 mg tablet, I don't think it's a lot, but we just want to kind of close that door before it becomes a problem.

Amber Figueroa: I move that the Medicaid Fee-for-Service Program implement the limitations for skeletal muscle relaxers and cyclobenzaprine listed on slide 37 and 38 as recommended.

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

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion passes. I think next up is deflazacort and there is a stakeholder for that.

Ryan Pistori: I will be presenting the deflazacort policy. So for this presentation we'll go over a little bit of background about the disease state that this is indicated for, which is Duchenne Muscular Dystrophy and also a little bit about the epidemiology. Then after that we'll move into the evidence on the safety and efficacy of deflazacort and then lastly onto the clinical policy.

Just a bit of background, and if these slides look familiar, they are actually the same ones that I used for [inaudible] back in February, but I figured it would be a good refresher to go over it again and we can also use this background information for the next presentation, as well.

Duchenne Muscular Dystrophy is an X-linked genetic disease that affects the dystrophin gene. And so what that gene is, is it is kind of that big gray complex that's on the middle right of the screen. It sits at the end of the plasma cell membrane of the muscle fiber cell and the extra cellular matrix, which is above and so what this protein does is it helps protect this entire glycoprotein complex at the cell membrane. This is necessary for normal muscle function. So you can imagine that with the deletion of this gene or the protein that it's not able to function properly and it can

result in the degradation of muscle fibers, which then results in muscle weakness, which is the primary symptom of Duchenne Muscular Dystrophy.

So Duchenne Muscular Dystrophy usually manifests as muscle weakness in males at ages 2 to 3 and it typically gets a formal diagnosis around age 5 usually through a muscle biopsy or genetic test. And genetic tests are used now to help differentiate between Becker Muscular Dystrophy, which is BMD and Duchenne Muscular Dystrophy DMD. They are very similar but there are some differences between them that they are able to differentiate and just for the record the Becker Muscular Dystrophy is a slightly less severe form than the Duchenne Muscular Dystrophy. So with the muscle weakness it usually begins in the distal limbs and this weakness then can result in difficulty running, jumping and even walking. From the CDC it reports that about 82% of the patients with DMD are restricted to wheelchairs between the ages of 10 to 14 years. So these are kids that are very young that are getting these difficulties and as they continue to age they find it more and more difficult to move. As they continue to grow older they continue to get other conditions of muscle weakness such as cardiomyopathy which can cause heart failure and arrhythmias when they are in their teens and then can also lead to other respiratory, bone fractures and mental health as other complications. The most common cause of death with Duchenne Muscular Dystrophy is acute respiratory failure and this usually occurs in their 20s although recent epidemiology shows that some are getting into their 30s based on improved comprehensive care for these patients.

In terms of the epidemiology the prevalence from a study of four U.S. states seems to be about 1 in every 7,250 males between the ages of 5 to 24. And then there have been other epidemiology studies and the prevalence is pretty similar in Canada, Northern England and Wales. They are all in that general 1 to about 7,000 males in that age group. It is higher among the Hispanics and non-Hispanic whites than among the non-Hispanic blacks and based on our review of our fee-for-service population we are estimating that we have about 100 in our population and that we get about six cases by birth each year. So there are some coming in, some going out. We think it's going to be generally around 100 as long as our population remains the same.

So the standard of care with Duchenne Muscular Dystrophy is the glucocorticoids. This was realized in the 70s and has been used pretty much as the standard of care since then and has been shown to help improve motor function, pulmonary function and reducing the risk of scoliosis. So typically, like I mentioned earlier, the diagnosis with Duchenne is around age 5. So children usually start the steroids around age 7, but it's not all patients. Only about 57 to 69% estimated by the CDC and for Duchenne and Becker Muscular Dystrophy are treated with steroids and per the CDC prednisone is the most commonly used between 64 and 78%. But not just the glucocorticoids obviously when I was going through the disease earlier it effects a number of different organ system and so general cardiac, pulmonary, orthopedic, mental health, you get the idea. Those are part of the standard care as well. So in terms of treating the disease it's the glucocorticoids that have the greatest effect.

So for the evidence on the safety and efficacy of deflazacort we had DERP actually do a review of the evidence, the comparative evidence between deflazacort and prednisone for us and these are the results of their review. So they were able to identify four randomized controlled trials and through their grading system they found that these studies have very low quality evidence on the outcomes of muscle strength, motor outcomes, weight gain and cataracts, and those are the primary outcomes of these studies primary or secondary or the safety, but these were generally what is reviewed between the deflazacort and prednisone for the treatment of Duchenne Muscular Dystrophy. The reason they were rated as very low quality of evidence is that they had risk of bias and precision in lack of applicability and their lack of applicability is primarily because a lot of the studies that were evaluated in the U.S. were done back in 1993 to 1995 and so, you know, over the course of 24/22 years, you know, standard of care has changed and may not be as applicable in today's environment as it was, you know, 24 years ago. It's also worth noting that they were not able to find any comparative effectiveness for deflazacort and prednisone beyond two years of use for Duchenne Muscular Dystrophy.

The first trial that was identified in the DERP report was a trial that recruited boys who either had Duchenne Muscular Dystrophy or Becker Muscular Dystrophy and the reason that this trial included both is that back then they didn't have the generic tests and it was difficult to differentiate between the two subtypes. So for this trial they did include both, but they weren't able to report who had Duchenne or who had Becker in this trial. They study had 100 boys. I believe the ages were between 5 and 15 years and the study was two years in duration from 1993 to 1995. Through the study they were not able to find a statistically significant difference in muscle strength. Muscle strength was rated by the Medical Research Council scale score or in motor outcomes between deflazacort and prednisone, but for the safety data they did note that prednisone had more weight gain. The data for that, unfortunately was not reported and that the deflazacort group developed significantly more cataracts. They also note that 20% did not complete the study with 14 discontinuing to weight gain, although they did not attribute to which arm they were in. So some limitations with the study is that the 1995 analysis that was published only had 67 boys at the time. It was more of an interim just to see how the trial was going and they really didn't actually report much in terms of the evidence. In fact, they didn't even differentiate between who was on which arm. It just has a graph of all the patients together and shows differences in weight and differences in muscle strength and motor outcomes.

And then the completed version in 2000 was presented at a conference workshop. The next study was done at a similar time and this one was actually used as part of the FDA approval. As you can see, the second citation by Griggs is in 2016. So for this study they also had boys with Duchenne Muscular Dystrophy and Becker Muscular Dystrophy. They weren't able to differentiate back then. But this one had 167 boys I believe also between the ages of 5 to 15 and for this study the primary outcomes was at 12 weeks or 3 months and then they continued the efficacy and safety data for up to one year. For this study they found that both deflazacort and prednisone were significantly more effective than placebo for both muscle strength and motor outcomes, but there was no difference between the active groups at 12 weeks or at 1 year. For this study they did actually have data showing that the prednisone group had statistically more weight gain at one year with a mean difference of

about 3.4 kg between the groups. And that deflazacort also had slightly more cataracts. So for this study it was originally presented at the 75th American Academy of Neurology meeting, but it was repurposed and redeveloped for the FDA clinical review and published more formally in 2016.

There were a couple of studies published in 2000 for a trial that was conducted in 2000 and for this one there were only 18 boys that were recruited and this was studied over a two-year period. For this trial there was, again, no statistically significant difference in muscle strength or motor outcomes, but for this one they only really reported the information graphically and not with any robust data representation. And then for this study the prednisone group had more weight gain as a mean difference from baseline while the deflazacort group, again, had more cataracts. For this one it is worth noting that the authors did find that there was a statistically significant improvement at 12 months with prednisone over deflazacort, but the author suggests that this is because the patients in the prednisone arm with more severe disease dropped out so there was some level of bias in who continued on that study for up to one year.

The last randomized controlled trial that was found in the DERP review was a study in Iran in 2012 and for this one they had recruited 34 boys and the study duration was 18 months. For this one deflazacort had a statistically significant difference in motor outcomes at 12 months, but no statistically significant difference at 18 months and for this trial muscle strength was not evaluated. They also note that the prednisone group had more weight gain at 12 months and at 18 months. But for this trial there were some significant lost follow-up. About 18% of the deflazacort and 29% of prednisone did not complete the trial and they did not use an intent-to-treat analysis. The authors did not even report on randomization, blinding, or baseline characteristics. So for this one there is some issues with being able to compare these against some of the other earlier clinical trials.

There have been three systematic reviews of the evidence of deflazacort versus prednisone for the treatment of Duchenne Muscular Dystrophy. It's worth noting that each of these systematic reviews had different

inclusion criteria and different levels of selection. So none of these reviews included all four trials. In fact, most of them only included about two of the trials that we talked about. Conclusions of two of the trials found that deflazacort and prednisone were similarly effective in muscle strength and motor outcomes, but deflazacort had less weight gain and that the third one was not able to find enough evidence to make a conclusion for motor outcomes and had very low quality evidence that prednisone was causing more weight gain.

In terms of clinical guidelines the American Academy of Neurology released guidelines in 2016 for glucocorticoid treatment for Duchenne Muscular Dystrophy and this guideline was reviewed by DERP and found to have good methodologic quality for a guideline, but the only randomized control trial that this medical society or at least included in their guidelines was the 1 in 2,000 that only included 18 patients. So the other ones were not included in this review. But they also did include a placebo-controlled trial so there is a little bit more evidence for the prednisone versus placebo and deflazacort versus placebo. And so this guideline as you might imagine was not able to recommend one corticosteroid over the other and cited low confidence in the quality of the comparative effectiveness, but it did go on to say that it gave B level evidence, which means a moderate value of benefit relative to risk and moderate confidence in evidence for prednisone to improve strength and improve pulmonary function. But all the other outcomes were evaluated for both prednisone and deflazacort received C level evidence. So that includes things like motor function, weight gain, cataracts, and other general safety. And so C level evidence means a small value of benefit relative to risk and low confidence of evidence.

About the price of Emflaza. Emflaza was approved by the FDA in December of last year and Marathon Pharmaceuticals who went through the FDA approval had announced a list price of Emflaza in February of this year to cost approximately \$89,000 per patient per year. This had a bit of controversy in the news. In fact, having a letter from Senator Bernie Sanders and Senator Cummings of Maryland requesting additional information about the pricing of this medication. It also had a bit of backlash from the Duchenne Muscular Dystrophy community, as well and so they withheld the price and said that they were going to re-evaluate

what they would charge going forward. In March, so just last month, PTC Therapeutics who is also developing another medication for Duchenne Muscular Dystrophy announced the purchase of Marathon Pharmaceuticals for \$140 million. So there has been no update on what the price has been since the initial release and now that it is with a new company we can expect to hear a new price when it is being prepared to launch. But the launch date hasn't been announced and there has been no new pricing information since the initial release in February of this year. Just to go into a little bit more detail of what that \$89,000 per patient per year is, the AWP or the average whole price for a single tablet was \$294. Just a note, the new AWP has not been announced yet. And since deflazacort is approved by the FDA to be dosed at .9 mg per kilogram per day that the... that it is possible that for children above 88 pounds that they may require multiple tablets per day and that the cost may be more than the \$89,000 per patient per year depending on how much the patient actually weight and how many tablets the patient needs to use to get to that appropriate dose. So deflazacort has been available to some patients. They have been importing it through other countries. The one that was cited most commonly in the news is that there is a pharmacy in the United Kingdom and that would cost about \$1,000 a year per patient to import the drug. For prednisone it is available at a maximum allowable cost of \$.05 per 20 mg tablet and so if we're trying to estimate how much it can cost per year if we're estimating about three tablets per day or about 1,100 tablets per year that's about \$55 per patient per year.

So the conclusions from the review are that based on the randomized clinical trials and the systematic reviews and treatment guidelines is that there is very low quality evidence that there is no difference in efficacy between deflazacort and prednisone and that there is very low quality evidence that prednisone is associated with more weight gain than deflazacort, but the clinical significance of the weight gain has not been studied or evaluated. I can go into that more if you have questions. And that prednisone is a lower cost alternative based on current pricing information.

So for the clinical policy that we're proposing is that prednisone would be the preferred corticosteroid for the treatment of Duchenne Muscular

Dystrophy and the rationale is that prednisone is a lower cost, equally effective alternative and that deflazacort would be reviewed on a case-by-case basis to determine medical necessity for the treatment of Duchenne Muscular Dystrophy. This is because there is very low quality evidence on its safety and efficacy comparative to prednisone and that deflazacort will not be approved for any off-label indications. And so deflazacort, as you might imagine, is a steroid and so it can be used for a number of other indications, however it is has not been evaluated by the FDA for use in the U.S. and we want to be looking to approve it for things like allergic conjunctivitis, epilepsy, juvenile rheumatoid arthritis, rheumatoid arthritis or solid organ transplant, just to name a few of the off-label uses.

Here are the citations that we used for this report. I can open up to the DUR Board for any questions or discussion.

Michael Johnson: There is one stakeholder, Jeff Forshey. You will have three minutes. If you could just reiterate where you are from when you get on the mike.

Jeff Forshey: I'm Jeff Forshey. I'm with Marathon Pharmaceuticals and I want to say thanks to Donna and Ryan for letting us present our clinical information about a month ago. We have no further clinical comment today. I think you covered it nicely. One thing I wanted to note for the group was that we did have a local EAP site at Seattle Children's. We have about 40 to 50 patients in the EAP. Roughly half of those kids have tried and discontinued prednisone so I wanted to make you aware of that and you may be seeing some prior auths, some attempts at some prior auths coming through and we would just ask you to weigh the consideration of these kids who have tried and discontinued prednisone and carefully decide whether or not you're going to re-challenge them or give a consideration to them being able to continue on Emflaza. Thank you.

Michael Johnson: Thank you. All right.

Donna Sullivan: I'm sorry. We didn't use our standard motion in this particular presentation. So if you're... when you're ready to make your recommendation if you could just craft a motion similar to the ones that

we used in the previous DUR presentations that would be helpful. Thank you.

Amber Figueroa: I move the Medicaid Fee-for-Service program implement the limitations for deflazacort on slide 19 as recommended.

Catherine Brown: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carries. I think this brings us to our last topic of the day and there is also one stakeholder for this as well.

Donna Sullivan: Next we're going to talk about Exondys 51. We talked about this in February and there was a policy that was reviewed by the board and the reason why we're bringing it back is since then we have really looked at the data that was submitted to the FDA and the evaluation from the FDA reviewers and so we felt that it was appropriate to really bring this back and re-visit the current clinical policy. So that is why we are looking at it again today.

So we'll go over an overview of Exondys 51. I'll look at the FDA findings. I'm going to walk you through our medical necessity determination so you can kind of see how this drug will be reviewed and then make some recommendations to the policy.

Exondys 51 or eteplirsen is an antisense oligonucleotide that binds to the exon 51 of the dystrophin mRNA. Ryan had a really great slide in his presentation. I'm not going to go back into that, but it really blocks the translation during the protein synthesis. This 'skipping' allows for the production of that dystrophin protein that Ryan was talking about. It's not a fully functional protein. It's a little bit shorter, but it does allow for some creation of dystrophin. Approximately 13% of patients with Duchenne's Muscular Dystrophy have a gene or the phenotype that's amenable to the exon 51 skipping. It is administered by IV infusion at a

dose of 30 mg/kg per week and there's no defined end-point for when a patient would stop therapy either that they are progressing or that they're... indication that it would be a cure. So the FDA approved this medication back in the fall of 2016 and in the label itself, I just put around the red box, that it is shown that there is no clinical benefit. There's no evidence that supports a clinical benefit from using the exon 51. So it was approved on its... the evidence that showed that there was a slight statistically significant increase in the amount of dystrophin protein in the patients that were in one of the studies.

I'm going to go through the FDA review and I want to caveat this that this is not my interpretation of the data. This is the interpretation or summary review of the two evaluators from the FDA that interpreted that actual data, did some of their own statistical analysis with the data and then an independent, a third reviewer, evaluated their findings, the two reviewer's findings, and then summarized and confirmed whether he agreed upon their conclusions from looking at the data. So I just want to make that clear. This is not my interpretation of the data. This is just a summary from the FDA review.

One of the primary studies – it's Study 201 and 202 where 12 patients were originally randomized into three treatment arms. There were four in each arm. One of the arms received 30 mg/kg/week, 4 patients received 50 mg/kg/week and 4 patients were started on placebo for 24 weeks and then they were switched to either the 30 mg dose or the 50 mg dose for an additional 24 weeks after that. The study was then... that was Study 201 and then Study 202 was an extension of those 12 patients being treated over the course of about 3-1/2 years. During the study the patients underwent muscle biopsies at baseline and at weeks 12, 24, 48 and 11 of the 12 patients received another biopsy at 184 weeks.

So the results of the trial that was reported by the applicant or the manufacturer was that the 30 mg cohort and the 50 cohort after 48 weeks were found to have a statistically significant increase in the dystrophin-positive fibers compared to the pre-treatment group. Meaning the baseline or the placebo group. And subjects in the placebo cohort that were randomized to get either the 30 or the 50 mg dose at 24 weeks... at the 48-week period so they have then been receiving

eteplirsen for 24 weeks. They were also found to have a statistically significant increase in dystrophin-positive fibers and based on these results the company had a publication or a press release and it essentially said that substantial increases in dystrophin in Study 201 were initially reported in a publication that stated the percentage of dystrophin-positive fibers was increased to 23% of normal. No increases were detected in placebo-treated patients. Even greater increases occurred at 48 weeks, 52 and 43% in the 30 and 50 mg/kg cohorts respectively. So that was... that publication was... or that was published after this study was completed.

Upon review with the FDA there were... the FDA was concerned with some of the methodological procedures with the company when they went into investigate the facility and they required that there be a re-analysis of those biopsies by three blinded reviewers. The original review, the reviewers were not blinded originally and then when they had the first results they changed some of the parameters and controls of the samples and then re-reviewed them again and it was that second review that supplied the statistically significant results. So on the re-reviewing this by the three blinded reviewers the 50 mg/kg arm only had increased from 15% at baseline to 17% at week 12 and 25% at week 48. The placebo group that then received the 50 mg dose had no increase in the distributive and positive fibers between baseline and week 48, which is really 24 weeks of active treatment. There was no difference between the 50 mg/kg group versus placebo at week 12. The 30 mg arm had a statistically higher amount than placebo at week 24, but the reviewers' comments, and this is just taken out of the report was, "However, the nominal p-value of .002 for the comparison between eteplirsen 30 mg and the placebo group can only be considered exploratory, as there was no plan to control the type-1 error due to multiple comparisons, and because the other primary endpoint comparison between the 50 mg/kg group and placebo was negative." He was thinking that even though it looked like it was statistically significantly higher at the lower dose and because of multiple comparisons you couldn't take away much from that finding.

This is just the table of the original review from the applicant and the re-analysis by the three blinded readers and it just shows the differences

where the 30 mg, the baseline was originally... was reported as 18 and the re-analysis, the baseline was 14 and at week 24 it was 41 compared to 27 and then week 48 it was 70 compared to 23. So there's a pretty big difference in the results of the analysis based on the two different analyses that were conducted.

As a result of that the FDA has basically said that the Western blots from the first three biopsies had over saturated bands, did not have appropriate controls or quality control metrics and so they were essentially uninterpretable. So they basically threw out those results and said there is nothing that you can really garner from those first three biopsies based on the methodology that was conducted on them.

The applicant then... the FDA recommended that they try to look at the week 180 biopsies compared to the actual baseline. The reason why is the fourth biopsy that was at week 180 they agreed upon a new standardized approach on how to do that Western blot that was accepted by the FDA. So they wanted to check and look at that week 180 compared to baseline. Unfortunately, at week 180 only three of the 12 patients had a baseline sample that was still available and only two of those three patients had a biopsy at week 180 and just for note that was patient 13 and 15. The week 180 biopsy where n=11 they were compared to the three eteplirsen-treated patients and then six external controls. So what the applicant did is they went to another randomized controlled study... or another study, I'm not sure if it was randomized. They went to another study they were conducting and took six patients from that group and got their baseline samples to compare the 180 week samples from the Study 202. So at baseline the three eteplirsen patients they were 1.1, 2.6, and 0.2 and then compared to the original analysis their baselines were 11.7, 17 and 18. So there was some difference between the original baseline analysis and the second... or the re-analysis at 180 weeks of those baseline samples and the thought behind that was they had been frozen for over three years, or close to three years and there was concern about whether or not there was some degradation of the dystrophin protein. There wasn't a lot of, I guess, comfort or confidence in why these numbers were so different.

Then when they compared the week 180 biopsies to the three baselines and the six external controls there was a mean difference of about 0.93, or actually the dystrophin level after the 180 weeks of treatment was 0.3%.

Additional information that was cause for concern regarding the sample and comparing the week 180 biopsies to the external controls was that the week 180 biopsies come from the deltoid muscle while the biopsies for the external controls and the preserved baseline muscle samples came from the bicep except for one patient. And it is known that the deltoid and calf muscles are known to atrophy in DMD so they would have potentially less dystrophin to begin with. There's also evidence that shows different muscle groups display different amounts of dystrophin in them, even in normal healthy patients. After looking at the comparison to the control group the reviewer said it's not clear to what extent differences in the dystrophin expression between muscle groups may have contributed to the change in dystrophin reported in the fourth biopsy and there was concern that the untreated controls from that external study were not randomly selected, that they were just picked from the study to be used as controls.

As a result of that and the lack of confidence in the evidence so far the FDA asked the company to look at some baseline samples compared to a 48-week treatment in a study that was already ongoing and that's called the PROMOTIV study. So that's an additional study. It was non-randomized. It's open labeled and there is an untreated control arm and the treatment groups are just the 30 mg/kg/week in DMD patients that are amenable to exon 51 skipping versus an untreated group of DMD patients that are not amenable to exon 51 skipping. The nuance here was that as a result of that publication of the Study 202 results that showed that big increase in dystrophin that there was a lot of concern about the ethics of doing another larger randomized-controlled placebo-controlled trial. So they decided that they were not going to do that because they felt it was unethical if the drug actually worked to not give it to everyone. So the untreated group of DMD patients not amenable to exon 51 skipping, exon 51 is not targeted to their phenotype so it wouldn't work. You wouldn't use it in those patients. However, the patients with DMD that have different phenotypes are typically not as

severe disease to begin with and they have a different progression, different progression of the disease over time. And in the demographics there were 13 patients at the time. It's an ongoing trial so they are still enrolling, but they looked at those 13 patients and they were males from 7 to 16 years old, they were diagnosed with DMD, they were on stable corticosteroids for at least 24 weeks, they had intact right and left alternative upper muscle groups, their mean 6-minute walk test distance was at least 300 meters meaning that they could walk 300 meters in a 6-minute time, they were stable pulmonary and cardiac function with the predicted values that are listed there. And exclusions were anybody that was previously treated with a gene therapy in the last six months or pre-treatment with an RNA antisense agent, or a patient that had major surgery within three months and those that had clinically significant illness.

So the results, the Western blot analysis between baseline and 48 weeks showed an increase from a mean of .16 to a mean of .44 of the healthy normal subjects, meaning the control group. So there was a mean change of .28%, which was statistically significant even though it was a small increase and to note that most of the patients, 60% of those 13 had no increase in dystrophin levels at all or it was less than detectable. One patient had an increase in dystrophin greater than 1% and no patient had an increase in dystrophin greater than 2% from this particular study.

So that is kind of a summary of the effect of Exondys 51 on the biomarker and now I'm going to talk about the evidence on the actual functional status. So what does this translate into a clinically-significant or functional status for these patients?

So Study 201 had a secondary endpoint that was the change in the 6-minute walk test from baseline after 24 weeks of treatment. Study 2 looked at the comparison of the 6-minute walk test distance at 48 weeks between patients who were originally randomized to receive eteplirsen to those that were originally randomized to receive placebo, but then were converted to eteplirsen either 30 mg/kg or 50 mg/kg.

So the results in Study 201 there was no statistically significant difference on the change from baseline to 24 weeks in the 6-minute walk test

distance between the two treatment arms or placebo. In Study 202, again there was no statistically significant difference. However, two of the patients in the 30 mg/kg group were unable to ambulate soon after the study initiation and they were excluded from the analysis. Once they were excluded from the analysis the company did a post hoc review looking at the six patients that were still able to ambulate at the end of the study at 48 weeks compared to the group that originally received the placebo to eteplirsen arm.

They claimed in the report that 48 weeks of treatment with eteplirsen resulted in unprecedented and clinically meaningful 67.3 meter clinical benefit on the 6-minute walk test compared to placebo for 24 weeks followed by eteplirsen for 24 weeks. The FDA determined that this did not meet scientific quality evidence due to it was being a post hoc analysis that there was post randomization exclusion of two patients that lost ambulation and also the challenges of bias from an open-label study and such a small number of patients that were in it. So as a result of this the FDA determined that there was no evidence of clinical benefit based on this study.

So the company then compared the results from the Study 202 to Duchenne's Muscular Dystrophy registry so there was a post hoc comparison of patients in Study 202 up to 144 weeks to a natural history cohort of patients that had not been treated with eteplirsen that were only being treated with corticosteroids and other clinical management and they were the Italian DMD Registry and the Leuven Neuromuscular Reference Center registry, which I think is in Belgium. So there were 13 external controls that were matched to the patients on the use of corticosteroid or not. They did not look at the dose. It was just yes, you used it, no you didn't. The sufficient longitudinal data for the 6-minute walk test was available meaning that they had enough years and observations of the test. They had to be over... equal to or over seven years of age. They had to have the genotype amendable to exon skipping and more specifically amendable to the exon 51 skipping. However, the patients did not match for baseline 6-minute walk test distances.

The baseline characteristics between the two groups were pretty well matched when you looked at the age, the height and the weight. The

review was concerned because the mean age of the initiation of the corticosteroid therapy was one year older in the control group compared to the eteplirsen group and that is notable because we know that the... if you can preserve function younger you're more likely to do better when you're older. That was a key concern of the reviewer. In addition, the control groups were often on like a sub-optimal steroid regimen therapy. So instead of having like a daily high dose they might have been on every other day or two days a week. They weren't on the same comparable regimens that could impact the outcome. And then in addition the North Star Ambulatory Assessment or NSAA scores at baseline were lower in the control group than they were in the treatment group, which means that they were already, you know, had already progressed more than the treatment group from the beginning.

So I'm going to go through some data and some graphs and I don't know how easy they are to read on the screen or in your handouts. So if you have questions let me know and I will try to explain. I think I might have a clearer view than you do.

This was just a graph from the 6-minute walk distance meters, which is on the Y axis according to the number of years of treatment the patient has been on, which is the X axis. So the yellow line is the external control group and the blue line is the eteplirsen treatment group. So what it shows is that after the first year they were... it looks like they are progressing about the same. It appears after the first year the eteplirsen group looks to be stabilizing a little bit through about year three and then it goes into a slight decline. Whereas the control group started a pretty rapid and steady decline after year one.

So some of the concerns the FDA reviewers had about the comparison to the DMD registry was that the identification of the registries and the selection of the control group occurred three years after the completion of the Study 202. So the treatment group the results were already known when... and so there is concern that was there bias in selecting which registry to control or to compare these patients to? The differences in disease severity at baseline could also affect the outcomes and I'll show you a graph of that in a few minutes. The interventional... there's interventional clinical trials going on right now not just with the

eteplirsen but there's another medication that is undergoing clinical trials and there was concern that some of the DMD patients that originally enrolled in this observational study disenrolled to go enter into the clinical trials because they met the criteria. You're going to remain observational or go be in a clinical trial that might actually help you improve. So they did see quite a bit of disenrollment from the observational study. When you were looking at the data, and we'll look at it, there is considerable overlap between the 6-minute walk test results for the eteplirsen treated patients compared to external controls, which the reviewers then started to ask the question, 'is it any different than what you would have normally expected?' and we'll look at that.

This is the first graph and again if you have any questions, let me know. What the reviewer did is you have the 6-minute walk test distance on the Y axis and then the number of years treated on the X axis. The red lines are the eteplirsen treated patients. The black lines are the control group. And so what they did is they plotted for each individual participant in the study, which... what group that they... where they lay. I think I can go up here. So if you look at this line here, this patient started off at 200 meters at a year. It looks like they improved slightly and then rapidly declined by year two at the next observation. So this treatment group... this person in the treatment group, actually these two are the ones that I mentioned that lost ambulation early on. They went into this rapid decline soon after entering the study and lost ambulation within the first year. And so here we have a patient that's in the control group that was about 450 meters, improved a little bit, and then started declining rapidly at about... shortly after one year through year four and then lost ambulation at age five. You can see that these treatment patients here are somewhere between the best patient that was in the control group versus, you know, the worst patient. So there's a lot of red and black overlapping. So that's what the reviewer was talking about, the overlap in the six-minute walk test. There's not a clear bifurcation of the two different groups.

Looking at it in a different way the reviewer looked at it and plotted, again, the 6-minute walk test distance on the wide graph, but now the X axis, and I'm sorry the label fell off, it's years. So a patient if they were 8 years old, 10 years old, 12, 14, 16. So the graph starts like we'll look at

this line. This patient started at 7 years old. Shortly after 8 it looks like they were improving on the medication and then they started this slow decline and it follows down into about here. So not quite reaching 12 years old they are losing ambulation. These two patients are the two right here that lost ambulation early. They started at about age 10 in the study and then lost ambulation and this patient was 7 years old in the control group and lost ambulation after the age 10 and this line here would be a 10-year-old that started in the control group and then, you know, got better and then slowly progressed. So that's kind of how you read it. Where the line starts is at the age of when they entered the study.

I just copied and pasted out of the text of the FDA report. He says it is noteworthy that although only two eteplirsen treated patients have lost ambulation by the time of cutoff, four patients younger than age 14 at the time of their last observation appear to have a disease course extremely close to that of controls of similar age and appear very likely to be on the path to loss of ambulation before or by the age of 14 and in fact one of them recently did. So he's talking about these four patients right here. So this one, this one, this one and this one in this blue box right here. They are basically on the same trajectory as the control group that is grouped around them. The other observation that he made was that two eteplirsen treated patients identified in the purple hexagon, so these two up here, still ambulatory after age 13, but having not yet reached age 14 at the time of their last observation appear to have a course no different than the two control groups. So there are these two control groups up here that are in that same area. So they are on relatively the same trajectory as the treatment as is the control. So this is the... the reviewers are starting to question whether or not the drug is actually doing anything even though it may increase the dystrophin. Is it actually making a difference clinically?

So the reviewer then went to look at the four individual patients that were still ambulatory at the end of the study. I'm not going to review all four of them for the sake of time, but I'm going to look at the two that had the highest 6-minute walk test distance after age 14. So patient 6 had the longest 6-minute walk test and what they have looked at is not just the 6-minute walk test, which is the blue line, but they looked at all

of the functional status measures that are in that North Star Ambulatory Assessment and the red line is the time to rise. So that is the time to actually get up off the floor. Then the NSAA total score, which is kind of a summary of all of these is the yellow line and then the green line is the run time velocity. I think it's a 10-second run time velocity or something like that. Or 10-meter run time velocity is what it is. This in patient 6. The reviewer commented they received the 30 mg/kg dose. He had the highest 6-minute walk test distance after age 14. There was a marketed decline though in the NSAA score overall at about the age of 12 and it was steadily declined over the age of 15 throughout the treatment of the study. His rise time velocity slowly declined steadily and it was greater than 20 seconds at the last observation. He declined 80 meters in the 6-minute walk test from week 216 to week 240. His dystrophin level at week 180 was 2.47 however there was no baseline sample retained so they can't tell if that was an actual increase from baseline or not.

Now we'll look at patient 12 who had the second highest 6-minute walk test distance after the age of 14. This boy received the 50 mg/kg dose and he had a marked decline, again, at age 12-1/2 years starting here on this yellow line. He lost the ability to rise at age 12. His 6-minute walk test distance was unknown because he fractured his femur and his dystrophin by Western blot at week 180 was 0.375% of normal. Again, there's no baseline so we don't know if that was an increase or not. And the reviewer his note is that the low level of dystrophin in this patient assessed at week 180 does not suggest that eteplirsen could have produced any significant amount of dystrophin for this patient who was on the highest dose of eteplirsen tested and that the maintenance of relatively high 6-minute walk test distance values at age 15 is not related to a drug effect and instead illustrates the variability in the natural history of DMD.

Other comments comparing patient 6 and patient 12 it's that these two patients illustrate that the temptation to assign the relative stability of patient 6 to his dystrophin level must be restrained by the very similar progression of patient 12 who, in fact, had very low dystrophin. And then in addition, a comparison with matched patients from the historical cohort PV12 and KB shows that the course of patients 6 and 12 is not exceptional for a DMD patient and is compatible with the natural history

of the disease. Specifically, the comparison of eteplirsen treated patient 6 to historical control PV12 who both entered the study or registry around age 10-1/2 years and shows the following.

This slide is even harder to see. But this is patient 6 up here and this is his North Star test, the yellow line. Here's patient PV12 who, you know, you could say it actually looks like they are doing a little bit better. But the blue line they are about the same level. The 6-minute walk test declines rapidly, but the red line and the green line are pretty much on the same trajectory. We just don't have as many observations out here to say what happened. This is patient 12 and again compared to the control they are not significantly different when you look at the entire NSAA assessment and not just the 6-minute walk test. And then the reviewers comment was this alone, in my opinion, is nearly sufficient to reject that a historical control design is capable of establishing the efficacy of eteplirsen as the best performing eteplirsen treated patient and Study 201/202 does not have a course clearly different from natural history.

The reviewer then looked at the correlation between the dystrophin levels and the 6-minute walk test. So this is the change in the 6-minute walk test here. So the higher you are on the graph the better you're doing and this is the amount of dystrophin that you have on the X axis. So the further to the right you are the more dystrophin you had. The four patients that were still ambulating at the end of the study, these two patients with very low dystrophin had very high 6-minute walk tests. These patients had very high levels of dystrophin and very high performance on the walk test and then the rest of them are just kind of scattered. So the comments from the reviewer is that it is apparent that the four patients whose 6-minute walk test distances were the best preserved, two had very low levels, two had very high levels. There's no apparent correlation between 6-minute walk test and the dystrophin levels. So that was his comment.

This graph then plots the progression of the NSAA scores over the years. So the NSAA score here on the Y axis, the number of years that the patient was followed is on the X axis. The blue line is the natural history group. The red line is the treatment group and what the reviewer is

really commenting on is that the blue line you can see it is clearly lower than the red line from the very beginning and they are pretty much progressing at nearly a parallel slope. After year one it appears the eteplirsen group gets a little more stable and then maybe through year three, but then again goes back to a parallel decline meaning that they are declining at the same rate, but they just started at different places. These are the confidence levels and there are extreme overlap so it's not a statistically significant difference in these NSAA scores because of that.

So other potential sources of bias that were mentioned by the reviewer – there was the observation that no boy in the Belgium or Italian registry had a rise time greater than 22 seconds, whereas two-thirds of the eteplirsen group did and some were as long as 40 seconds. It was thought that... it was pondered upon by the reviewer if after 22 seconds if it was the standard procedure for those reviewers to say they can't rise. So it was unclear. They didn't have the access to the protocol that the natural study reviewers were looking at. However, it was found out or revealed at the advisory committee meeting prior to approval that boys in the eteplirsen group, once they reached a certain rise time were allowed to receive external support or use a fixed object to help them rise. That was not stated in the actual protocol. It came out, I think, in comments at the advisory group. There was also the observation that some boys in the Belgium or Italian registry had recorded a 10-meter run/walk test, but at the same observation were declared unable to ambulate. So they learned that... the FDA found out that it was the standard in the control protocol to categorize a patient as non-ambulatory if they couldn't finish the 6-minute walk test. And that's important because some of the patients started the 6-minute walk test. They might have walked for a certain amount of time, a certain distance, but they would be recorded as zero as opposed to recorded at the distance that they actually walked. I have a comment about that. In addition, the eteplirsen treated patients had two opportunities on consecutive days to perform the functional test whereas the natural history patients really only had that one opportunity when they were in the provider's office.

Other sources of bias – it was noted that for at least two or three of the 13 exon 51 skippable natural history patients selected by the applicants

as controlled, a value of zero was recorded for 6-minute walk test apparently prior to loss of ambulation as documented by the ability to perform the 10-meter walk test, similar discordance between the 6-minute walk distance and the 10-minute walk/run was identified for at least six patients in the control group. So there was some discord between recording the two different tests. So a question again about how they were being recorded. When I talked about the rise test there was one examiner that noted in the chart that the patient no longer wanted to continue, could still continue, but had back pain. So that patient was recorded as zero in the study even though they could have kept walking.

This is important because, on this next slide, the study manual for the treatment group, the 6-minute walk test evaluators were encouraged to walk along directly behind the patient at a distance of about two meters giving positive verbal encouragement at approximately 15-second intervals and the encouragement was such as: "You're doing a great job! Keep it up! Remember to walk as fast as you can!" You know, encouraging the patient along on the test. And it was also stated that if the patient fell or could not rise from the floor the test was over and the distance should be recorded. So on the other hand the protocols in the history group they were very scant and included no time how... raise scant included no time how to rise time test was to be performed. There was no mentioned with respect to encouragement during performance of the 6-minute walk test, and no discussion about the situations under which boys should be declared unable to perform the test even though they hadn't attempted it. So there was a time where it appeared that the evaluator assumed the patient couldn't perform a function and so didn't measure it. This really shows you was the difference in those 6-minute walk tests in those graphs that we looked at a result of the positive encouragement the patients were receiving versus the... probably the lack of any encouragement or not knowing if there was encouragement for the control group.

So finally the reviewer... I'll just read the yellow part. In the context of this considerable variability among patients, the clinical course of eteplirsen patients over more than 3-1/2 years of treatment with

eteplirsen has been generally similar to expected natural history of patients provided with intensive supportive care.

The review felt that the applicant had not provided substantial evidence of effectiveness required by the code of federal regulations to support approval based on either endpoints measuring clinical benefit, or biomarker endpoints that might be considered reasonably likely to predict benefit under accelerated approval provisions. And then they go on to say that there is some evidence that eteplirsen increases the expression of the functional Becker-type dystrophin protein to a level approximately 1% of normal, but the evidence is less than the amount that is generally considered substantial evidence. And then it goes on to say the amount of Becker-type dystrophin that may be produced by eteplirsen approximately 1% of normal is low enough that a conclusion that the amount would be reasonably likely to predict clinical benefit would have to be based on a low threshold for reasonably likely.

And this is the point of contention with the approval and the FDA that the board... the advisory board actually voted not to approve this medication based on these recommendations, but Janet Woodcock who I'm not sure if she's the director of the FDA or the CDER, but has the authority to overrule that. So her determination was that... to use all flexibility within the purvey of the FDA and overruled the decision and the drug got approved based on the evidence and testimony of patient advocates, patients themselves and several politicians that attended the meeting.

So now I'm just going to go over the determination of our medical necessity. When we do prior authorization we have to determine, you know, whether or not a service or treatment is medically necessary and our Washington administrative code has us follow a very specific and defined procedure. So we have a hierarchy of evidence and the hierarchy starts with the highest level of evidence being a meta-analyses done with multiple high... well-designed controlled studies. Type II would be one or more well-designed experimental studies meaning randomized control trials. Type III would be well-designed, quasi-experimental studies such as nonrandomized controlled, single group pre-post, cohort, times series, matched case-controlled studies, but again well designed. Type IV would be well-designed, nonexperimental studies, such as comparative and

correlation descriptive, and case studies. Or V would be credible evidence submitted by the provider, which could include patient-specific information.

So what do we do with this evidence? We grade this evidence like A, B, C or D. And a grade A shows that the requested service or equipment is a proven benefit to the client's condition by strong scientific literature and well-designed clinical trials such as Type I evidence or multiple Type II evidence or combinations of Type II, III and IV. B level evidence is supported by multiple Type II or III level evidence or a combination of II, III and IV with generally consistent findings or singular Type II, III, IV evidence in combination with agency-recognized clinical guidelines, which are external clinical guidelines, not agency developed. So that would be like NCCN guidelines. Treatment pathways, or guidelines that use hierarchy of evidence in establishing the rationale of existing standards. So a guideline that is using some other form of graded evidence. Level C shows only weak and inconclusive evidence regarding safety or efficacy or both. For example, Type I, II or IV where there is inconsistent findings or only Type V evidence is available. And then D level evidence is not supported by any evidence regarding its safety and efficacy. For example, that which is considered investigational or experimental.

And so after we classify the evidence into its rating HCA will approve services or treatments that are graded A or B. We would approve a C-rated request only if the provider shows the requested service is the optimal intervention for meeting the patient's specific condition or needs. And it doesn't place the patient at greater risk of mortality or morbidity. It is less costly to the agency than the equally effective alternative treatment and it is the next reasonable step in the patient's care. We would deny D-rated requests unless the requested service or equipment has a humanitarian device exemption from the Food and Drug Administration. So that would normally be if something is considered experimental and investigational, but the FDA has approved use of it we would potentially cover it. And it is approved under a humanitarian approval. It's not FDA approved, but the FDA has allowed it to be used. I want to clarify that. There is a local institutional review board protocol addressing issues of efficacy or safety of the requested service. Meaning

if something is investigational or experimental if they are enrolled in a clinical trial that is governed by an IRB we might consider covering the service in those instances.

So for Exondys 51 the Health Care Authority going forward will determine the medical necessity for use of Exondys 51 to treat DMD on a case by case basis using our medical necessity criteria. And just of note to you all that it will be carved out of the managed care contracts and be paid for by the HCA Medicaid Program or the Fee-for-Service Program and that's really to make sure that the policy is consistently applied across all patients that might have Duchenne's Muscular Dystrophy that would request Exondys 51.

And that's just the citation for the FDA review. Any questions?

Nancy Lee: I just want to thank you, Donna, for your really great presentation. Thank you for that thorough presentation.

Donna Sullivan: Thank you. I think we have one stakeholder.

Michael Johnson: We have one stakeholder. This would be a good time for Pratik Parikh. I'm going to actually rephrase that. There are actually two more. Two stakeholders total.

Donna Sullivan: Okay.

Michael Johnson: Go ahead.

Pratik Parikh: My name is Pratik Parikh. I'm the senior medical science liaison with Sarepta Therapeutics. I'm here to address the committee on eteplirsen or Exondys 51 as commercially known. It was approved on September 19, 2016 under accelerated approved pathway by the FDA for a broad DMD population that is unrestricted by age or ambulatory status. As you heard earlier, DMD is a very rare disease that characterized by progression of muscle degeneration and it is caused by mutation of a gene that is responsible for producing dystrophin and dystrophin, as you heard earlier, is needed for proper muscle functioning and it acts by providing stability to the muscle fiber. In the literature people refer to it

as an anchor or a shock absorber and this is a rare disease. There's only 9 to 12,000 or an estimated 9 to 12,000 patients in the entire United States with only 13% of that population being amendable to Exon 51 skipping. So ultimately the estimate would be about 1,200 to 1,500 patients in the entire United States who could be potential candidates for eteplirsen.

It's only for those... like I said confirmed who have a DMD mutation that is amenable to Exon skipping 51 and it was approved under the accelerated approval pathway by the FDA based on an increase in dystrophin that was found in skeletal muscles of some patients. A clinical benefit of Exondys 51 has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

With the remaining time I really wanted to take the time to have the committee, if you have any questions that I can address regarding any of the information you may have seen or you may that you have seen on the label or in the presentation provided. Okay. Thank you.

Michael Johnson: I think the next stakeholder is Mindy Leffler.

Mindy Leffler: So my name is Mindy Leffler and I'm a Washington State resident. My son is 13-1/2 years old and he's been on this drug for 2-1/2 years. I have brought evidence with me that I'm aware that I am not allowed to show here, but I have video evidence of him regaining the ability to get himself into the car independently over the course of treatment on this drug over the first seven months—something that he had lost the ability to do eight prior to starting the medication, which if anyone here is an expert in DMD will tell you that that defies the natural history of this disease and no one has been able to find someone above the age of 11 who has lost... or regained a definitively lost milestone. It does not exist in the course of this disease.

Over the past four years I have spent a significant portion of my life attending meetings with the neurology division at FDA up to eight meetings and I have litigated this data with Dr. Ronald Parkus, who is the reviewer that's been mentioned in the presentation over seven times. I want to come up with a couple of discrepancies in the presentation that

were reiterated here today that are errors in his interpretation of the data set.

Number one, it is very popular to say that this company did not do additional studies in DMD because we objected ethically to doing additional randomized control data sets. The reason is because there was a competitor drug that had recently failed that took all of the patients of which my son was one. And you cannot simply take a set of boys who have already spent a significant portion of their life on placebo and then gotten into a clinical trial and then say, "Hey, don't worry kids, you can go back on placebo for another year. We're just going to cut you open a couple more times again and do a couple more muscle biopsies." You cannot do that to the same population of children and Janet Woodcock at the FDA was wise enough to understand that you cannot consider the design of a study in a vacuum. That you have to consider what has happened sequentially to the patients that you're going to be putting on drug as a matter of the course of this trial. She also considered the fact that for me having spent two years of my life flying back and forth every single Wednesday from Seattle to Canada that there are ramifications to participation in this type of clinical trial program that have nothing to do with just establishment of significant harm. My family spent over \$60,000 participating in clinical trials for muscular dystrophy in lost wages and child care. So she took all of those things into account and plotted a regulatory path forward for this drug that was ethical and human for the patient's that were involved. So I want to state that.

Secondly, there was a draft guidance that was published with the community in Duchenne in conjunction with FDA that stated that multiple forms of dystrophin assessment should be used in deciding whether there is efficacy of a particular drug. However, then when FDA came down to actually evaluating the dystrophin that was produced by this drug into his clinical trial, they only used Western blot and there's a doctor at the University of Washington named Jeffrey Chamberlain who is one of the top experts in the identification of dystrophin in [inaudible] tissue and he told me that he has a huge concern with that and the reason is because in preparation for Western blotting the dystrophin protein is such a large protein that it will tend to degrade in a process for the preparation of Western blotting and therefore will become

undetectable. So that was his huge concern, a concern that was large enough that he flew himself across the country to participate in the ad comm meeting at which point he was silenced halfway through his presentation when he was trying to describe the fact that even one dystrophin positive muscle fiber confers a protective effect for the fibers around it. So if you have a very small level of dystrophin protein that positive fiber will protect the fibers around it, which is why sometimes very, very low levels of protein can confer a clinical benefit.

In addition I want to say I know these kids in this data set. There is one patient that had .37% dystrophin at baseline and untreated in the PROMOTIV study. And the interesting thing to me was when I was looking at that data set and reading through all these documents, I know that child. He's a 15-year-old boy with DMD that can still go upstairs leg over leg. So what that told me is somebody who has a familiarity with the disease is that .37% can keep a 15-year-old able to go up the stairs independently, which anyone who is familiar with muscular dystrophy will tell it's highly unusual. So what that indicated to me is that very, very low levels of dystrophin will lead to a clinical course that is markedly different than the majority of patients with Duchenne.

I know the presentation today included a lot of bias in the favor of lack of efficacy. However, just like the FDA's evaluation there was no discussion of the factors that were biased in favor of efficacy. For example, the patients in the European studies received larger amounts of physical therapy than the patients in the United States and the FDA themselves even expressed the fact that receiving regular physical therapy is something that can extend patient's walking ability and that is a factor that was biased in favor of the natural history controls, not in favor of the [inaudible] patients. That was not discussed today nor was it included in the FDA's assessment of what was happening. In addition, steroid use, the boys in the [inaudible] study did not increase their steroid dose with weight gain, which means that they were essentially being weaned off the steroids.

Michael Johnson: I'm sorry, the three minutes are up.

Mindy Leffler: Okay. How do you make the right decision if I can't tell what's wrong with this data and there is no one speaking on behalf of this population?

Michael Johnson: I hear you. I'm sorry. Time's up.

Mindy Leffler: Well, I guess if somebody wants to see the videos that prove that children can [inaudible] I have them if you want to just watch them after the presentation. [inaudible]

Michael Johnson: All right.

Donna Sullivan: Are there any questions from the committee? Comments?

Dale Sanderson: Did you get any input from the physician at Children's?

Donna Sullivan: No, I was not able to do that.

Michael Johnson: I think what we're looking at proposing is whether this is a case-by-case basis?

Donna Sullivan: Right.

Michael Johnson: Pardon?

Donna Sullivan: We can either write a motion or you can say it and I'll type it as you say it, but that is what is up for consideration.

Po Karczewski: Just for clarification what's the current status?

Donna Sullivan: The current status right now is we looked at the trial inclusions design and basically had a policy that would allow patients that met with... met most of those criteria. We lacked some of the criteria based on whether or not they were still ambulatory or not. That's what was reviewed in February. Just to note we've had only one request for Exondys 51 and it was for a patient that was coming out of the clinical trial and it was approved.

- Amber Figueroa: I guess the question for me, which may not be the form at this point since we're talking about initial approval, but knowing the cost of the drug or having an idea the end point is when? I mean...
- Donna Sullivan: The rest of their life. There is no end point. So the question would be is, would you stop it when they start declining rapidly or do you continue it with the hopes that the decline would be slower? You can't tell and from the data you can't really tell that there is a difference between the natural history. There's more information out there that says 25% of boys with Duchenne's Muscular Dystrophy would be ambulatory at the age of 15. And they are actually getting more and more data that says that 15% are still ambulatory at the age of 18. The treatment for the disease is changing the natural history because now we're using high-dose steroids. We're doing intensive therapy, physical therapy, surgeries potentially, really supporting cardiovascular and pulmonary functions. So the natural history of the disease of what to expect is also changing. So it's this moving target. So it makes it really difficult in small numbers to tell if it's... would it have happened anyway or is it really the drug? And that's the conundrum that we're in.
- Amber Figueroa: I think for that exact reason when we're considering drugs like this that are so new I think it's important for us to revisit it frequently as new evidence comes out to maybe direct us as to how long the treatment should be once they do studies with further... with patients who have been on it more time and stuff.
- Michael Johnson: I look at this agent just as I did with hepatitis C medication. I mean you can look at... there's really a specific criteria here and we have to have some criteria to start with and so, you know, determining medical necessity is basically a set of criteria that we would start following and I don't professionally or ethically have any issues with that. I think we have to say, 'here's how we're gonna use it' and then it's case-by-case. I don't see any other way. You can't just carte blanche approve it. They have to make criteria. I don't hear anyone else proposing anything other than that. Right? Unless I'm missing something. Are we asking for...
- Donna Sullivan: The question is what the difference would be? So instead of using the established set of criteria that you reviewed in February we will look at

these on a case-by-case basis based on the determination of medical necessity and the individual circumstances of the patient that it is being requested for.

Michael Johnson: Just my opinion, I would think this would be case-by-case.

Donna Sullivan: Yes.

Michael Johnson: That's how we should do this. I mean, you know, everyone is at a different point in their disease or at different ages. They've been on different treatments, maybe even on other agents in other trials, so that would be what I'm in favor of. Would the board like to discuss other options? I'm open to that.

Po Karczewski: It seems like we're reconsidering our action in February on the basis of, you know, new information. There's been some question about the methodology of that new information brought by our public testimony and I think that in order to reconsider the previous decision that we ought to be more sure of what basis we're using for reconsideration and if there are some questions about... I mean I thought those were valid points about the methodology there, particularly the PT for the control from Europe. I think maybe we ought to let this sit and then revisit it when there is more information. It sounds like there is quite a bit of ongoing discussion and perhaps litigation on this issue.

Michael Johnson: Do we have the previous criteria on a slide? Are we able to access that?

Donna Sullivan: I probably have it on my computer.

Amber Figueroa: I'm just clarifying, who makes the final decision on this determination of medical necessity? Is it a group of people? Is it a pharmacist? Is it a physician? Is it a consultant?

Donna Sullivan: At this point in time it would be probably one of our physicians. Dan, do you want to jump in on this?

Dan Lessler: Yeah, this would definitely come to us as, you know, as the physician leadership. I just want to go back to the point that was made earlier. So

what we really are proposing is, you know, case-by-case determinations of medical necessity. So looking at sort of the total picture of, you know, the clinical circumstances. I mean it is what Michael was referring to earlier. But, you know, given in a... at this point that there is very, you know, very limited evidence around particularly... no evidence really from clinical trials yet around, you know, clinical outcome efficacy and some data around a surrogate end point. You know, just that needs to be carefully considered on a case-by-case basis.

Amber Figueroa: So if... let's say someone's case were to be denied is there an appeal process or can they ask for it to be reviewed by another provider?

Dan Lessler: No, there is a formal appeal process, yes.

Lisa Chew: I think looking at the data with the limited evidence and I think there was biases presented by both ways, I think given what we know, I think a case-by-case basis is a reasonable approach. It's not an automatic rejection that the patient can get the medication, but that there will be a thoughtful review of the need for that based on the patient's circumstances and I think given what we know I think this is a reasonable approach.

Jordan Storhaug: I definitely agree with that statement. I think with diseases like this that it is common that... it is just really hard to get good evidence, which is difficult for that case. Where I think we are is with the limited evidence that we have that a thoughtful review, rather than a policy that will sit for a while, you know, without review, is not the best and a case-by-case review would be best for our patients.

Dale Sanderson: Do we have any sense of how other states are handling this across the country?

Donna Sullivan: I don't at this point in time.

Michael Johnson: I think Donna is looking for what we did last night. I think I copied the wrong presentation. What I'm sensing here is that... I think most of us are in favor of the fact that we should do a thorough review of each case

as they come up for request and so if that's all we need to really say is there anyone who is opposed to that philosophy?

Po Karczewski: I guess I am although I'm struggling with it because I know some of the issues here. It just doesn't seem to me that a clear case has been made to call into doubt the approval. Certainly a case has been made, but I think it has got some question to it. And the case-by-case review I guess I don't have confidence that the bias for that will be toward the patient. Not to cast dispersions on anybody, but these are very difficult decisions to make. I know sometimes in the area of the arena I work in [inaudible] at benefit and we really can't tie that to any kind of biological or chemical marker, but we've got a benefit and I have two friends who are physicians who both have young men with DMD and they both... one of them is on Exondys and she seems to think it has had a lot to do with preserving his function.

Amber Figueroa: Remembering back to that meeting it seems that the criteria we set was somewhat more restrictive. I think this would work more to the benefit of the patient than what we had done before where they had to meet some certain criteria. I think this actually is more general. Like say for patients coming out of a study or someone who has already been on it and showed benefit then I think that clearly falls into one of these categories of medical necessity or if they've tried and failed everything else that's out there. I think it's less restrictive and would work in the favor of the patient.

Michael Johnson: We're just trying to give her a little time so we can review it before we make a motion. I look at what we did with the hepatitis agents. We had a lot more criteria laid out, but that would effect a lot more people. So it made it a much easier, you know, you looked at what level of fibrosis, etc. and it made it easier for a higher volume of people. This is going to be a much smaller population and I think it's going to be much easier to do a thorough review to look at medical necessity. So I think if we laid out criteria I think just like was pointed out that criteria sets in stone until the... whenever the DUR gets around to meeting the next time. I think case-by-case review of medical necessity is really... it opens it up. If new evidence came out, you know, in six months we don't have to review this

again because that's now... there's more evidence for new medical necessity criteria. That's my thought.

Donna Sullivan: I got what was approved from the February was that they had Duchenne's Muscular Dystrophy specific to the exon 51 skipping. We lowered the age to four years old as opposed to seven, which was originally proposed. That the patient has some physical function that can be maintained. That was changed from a requirement of requiring ambulation, which was originally proposed. And then the patient needs to be receiving glucocorticoid steroid therapy at the highest tolerated dose, have stable pulmonary function, stable cardiac function, and that it needed to be prescribed in consultation with a pediatric neurologist or other with expertise treating DMD, that they aren't on any other RNA antisense agents, and that they would be approved if they met criteria for 30 mg/kg/week and that they must be getting supportive treatment according to the standard of care for treating DMD.

And then for renewal that the patient has observed an increase in physical function from baseline or have maintained baseline function or progression has been slower than otherwise would have been expected. And then if they were receiving glucocorticoid therapy and it was discontinued at the recommendation of the treating physician it would still be allowed to be continued.

Dale Sanderson: It would be helpful to understand a bit more on what goes into that case-by-case review, you know, are these criteria going to be applied or are there additional criteria that are not listed here that will be considered, you know, how does that case-by-case evaluation...

Donna Sullivan: Well, one of the things that happens when we do our case-by-case reviews, and it's why I went through the medical necessity determination, is we look at the available evidence and we look to see, 'is this good quality evidence that supports a benefit?' And so we would make that determination. There's another... option five was like the physician submitted evidence where there might be patient-specific evidence and that would be where there is, you know, functional status scores that shows a patient that's already on it is doing just as good or

better than they would have expected. So that is what would... the process that would go through.

Dale Sanderson: So we're looking more at individual responses as opposed to epidemiology?

Donna Sullivan: Correct.

Michael Johnson: Anymore thoughts on this?

Dale Sanderson: Are we going to withdraw then the previous motion that was accepted before?

Donna Sullivan: That would be your motion would be to change from the established criteria to a case-by-case basis, yeah.

Michael Johnson: I think that I would be in favor of removing the previous criteria and going case-by-case. Having heard that the review would consider all of those, but consider actually a clinical response and evidence of, you know, the weight of evidence, etc., I move that the Medicaid... we'll write this as we go. I move that the Medicaid Program determine the medical necessity for the use of Exondys 51 to treat DMD on a case-by-case basis using our medical necessity criteria. Do we need the second piece?

Donna Sullivan: No, you don't.

Michael Johnson: Okay.

Susan Flatebo: I second the motion.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign.

Man: Aye.

Michael Johnson: All right. Thank you.

Donna Sullivan: I think that's it.

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

Donna Sullivan: Thank you.