Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
Meeting Transcription
June 26, 2024

Laura Beste: Good morning. This is Laura Beste. I am the Co-Chair, and I will be running it until Kavita gets here today. So welcome to the June 26, 2024 Washington P&T Committee and DUR Board Meeting. We will now convene the P&T Committee Meeting. I will read the names off of the participating attendees. Please say, "here" when I call your name. Peter Barkett.

Peter Barkett: Here. Kavita Chawla. I think we will be doing this later. Michael Corsilles will not be here today. Kevin Flynn?

Kevin Flynn: Here.

Laura Beste: Greg Hudson.

Nonye Connor: He might be brought on late.

Laura Beste: Okay. Jon MacKay.

Jon MacKay: Here. Good morning.

Laura Beste: Good morning. Zoe Taylor.

Zoe Taylor: Here.

Laura Beste: And Christy Weiland.

Christy Weiland: Good morning, here.

Laura Beste: Next, we will move to the Healthcare Authority members. We have Nonye Connor.

Nonye Connor: Here.

Laura Beste: Leta Evaskus.

Leta Evaskus: Here.

Laura Beste: Amy Irwin.

Nonye Connor: She'll be [audio cuts out] joining us later. [Cross-talk] --

Amy Irwin: [Cross-talk] Here.

Nonye Connor: Sorry, Amy.

Amy Irwin: Just a second, Nonye.

Laura Beste: Ryan Pistoresi?

Ryan Pistoresi: Here.

Laura Beste: I am not sure if I pronounced that correctly. Elizabeth Punsalan. Not here yet? Um, Donna Sullivan?

Nonye Connor: I don't see her [cross-talk] --

Laura Beste: [Cross-talk] Marissa. [Cross-talk] --

Nonye Connor: [Cross-talk] -- later.

Laura Beste: Marissa Tabile?

Marissa Tabile: I am here.

Laura Beste: Okay. Ryan Taketomo.

Ryan Taketomo: I'm here.

Laura Beste: Joey Zarate.

Joey Zarate: Here.

Laura Beste: Next, we have Labor & Industries members, and we have Jaymie Mai. Uh, Drug Effectiveness Review Project presenters, Andrea Vintro.

Leta Evaskus: Nonye, she has to be moved over to a panelist. She is in the attendee list.

Nonye Connor: Oh, thank you.

Laura Beste: Do you want me to keep going and come back:

Nonye Connor: Yes.

Laura Beste: Okay. And we have the Magellan Medicaid Administration presenters, Nina Huynh. I thought I saw [cross-talk] --

Nina Huynh: I'm here.

Nonye Connor: Okay.

Laura Beste: Umang Patel.

Umang Patel: Hi, everyone.

Laura Beste: And we have the Managed Care Organization representatives, and I am just going to read their names off. You don't need to say, "here." Greg Simas, Molina Healthcare; Heidi Goodrich, Molina Healthcare; Petra Eichelsdoerfer, United Healthcare; Omar Daoud, Community Health Plan of Washington; and Geoffrey Natividad, Community Health Plan of Washington. Now, Nonye is going to go over the meeting logistics for us.

Nonye Connor: Yes. Good morning. The Committee and presenters can mute and unmute themselves at any time, but please mute yourself when not speaking so as to limit background noise. Presenters, please share your webcams when presenting. Committee, please share your webcams during discussions and motion considerations. For stakeholder participation, to share, we will read the list of shareholders' names who pre-registered to speak. We will unmute you. After the share, we will ask if there are any other shareholders. If there are, please raise your hands. We will call upon you and unmute you. You can also use the Q&A box, and we will address your questions during the stakeholder time. If you did not fill out the stakeholder conflict of interest form, please answer the questions we will post on a screen. Your three minutes will start after you answer the questions. And lastly, this meeting is being recorded. Please state your name -- not necessarily -- I just spoke to

our transcriber -- every time you speak, but you don't have to say your name because they are kind of familiar with us now.

Laura Beste: Okay. Then at this time, I invite Andrea Vintro to talk to us about Antiemetics that we will be archiving me.

Andrea Vintro: [Audio cuts out] Do you hear me?

Nonye Connor: Yes.

Andrea Vintro: Oh, good. Okay. I was trying early on, and I was a little anxious, but thank you for moving me over. Okay. So welcome, everyone. My name is Andrea Vintro. I am a Research Associate at the Center for Evidence-Based Policy. In February of this year, we presented for drug classes for this drug archiving project, and today we are finishing up by presenting the final five drug classes to be considered for archiving. So for this first presentation today, we have newer Antiemetics. So the aim of the work is for the Drug Effectiveness Review Project, better known as DERP, to develop and present information to the Washington State Pharmacy and Therapeutics Committee on nine drug classes that are candidates to be archived from active review by the Committee. So you can see the list of drugs, drug classes that are included in this project at the bottom of this slide and the topic for this presentation, New Antiemetics, is highlighted there in green.

Kavita Chawla: Andrea?

Andrea Vintro: Yes.

Kavita Chawla: Are you moving your slides yet?

Andrea Vintro: Oh, my goodness. That would be helpful. Okay. Let me go back here. Okay. How about now? Perfect. Perfect. Apologies for that. Okay. So here we have the aim of the project. So now the overview for this presentation. We are going to review the topics in those darker green boxes for antiemetics. So starting on the left there. I will first define the health condition of interest that this drug classes intends to address then summarize the general epidemiology and management for the condition, then I will review the key information and the most recent DERP reports for this drug class, including the PICOS, Key Questions, a high-level summary of those Key Findings of that report, and general Findings of any surveillance that was completed after

that last systematic review, and then I will move to New Actions. Any new actions by the FDA since that last report, including any new approved drugs, Serious or Box Warnings, and any new Indications, and they all also present the current FDA-approved Indications for all of the drugs of interest. And then, finally, I will provide a high-level summary of recommendations from relevant clinical practice guidelines for the treatment of the condition, which includes guideline recommendations about how and where these drugs are used along the treatment pathway for that condition, and then we will answer questions. So the condition of interest for this drug class are nausea and vomiting that are associated with chemotherapy, radiation therapy, anesthesia, and surgery. So nausea is not necessarily defined as pain but rather an uneasy sensation that comes with the urge to vomit, so basically a symptom, which is typically the precursor to vomiting, also known as emesis. So nausea and vomiting are common side effects of chemotherapy for cancer and also for radiation treatment. They can result in complications, some of which are Serious. Examples of Serious complications can include metabolic imbalances of fluids and electrolytes, resulting in low potassium or high calcium blood levels, and those can lead to life threatening cardiac events. Patients who are more likely to experience nausea and vomiting with chemotherapy include those who have prior nausea and vomiting with past courses of chemotherapy, individuals with a history of alcohol use, people with advanced age, the female gender, and also in non-smokers, as well as in people with a history of nausea and vomiting due to other causes, such as pregnancy. Tumor invasion and certain tissues can also contribute to the condition and also some concomitant medications and the type of chemotherapy where treatments are rated according to their emetogenicity, or their likelihood to cause nausea and vomiting, also known as the Hesketh scale. Nausea and vomiting are also frequently associated with surgical procedures. So a quarter to a third of all surgical patients experienced these symptoms after receiving general anesthesia, and postoperative symptoms increase risks for reopening of surgical wounds, esophageal ruptures, aspiration, and dehydration, among other symptoms. Individuals who are more at risk for these symptoms after surgery include those who undergo certain procedures, such as ear, nose, and throat surgical procedures or open abdominal surgeries for example. Also if the surgery is prolonged where individuals might receive additional anesthesia and certain types of anesthesia are more or less likely to trigger these symptoms as are certain patient characteristics, and those are similar to those listed for chemotherapy. So the etiology of pregnancy-induced nausea and vomiting is unclear, but researchers think it may follow a similar neurophysiologic

pathway as that nausea and vomiting that is triggered with chemotherapy and postoperative. However, some additional theories do include changes in hormones associated with pregnancy. The condition is quite common during pregnancy and affects up to 85% of pregnant individuals. Symptoms typically start by six to eight weeks gestation and subside before 20 weeks. The most severe form known as hyperemesis gravidarum affects between less than 1% and up to 3% of pregnant individuals, and it is characterized by a debilitating chronic nausea, intractable vomiting, dehydration, electrolyte imbalances, ketosis, nutritional deficiencies, and weight loss. A recent systematic review reported an association between the severe form of condition and preterm delivery as well as infants who are small for gestational age. Pregnant individuals who are more likely to experience these symptoms include those with a family history of nausea and vomiting or prior history with pregnancy or other scenarios, multiple gestation, as well as some genetic fetal conditions. So historically, pharmacologic treatments that were commonly used as antiemetics included histamine-1 blockers, dopamine antagonists, metoclopramide, and also droperidol, which actually declined in use for the prevention of postoperative nausea and vomiting in the early 2000s because of the New Boxed Warning about risks for cardiac complications. And to note, all of these agents are still being prescribed and used. However, drugs for the prevention of nausea and vomiting are becoming more common now, and sometimes they are called anticipatory antiemetic therapies. These agents work more in the central nervous system versus agents that are directed more at modulating the GI motility, also known as prokinetic agents. So for the prevention of nausea and vomiting with chemotherapy clinicians first look at the emetogenic capacity of the chemotherapy, and then they also consider the likelihood for these symptoms to be classified as acute, delayed, anticipatory, breakthrough, or refractory. For chemotherapy with low-to-moderate emetogenicity. Serotonin agonists alone are commonly prescribed or in combination with dexamethasone, and the number of doses also is a variable which is adjusted depending on other risks for nausea and vomiting. And then for chemotherapy with higher emetogenic potential, a combination of these drugs is often used. So ginger and acupuncture and acupressure are also commonly recommended, and those are non-pharmacologic interventions, of course. So to prevent the symptoms after surgery, it is first recommended to find ways to use less anesthesia, including using regional versus general anesthesia, if possible, and also to provide adequate oxygen and hydration during surgery. And then for pharmacologic prophylaxis, the most common agents that are used include the newer serotonin antagonists, dopamine antagonists, corticosteroids like dexamethasone, and also

antihistamines and anticholinergics. So for pregnancy-induced nausea and vomiting, non-pharmacologic treatments are typically recommended for more mild symptoms, which include changes in diet, hydration, and also stress reduction techniques. And then for more severe symptoms, these agents listed here are more commonly prescribed. So noting that corticosteroids are considered as third-line treatments and also not recommended for use earlier in pregnancy because of some reported risks for oral clefts in fetuses. Okay. So four reports prepared by DERP on this topic. The last DERP systematic review for antiemetics was completed and presented in January of 2009, which is about 14 years ago. The sources were searched through April of 2008 for that report. DERP conducted eight surveillance reports, or scans as they were called back then, since the last report with the last surveillance presented in August of 2018, and the sources searched for that surveillance were through May of 2018. So the next few slides was the PICOS for the DERP Products for Antiemetics. The population included adults and children at risk for or with nausea and/or vomiting if they were related to chemotherapy, radiation therapy, surgical procedures, and pregnancy. For comparators they included another listed intervention, so any head-to-head study. Also another FDA-approved medication used to treat nausea and vomiting, and also placebo-controlled trials were considered if there was limited or no other evidence for that particular drug. For study designs, they included randomized controlled trials, systematic reviews, and also observational studies only for the purposes of reporting Safety outcomes. So this table lists the newer antiemetics that were included in the last report. They are in alphabetical order. So we have aprepitant at the top, which is a neurokinin-1 receptor agonist. So neurokinin-1, which is also known as substance P, was found to also attenuate that responsiveness of serotonin receptors, so sometimes they include it under the category of serotonin antagonists. The oral formulation was approved in 2003, then in 2008, a phosphorylated analog of aprepitant called fosaprepitant was developed for injection delivery, and the brand name for both of these formulations is Emend. Then the next three listed drugs are considered first-generation serotonin receptor agonists with dolasetron approved in 1997, then granisetron approved both as an oral agent and an injection in 1993, and then as an extended-release transdermal film in 2008. And then ondansetron with the brand name Zofran was approved in 1991 and has both oral and injection formulations. The bottom row there we have palonosetron or Aloxi, which is considered a second-generation serotonin receptor agonist, and this drug was approved in 2003 also both as an oral and injection formulation. So outcomes for the most

recent report included success at different time points, which is defined as sort of absence of nausea and vomiting episodes, the number of emetic events, the degree of nausea, the number of emesis-free days, time delay until the first emetic event, the need for rescue medications, patient satisfaction of quality of life, the length of hospital stay, and several measures for Adverse Events. There were three Key Questions in the most recent report. So Key Questions 1 and 2 asked about the comparative Effectiveness and Harms evidence of the included agents for treating and preventing nausea and vomiting. And then Key Question 3 asked about any differences in these outcomes across patient subgroups, including people of different ages, racial groups, gender, or conditions of pregnancy among other patient characteristics. So to answer these Key Questions, the most recent report included 185 studies of which there were 81 head-to-head trials, 77 placebo or active controlled trials, 14 systematic reviews, 12 observational studies, and one pooled analysis. For the summary of Key Findings, as a reminder, these are very general and high-level. So, overall, they found no differences in Effectiveness for the dolasetron, granisetron, and ondansetron in adults for prevention of chemotherapy-induced or postoperative nausea and vomiting, and there were no differences between the dolasetron and ondansetron for prevention of postoperative nausea and vomiting in children. There was some evidence that ondansetron was less likely to reduce the need for rescue therapy compared with dolasetron, but there was no difference in response compared with granisetron. And then, finally, at the bottom there, ondansetron may be associated with more frequent specific Adverse Events compared with granisetron, mainly dizziness and abnormal vision. However, there were mixed results compared with dolasetron in adults treated with chemotherapy. Also ondansetron demonstrated inconsistent results in studies of postoperative nausea and vomiting. For aprepitant, they found it was more effective compared with dexamethasone in adults for chemotherapy-induced nausea and vomiting and noninferior with ondansetron in patients with -- for the prevention of postoperative nausea and vomiting, but there were no differences in Adverse Events between these treatments. For palonosetron, they found it was more effective or noninferior compared with dolasetron and ondansetron in adults with chemotherapy-induced nausea and vomiting and may be more effective in children compared with ondansetron. Again, there were no differences in Adverse Events between these agents. And then they also reported that there was a -- they had a concern around a lack of evidence for the topics that are listed here. So treatments for or prevention of the symptoms in children undergoing either chemotherapy or who are postoperative, also individuals

undergoing radiation therapy and some quality of life measures, studies for pregnancy-induced nausea and vomiting as well as these outcomes of Serious Adverse Events across all of these drugs. Surveillance after the most recent DERP report was through May of 2018, and within that time period three newly-approved antiemetic agents were identified. Doxylamine succinate plus pyridoxine hydrochloride was approved as two different dose oral tablets by two different manufacturers in 2013 and 2016. This drug is a fixed-dose combination product of an antihistamine plus a vitamin B-6 analogue. Netupitant plus palonosetron, with the brand name Akynzeo was approved as both an oral capsule and intravenous infusion in 2018. This drug is a combination agent of neurokinin-1 receptor antagonist plus a 5-HT3 serotonin receptor agonist. And then, finally, we have rolapitant with brand name Varubi, available as both an oral tablet and intervention infusion solution, with that oral agent first approved in 2015, and that agent is a neurokinin-1 receptor agonist. So this period of surveillance also found eight new formulations or generic approvals. No new boxed or Serious Warnings are identified, and 76 new eligible studies were identified of which 34 were head-to-head trials, 22 trials compared the addition of a neurokinin-1 agonist with standard therapy, and then there were also 20 potentially eligible placebo controlled trials. Now we will switch over to the new FDA actions since the most recent DERP report. So the first agent listed at the top is amisulpride, with brand name Barhemsys. This is this agent was approved in 2020 for the prevention of postoperative nausea and vomiting in adults. This agent is a dopamine receptor agonist. It is delivered intravenously. And the next three listed agents were those that were identified in the surveillance. So we have doxylamine succinate plus pyridoxine hydrochloride, which was approved for the pregnancy-associated nausea and vomiting, and then netupitant or fosnetupitant plus palonosetron as well as rolapitant, and those are both approved for the prevention of chemotherapy-induced nausea and vomiting in adults. So for new FDA Indications since that last report, we found both new and removed or retracted Indications for three drugs. So the Emend brand oral capsule of aprepitant was expanded to include pediatric patients at least 12 years of age in 2015, for chemotherapy-induced nausea and vomiting, and then in 2019, the indication for postoperative nausea and vomiting in adults was actually removed. For the indication, the injection formulation of Emend, which is a fosaprepitant, this agent was approved for expansion to include pediatric patients six months of age or older, and that was in 2015. And then for palonosetron, the FDA removed the indication for pediatric populations in April of 2020, primarily due to the lack of evidence in that group. So here are the FDA-approved Indications for the included

antiemetic agents in this report as of January of this year. So first you can see that in row three of the included agents, dolasetron was discontinued. As we move along the top row of Indications to the second column, we see the indication for the prevention of postoperative nausea and vomiting in adults. So three drugs have been approved for this indication, and you can see as we walked down the column these agents are amisulpride, granisetron, and ondansetron. In that next column we see six of the eight agents currently on the market are approved for the prevention of nausea and vomiting associated with chemotherapy. I do note that that notation with that letter B there indicates that this is a conditional indication, which means that the approval for aprepitant, netupitant plus palonosetron and rolapitant is in combination with another antiemetic agent. In other words, these are not indicated to be used as monotherapies for nausea and vomiting. Next, we go to the indication for nausea and vomiting during pregnancy, and we can see as we scan down this column for #4, we see only one agent is approved for this indication, and this is the fixed-dose combination product of doxylamine succinate plus pyridoxine hydrochloride. And then in the far right column, we see that only ondansetron has been approved for the prevention of nausea and vomiting that is associated with radiation therapy. So since the most recent report, there were no new Serious or Boxed Warnings identified, but there were a few Warnings or Precautions that might be of interest to you, so those are listed here. So for generic status, in these first two slides, you can see in the bottom row of this table that granisetron was already available as a generic drug in the 2009 report. Since 2009, two more agents became available as generics, and those include aprepitant and its injectable formulation, fosaprepitant, and the fixed-dose combination product of doxylamine succinate plus pyridoxine hydrochloride as a delayed-release tablet, it was estimated that the developer of no surprise will lose exclusivity status in February of 2024. That information is based on IPD analytics, but there were no applications for generic manufacturing submitted at the time that this report was prepared. Then dolasetron in that row 4, as you can see, it was discontinued, as I mentioned earlier. So on this slide, two have generic status of the drugs. We see that ondansetron was already available as a generic in the last report. Palonosetron monotherapy is newly available as a generic since 2009, and then the developer for netupitant plus palonosetron and the developer for rolapitant have exclusivity through 2031 and 2028, respectively, so we likely won't see generic versions of those agents for some time. There were no new pipeline therapies identified for nausea and vomiting for the conditions of interest. I did want to mention these two points for completeness of this report. So dronabinol, which is a cannabinoid,

it was approved in 1985 for chemotherapy-induced nausea and vomiting, and scopolamine has been approved since 1979 for postoperative nausea and vomiting in addition to motion sickness. Of course, these have not been included in any prior DERP report, so we are not including them as new agents for this archive report. So on the next four -- this and the next three slides we are providing a general summary of clinical practice guideline recommendations for the treatment of these symptoms, including recommendations for how and when to use these agents along the treatment pathway. For this section, we began with the information from the up-to-date clinical decision support online resource and then cross-referenced that information with key practice guidelines from professional medical associations, which are listed on the last slide of this deck. For chemotherapy-induced nausea and vomiting, the guidelines recommend treatments based on the expected emetogenicity of the chemotherapy. The four categories of drugs recommended to consider include serotonin receptor agonists, neurokinin-1 receptor agonists, glucocorticoids, and olanzapine, either alone or in combination with each other antiemetics. Also, combination therapy is recommended for those chemotherapy treatments that are considered more highly emetogenic. For serotonin receptor agonists, some guidelines don't specify a preferred drugs while others report evidence for palonosetron as being more effective. They do warn that first-generation agents should be avoided in patients with congenital long QT syndrome and also to measure potassium and magnesium levels while patients are on these agents and correct those metabolic imbalances as needed. They also mentioned that injected dolasetron is contraindicated in both children and adults. But as I noted earlier, it appeared that that agent may be discontinued at this time. For neurokinin-1 receptor agonists, they do not call out one drug over the other in that category. So for glucocorticoids, dexamethasone was mostly recommended, and then when olanzapine is indicated, -- the recommendation was to use it in combination with other antiemetics. And they acknowledge that when using olanzapine, it would be considered an off-label use for this drug. So for radiation therapy and surgery, we have those two on this slide. The recommendations are similar to those for chemotherapy. And also like chemotherapy, treatment is based on the likelihood that these symptoms with a particular treatment, so the location of the radiation and the exposed -- the volume of the exposed body surface are considered typically. For example, if the treatment is a total body radiation directed towards the head or abdomen, these may -- there may be -- they may be more -- considered more emetogenic. For lower or minimal risk of nausea and vomiting, prophylactic treatment is typically not recommended.

And also of note, the guidelines mentioned that there was less evidence for treatments attributed to radiation therapy. For postoperative nausea and vomiting, the guidelines recommend to include antiemetics as part of the opioid-sparing postoperative pain control plan for all patients. Delivery is typically a single intravenous dose after surgery. That was recommended as typical. And the guidelines then mentioned that treatment plans should be based on risk scores for individual patients where type of duration of surgery should be considered, as I mentioned earlier, and treatment plans can include one to three antiemetics from different drug classes. Also regional anesthesia is preferred over the general anesthesia, if possible, and then non-pharmacological techniques of acupuncture was reported as having demonstrated some Effectiveness compared to other antiemetic drugs, and just noting that acupuncture is not a common treatment in children. For pregnancy-induced nausea and vomiting, the guidelines mention that treatment goals should include reducing the severity of nausea and vomiting to improve the quality of life during pregnancy. Also correcting any fluid and electrolyte imbalances preventing Serious complications of persistent vomiting like weight loss and to minimize any risks to the fetus should the individual require pharmacotherapy. First-line recommendations are non-pharmacologic, and those include dietary changes to foods that trigger nausea, taking the prenatal supplement with food, or trying one without iron, ginger supplements, acupressure, wristbands, and then if symptoms worsen or are persistent during pregnancy, the guidelines recommend these next steps, and those are in order on this slide as we walk down the bullet points here. So first is vitamin B6, also known as pyridoxine, should be considered alone or in combination with the antihistamine doxylamine. They also mention that if the symptoms are without hypovolemia, other antihistamines can be considered, including diphenhydramine and dimenhydrinate. If those treatments remain unsuccessful and the condition continues to be more Serious, other options could include in this order. So we have dopamine antagonists, which are prokinetics and then, lastly, serotonin antagonists can be considered, specifically ondansetron or granisetron because of availability of some evidence for this in this population. However, the guidelines were clear that evidence for Safety of serotonin antagonists in pregnancy is very limited. So on this last content slide here, we list the relevant key clinical practice guidelines, which were also referenced in that guideline section. They are listed in alphabetical order by author or professional association, and the publication or guideline update date ranges are from 2018 to 2020 for this drug class. So that is the presentation. Thank you for your attention, and I will pass it back to you all.

Laura Beste: Thank you very much, Andrea, for that. And Kavita has now rejoined us, so I will pass it on to her as the Chair to take over. I did have one question for you, Andrea. So I know that aprepitant, the emulsion formulation we are now using preoperative for patients who have a high risk of postoperative nausea/vomiting, and I believe that it was only the Emend capsule brand that had the indication for postoperative nausea and vomiting removed. Would that be an issue for any patient that would need that medication postoperative if we did this update and didn't include the fact that the generic was still available for that indication?

Andrea Vintro: Um, that is a good question. I can look into that and get back to you. Um, I don't know if Rhonda or [indistinct] is on the call. Maybe they can comment to that. I can look into that and get back to you.

Laura Beste: Sounds good. We just recently approved the IV aprepitant prior to high-risk patients for high-risk nausea/vomiting after postoperative for postoperative. So that is kind of what I knew that.

Kavita Chawla: Great. Thank you, Laura. I have a very basic question, more from a clinician standpoint. I am looking at the medications included in this review, and a couple that come to mind that we often use our metoclopramide and promethazine. Are they not considered antiemetics officially to be included in this review?

Andrea Vintro: I believe that we had a list that was given to us to include, but that -- what was the other one? Metoclopramide and the other one was --

Kavita Chawla: Promethazine. And then the what -- the reason I am asking the question is because as I am reviewing the motion looking ahead, we are going to list all of the medications that you reviewed, and we are going to say that the Preferred Drug List must include at least one of these medications. And so I am wondering, and I wonder what the rest of the Committee thinks about this as well as should those medications that we commonly use in clinical practice also be included in this med list, especially for the motion.

Ryan Pistoresi: So this is Ryan Pistoresi. I can provide a bit of historical context.

Kavita Chawla: Thank you.

Ryan Pistoresi: So for the medical provider and the [indistinct], those were also used for other Indications, and so this was supposed to be more of newer antiemetic drugs. So for our Washington PDL, which we are making this motion for, we have always just looked at this more narrow list of the newer antiemetic medications, just knowing that there are other medications in other drug classes that also are used for other Indications that can be used clinically.

Kavita Chawla: I see. So they might already be on the Preferred Drug List but just under another umbrella.

Ryan Pistoresi: Right. [Cross-talk] So for UMP -- exactly, yeah. So for UMP, they are covered as preferred alternatives, it is just that these were the newer, the more expensive ones back in the early 2000s, which is why the states created this as a report, and also over the years this has changed, and that is why we are no longer getting updates on this report. There are fewer newer drugs coming out in this class. The evidence is pretty stable, and we are not seeing a lot of -- too many changes. I mean, obviously, what was reported today encompasses a lot of changes that we have seen over the last, I think, six years, or six or seven years, so that is a lot. But again, it is not something that we are updating every year like we are trying to do with some of the other drug classes where we are seeing a lot more new evidence being published, new drugs coming to market, or new Safety concerns being discovered.

Kavita Chawla: Great. Thank you, Ryan. Other questions or comments from the Committee members? All right. I am seeing none. So, Nonye, I am going to lean on you here. Do we do the motion any differently if it is for an archive drug class if we are proposing an archive goal of the drug class?

Nonye Connor: [Laughter} No. Excuse me. No, we don't do anything different. Only towards the end you will see that we are going to do a motion to archive all the drug class that we are going to go over today.

Kavita Chawla: Oh, got it. Okay.

Nonye Connor: Mm-hmm.

Kavita Chawla: Great. Thank you. So Committee, are we ready to review the motion then?

Nonye Connor: I also do not see anyone [cross-talk] raised [cross-talk] --

Kavita Chawla: [Cross-talk] Oh, stakeholders. [Cross-talk]

Nonye Connor: [Cross-talk] Any stakeholders have raised their hands. [Cross-talk] --

Kavita Chawla: [Cross-talk] Yes, thank you. [Cross-talk]

Nonye Connor: [Cross-talk] So let me go ahead and share my screen.

Kavita Chawla: And if we can have you blow it up a little bit, like zoom in some, that would be very helpful. Thank you, Nonye.

Nonye Connor: Mm-hmm.

Kavita Chawla: All right. Any comments on the motion, Committee? And thank you, Nonye, I see that you already updated the list of medications with the new one that we reviewed today. So, yeah, whenever the Committee is ready, we will proceed with a motion if there are no comments or questions.

Laura Beste: This is Laura Beste. I will make a motion that after considering the evidence of safety, efficacy, and special populations, I move that amisulpride, aprepitant/fosaprepitant, dolasetron, doxylamine/pyridoxine, fosnetupitant/palonosetron, granisetron, netupitant/palonosetron, ondansetron, palonosetron, and rolapitant are efficacious for the FDA-approved Indications. The Preferred Drug List must include at least one medication that includes alternate routes approved in both adults and children. Antiemetics can be subject to therapeutic interchange within their mechanism of action in the Washington Preferred Drug List. The Preferred Drug List must include a neurokinin-1 antagonist for patients receiving highly emetogenic chemotherapy and/or radiation therapy.

Greg Hudson: This is Greg Hudson. I second.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? All right, with that the motion carries. Thank you, Committee. And so we will go back to Andrea and then to Ryan. First to Andrea for reviewing the asthma controllers, and then the asthma COPD agents with Ryan. So take it away, Andrea.

Andrea Vintro: Great. Let me get organized and swap out the presentation here and share it with you this time. Okay, we have it up.

Kavita Chawla: That's great.

Andrea Vintro: Great. Okay. Thank you. So, yes, Andrea Vintro here, a Research Associate at the Center for Evidence-Based Policy. So this is the fifth out of eight presentation reports for the nine drug classes of interest today. This is our second presentation. So for those of you who were with me during my previous presentation just a few minutes ago, a reminder that I will be repeating all the topics for this presentation and those in the upcoming ones because there may be some new audience members, so bear with me. Thank you. So this is the first two drug classes that are included in this archiving project for the condition of asthma. So in this report, we are going to be focusing on the controller medications or long-acting medications for asthma. So the aim of the work is for the Drug Effectiveness Review Project, also known as DERP to develop and present information to the Washington State Pharmacy and Therapeutics Committee on nine drug classes that are candidates to be archived from active review by the Committee. So you can see the list of the drug classes that are included in this project at the bottom of this slide and, of course, the topic for this presentation, Asthma Controllers, is highlighted in green. So for this presentation, we are going to review those topics in the darker green boxes on this slide for asthma controllers. So starting on the left, I will first define the health condition of interest that this drug class intends to address, then summarize the general epidemiology and management, common management for the condition. Then we will review the key points around the in the most recent DERP reports for this drug class, so the PICOS and the Key Questions. I will provide a high-level summary of the Key Findings in that report, also general findings of any surveillance that was completed after that last systematic view, then I will move to new actions by the FDA for this drug class since that last report, including any new approved drugs, new Serious, or Boxed Warnings, any Indications, and then I will move on to report on any new pipeline drug findings in this class, and then also generic status of existing FDA-approved drugs. And lastly, I will provide a high-level summary of recommendations in relevant clinical practice guidelines for the treatment of asthma, which include recommendations about how and where these agents are used along the treatment pathway, and then we will have time for questions. So because of the larger number of agents in this drug class and the large volume of

information or text in general in this presentation, we thought it would be best to abbreviate many of the terms in this PowerPoint presentation to improve readability. So these are the terms that are commonly abbreviated in the clinical literature, or they are the abbreviations that were used for the drugs included in the last direct reports with the intention of providing some continuity between the report and this presentation. So this slide is here for your reference as the key to those abbreviations. So asthma background is a chronic lung disease characterized by inflammation of the lining of the airways in the lungs. This inflammation causes the airways to narrow and that lining to secrete that lining tissue to secrete extra mucus resulting in a reversible airway obstruction. Asthma also increases airway responsiveness which is often called hyperresponsiveness. This is a predisposition for those airways to narrow excessively in response to stimuli that would produce little or no effect in otherwise healthy individuals. These stimuli are often triggered -- considered triggers for asthma attacks, and they could include things like tobacco smoke, pet dander, cold air, etc. So symptoms of asthma include wheezing, difficulty breathing, or shortness of breath, also coughing, particularly at night, or in the early morning, and then also feelings of tightness in the chest. Asthma symptoms can also interfere with sleep or prevent individuals from exercising or participating in other activities that can affect overall health and increase risk for certain other health conditions. People can die from untreated asthma attacks, but it is very rare. There are long-term risks for people with more severe forms of asthma, and those include worsening lung function over time and side effects that come with those long-term -- that long-term use of certain medications like oral corticosteroids. For example, diabetes and osteoporosis are a couple of those serious side effects of those agents. According to recent CDC statistics, nearly 25 million people in the US are considered to have asthma, 3% to 13% of individuals have the severe form of a condition, and that comes with higher -- hospital utilization rates and higher medical costs than those with a non-severe form. Asthma is the leading chronic disease in children. Male children are more likely to be diagnosed with asthma compared with female children, but that is reversed in adults, so more female adults are likely to have asthma. There are also racial disparities in prevalence of asthma with non-Hispanic black children being twice as likely to have that condition compared to white children. And then exercise-induced asthma is where exercise can trigger symptoms in people with asthma. There are some reports that individuals without a clinical diagnosis of asthma can experience these symptoms, but it is supposedly rare. The exact cause of asthma is unknown. It is thought to be a combination of genes and environmental factors.

Common risk factors are listed here in the green table at the bottom there, and they include family history of asthma, allergies, viral respiratory infections during childhood, occupational, and environmental exposures, including certain dusts, chemical fumes, or vapors, molds, and air pollution or smog, and then obesity is also listed as a risk factor, but the causal mechanisms appear to be less clear. So for treatment of asthma, the primary goal is to optimize controlled symptoms, also reduce the risk of asthma exacerbations or attacks, and then reduce long-term complications, such as loss of lung function and those negative side effects from those asthma medications. Clinically, asthma is typically classified into intermittent or persistent disease, where persistent asthma is when an individual has symptoms more than twice per week, and then with persistent asthma, it is further classified by disease severity. Treatment typically starts with non-pharmacologic interventions, including breathing exercises, more physical activity, and avoiding those environmental triggers like allergens or tobacco smoke. The more common medications used to treat asthma are categorized into two drug classes that we are presenting today. So the first two bullet points in that lower light green box on the right. The quick-relief medications for acute symptoms, which are also known as bronchodilators, which all are short-acting β2 agonists, and then controller medications, of which is the drug class that we are reporting on for this presentation. These are agents that help prevent symptoms and slow the progression of the disease. Those include inhaled corticosteroids and also sometimes oral systemic corticosteroids if treatment continues to be challenging, as well as long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). More recently, combination, quick-relief, and controller medications have become available. And biologics in that bottom bullet point, there are even newer, and those are typically indicated for individuals with the more severe forms of asthma. Those biologics are typically taken with other controller medications with the aim of trying to stop that underlying biological response that causes that inflammation of the lungs. So for our reports prepared by DERP on this topic, the last systematic review for controller agents for asthma was prepared in June of 2016. Sources for that report were searched through October of 2015, so that is over eight years ago. There were two DERP surveillance reports since that last report systematic review with the search dates through May of 2018. The next few slides list the PICOS for the DERP products for this drug class and for this condition. So there were some criteria that most recent DERP report that were not of interest for this archiving report, and those topics and criteria are in red on this and some upcoming slides. The populations of interest for

today's archiving report are adults and pediatric patients with persistent or chronic asthma only. So the condition of COPD, which is in that last report, is not of interest for today's report. Comparators included another listed intervention, so any head-to-head trial, including the same drug utilizing two different delivery methods or formulations. Also listed were some comparisons that were explicitly excluded, and those are listed here. For study designs, they included randomized controlled trials that were at least 12 weeks in duration and with at least 100 participants. Comparative Effectiveness Systematic Reviews were also eligible as were observational studies for Safety outcomes only. So this and the next two slides list the interventions included in the last report. And, again, the drugs in red are not included or part of this archived presentation, again, primarily because they are indicated for COPD and not for asthma. So agents on this slide that are included in this report are two long-acting β2 agonists at the top there, including formoterol fumarate, which was first approved in 2001, and salmeterol xinafoate, which was approved in 1997. At the bottom there, we have the long-acting muscarinic antagonist tiotropium bromide, and that was originally approved in 2004. For inhaled corticosteroids (ICS) agents, we have seven that are included today; those are beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate, and the included fixed combination agents of corticosteroids plus LABAs are at the bottom there. We have budesonide plus formoterol, mometasone furoate plus formoterol, fluticasone propionate plus salmeterol xinafoate, and at the bottom we have fluticasone furoate plus vilanterol, and the range for FDA approval for these agents were between the year 2000 and 2013. So for this final intervention slide for asthma control is none of the fixed combination products of LABAs plus LAMAs nor the phosphodiesterase-4 inhibitor, Roflumilast, were included in this archive report. So three leukotriene modifiers are included, and those are montelukast sodium, zileuton, and zafirlukast, and for those agents, the FDA approval base ranged from 1996 to 2007. So overall, there are a total of 17 drugs that are included in this drug archiving report. For Outcomes, the last report included measures for asthma controls such as frequency of exacerbations or symptoms, also quality of life, levels of function as in participation of work or school, also measures for healthcare utilization, mortality, and several measures for Adverse Events. So the three Key Questions in that most recent report for asthma controllers asked about the comparative Efficacy and Harms of those agents and then Key Question 3 asked about any differences in those outcomes across those various patient subgroups. In the most recent report for these controller agents, there were

87 studies that were included for both asthma and COPD conditions, and 77 were randomized controlled trials, five were observational studies, and five were systematic reviews. Unfortunately, the number of studies included for asthma alone was very challenging to identify, so we are only able to provide that total number of studies that included that were for both asthma and COPD, but these Key Findings that I have listed here are only for the condition of asthma. It would likely, if you did a little bit of teasing out, it is possible with some time to sort of identify some studies that included both of those conditions. First are the Findings for the intraclass comparisons between drugs with the same mechanism of action. So on this slide, we start with different inhaled corticosteroids. In adults, in general, there were no differences in Effectiveness or Harms outcomes between these agents. There is very little evidence for healthcare use and quality of life outcomes. There was some evidence for lower risk of oral candidiasis (thrush) with ciclesonide compared with fluticasone propionate. In children, results were relatively similar to those seen in adults, but there was less evidence overall. They also found some evidence for better growth velocity with fluticasone propionate compared with beclomethasone dipropionate and with budesonide, and then, of course, poor growth would be considered and adverse advents. For the intraclass comparisons of combined fixed products of inhaled corticosteroids (LABAs). They found no differences in Efficacy or Harms between these agents here. We have budesonide plus formoterol and fluticasone propionate plus salmeterol, and then also between fluticasone propionate plus salmeterol and mometasone furoate plus formoterol. There were no differences in quality of life or Harms between fluticasone propionate plus salmeterol and the combination agent of fluticasone furoate plus vilanterol. So Findings for interclass comparisons are on this and the next slide. So these are comparisons of agents with different mechanisms. So, we begin with inhaled corticosteroids compared with leukotriene modifiers. So the inhaled corticosteroids demonstrated a greater Effectiveness and quality of life in the studies compared with the leukotriene modifiers in adults and children. In children, there were fewer visits to the emergency department, but there were no differences in withdrawals due to Adverse Events. Then for inhaled corticosteroids compared with phosphodiesterase-4 inhibitors, individuals who received roflumilast were more likely to experience asthma attacks and to withdraw because of an adverse event compared with inhaled corticosteroids. And, yes, understanding that this is just a note that the phosphodiesterase-4 inhibitors or roflumilast is not currently approved for asthma, but the study included that, and that was for the condition of asthma. In the fixed combination product of inhaled

corticosteroids plus LABA compared with different inhaled corticosteroids, they found no differences in Effectiveness, quality of life, or Harms between fluticasone furoate plus vilanterol as well as -- and that is one agent compared with fluticasone propionate, but there were more asthmatic exacerbations and more Adverse Events and also greater quality of life scores with ciclesonide compared with fluticasone propionate plus salmeterol. Okay, continuing with the Findings for intraclass comparisons, and I do want to point out that some of these drug combinations are not fixed-dose products but rather add-on therapies to another agent to consult for the condition of asthma in this report. So all comparisons on this slide include the fixed-dose products of inhaled corticosteroids plus a long-acting β2 agonist. So compared with leukotriene modifiers, the corticosteroid plus LABA combination was more effective in adults and children, but there were no differences in withdrawal due to Adverse Events compared with leukotriene modifiers as an add-on therapy to inhaled corticosteroids. The fixed-dose products of corticosteroids plus LABAs were more effective but also were with higher rates of Serious Adverse Events, and there were no differences in quality of life between those groups. So lastly, compared with leukotriene modifiers as an add-on therapy to LABAs, the inhaled corticosteroids plus LABA fixed-dose products demonstrated longer time to treatment failure in both adolescents and adults. So in other words, ICS/LABA products controlled symptoms for a longer period of time. So this last slide for Key Findings for the most recent report for controller agents, here they addressed Key Question 3 regarding differences between population subgroups for these outcomes. So, in general, as the patients who were younger experienced more exacerbations and Serious Adverse Events with the leukotriene modifier, montelukast sodium prepared with the inhaled steroid of budesonide. In a stratified analysis, African American patients experience more withdrawals due to Adverse Events and Serious Adverse Events with a formoterol tartrate compared with formoterol fumarate, while there was no difference in Caucasian patients. And another note here, these two drugs are not indicated for asthma at this time, although this study was done in patients with asthma. That last bullet point here shows that there were no differences in linear growth velocity between genders in children comparing the three drugs of montelukast sodium, budesonide, and fluticasone propionate, and this is in one observational study. Okay. For the Findings now in surveillance reports for controllers. So this was from since the systematic review through May of 2018. So there were no new Indications and no new novel of drugs. In this drug class, there were two new fixed-dose combination products that were listed under new

formulations in that last surveillance. So although I recognize new formulations are not necessarily of interest, I included the list here for completeness since it was reported in surveillance. That first and last bullet point are for products only indicated for COPD so likely not of interest. So the other three agents that are not in bold, there are new formulations of existing agents. However, the drug and bullet there is a new fixed-dose combination product indicated for asthma and approved in 2017. This is a triple therapy that includes fluticasone furoate, umeclidinium bromide, and vilanterol trifenatate, and this is with brand name Trelegy Ellipta. So while the individual agents of Trelegy Ellipta have not been newly approved, this is the first triple-therapy combination agent that is indicated for asthma. Also with surveillance, there were no new Boxed Warnings. However, one Warning was removed from the fixed combination dose products of inhaled corticosteroids plus LAMAs, and that was in December of 2017, and that Warning that was removed was for an increased risk for asthma-related hospitalizations, intubation, and deaths compared with the steroid alone. They also identified 25 new eligible studies in the surveillance of which 13 were for asthma. So one of these 13 was a systematic review and 12 were head-to-head randomized controlled trials. But noting that four of those trials were comparisons of the same drug with different formulations or delivery methods. Since the last DERP report, this includes, of course, the Findings from the surveillance and from the new searches for this archiving report. Other than the new fixed combination triple-therapy Trelegy Ellipta, there were no new asthma controller agents identified, but we did find seven new Indications for these agents, all of which were new since the last surveillance report in 2018. The first three were on this slide. In February 2017, the Indication for tiotropium bromide was expanded to include the treatment of asthma in patients six and older. Before 2017, it was only indicated for COPD. And as a reminder that Spiriva inhaler powder for this drug is not indicated for asthma, just this Respimat product, which is this soft mist formulation. Also a new formulation of the inhaled corticosteroid, beclomethasone, was developed and came to market in 2017, and it came with an expanded indication to include patients four years and older, where before it was only for ages five and up. In 2018, the FDA also expanded the Indication for fluticasone furoate, and that is an inhaled corticosteroid to include children as young as five years. So continuing on with new Indications. At the top there we see inhaled mometasone furoate with brand name and formulation Asmanex HFA that was expanded to include children as young as five years. And the next three agents listed our fixed-dose combination products of inhaled corticosteroids plus LABAs. So we have

budesonide plus formoterol and mometasone plus formoterol both expanded for use in younger patients for asthma in 2018 and 2019, respectively. And then at the bottom, we see fluticasone furoate plus vilanterol that was expanded for the maintenance treatment of asthma in patients ages five and older, this agent -- this combination drug was not indicated for asthma prior to 2023. Okay. So this in the next few slides was the FDA-approved Indications for the 18 controller agents, which one of those is the new agent identified during surveillance. So for the long-acting β2 agonists or LABAs, formoterol fumarate and salmeterol are both approved for the treatment of asthma as an add-on to a long-term asthma control agent and for the prevention of exercise-induced bronchospasm in children and adults, while only formoterol fumarate is also approved for the maintenance treatment of COPD. For LAMAs, we have tiotropium bromide. This is approved for the overall treatment of prevention of asthma, and then and then in the bottom row is the fixed triple combination product at trelegy. Ellipta is approved for the overall treatment and prevention of asthma as well as the prevention of exercise-induced bronchospasm. So on this slide we see we have all of the inhaled corticosteroids, and they are all approved only for the treatment and prevention of asthma. For inhaled corticosteroids plus LABAs at the top here, all four agents are approved for the treatment and prevention of asthma, but only three of those four agents are approved for the maintenance treatment of COPD, only mometasone furoate plus formoterol is not indicated for COPD. At the bottom here we see all three leukotriene modifiers are approved for the treatment and prevention of asthma, and only montelukast sodium or Singulair is also approved for the prevention of exercise-induced asthma. For Boxed or Serious Warnings, there was one new Boxed Warning for montelukast sodium and, again, this is a leukotriene modifier. This Warning was added to the label in 2020. It was for serious neuropsychic psychiatric events, which were reported in patients taking Singulair. And then #2, the removal of Boxed Warnings is that last report. So the first listed here is the removal of the Warning that I mentioned earlier for all ICS/LABA products, which [indistinct] at increased risk for asthma-related hospitalizations, intubations, and deaths compared with steroid -- using the steroid alone. And then in 2018 and 2019, the Boxed Warning for risk of asthma related to asthma-related deaths was demoted for all monotherapy LABAs, and it is downlisted as a more general Warning and not a Boxed or Serious Warning when used as monotherapy. We found four pipeline therapies for controlling asthma medications. For three of these four pipeline therapies are fixed combination products, and all of our inhaled products are currently in Phase III trials. So Breztri Aerosphere HFA is the triple inhaler therapy of

budesonide plus formoterol fumarate plus glycopyrrolate, which is a long-acting muscarinic antagonist (LAMA). Next, we have Fostair, which is a dual therapy of beclomethasone plus formoterol fumarate, and then we have PT001, which is glycopyrrolate, and this is a long-acting muscarinic antagonist or LAMA. And then we have QMF149 as also a fixed combination dual therapy of mometasone furoate plus indacaterol acetate. So this is an inhaled corticosteroid plus a LAMA. So for generic status this first of three slides shows the status of the inhaled corticosteroids. So only budesonide and fluticasone propionate are available as generic agents, and they became newly available since the last report. Next, are at the top here. We have the long-acting β2 agonists. So formoterol fumarate became newly available as a generic since the last report. And there appears to be also applications pending for the generic manufacturing of salmeterol xinafoate, but those have not yet been approved. Next, we have to tiotropium bromide and the fixed-dose triple therapy at the bottom there. Those have exclusivity rights until 2025 and 23, respectively. So three of the four fixed combination products of corticosteroids plus LABAs are now available as generics. Those include budesonide plus formoterol, fluticasone propionate plus salmeterol, and fluticasone furoate plus vilanterol. For mometasone furoate plus formoterol, which is Dulera, there was some conflicting information between IPD Analytics on the FDA websites. We do know that that the estimated generic launch date was in 2023, and there may be litigation holding things up, but it wasn't clear if that was available yet. And then at the bottom, we see that all three leukotriene modifiers are available as generic agents there, and they were likely available since -- with the last report in 2016. So on the next five slides, we are providing a very -- that general summary of clinical practice guideline recommendations for asthma in the populations of interests, including how and when the drug class of interest is used along the treatment pathway. And please note that the agents in blue there are controller agents, which is the topic for this report. So we can differentiate from the quick-relief agents that we will be presenting in the next report. So, in general, the recommendations mention that all patients should receive patient education and an individualized treatment action plan when diagnosed with asthma. Education should be around self-monitoring, how to use all of these prescribed medications, and how to avoid environmental triggers, and the pharmacotherapy was typically described in the recommendations as the cornerstone of asthma treatment. First, here, it was recommended that all patients have access to an inhaled bronchodilator, which is that quick-relief agent for those asthma symptoms. And then patients with moderate or severe asthma or in those who have severe

asthma attacks, low-dose corticosteroids were also a recommended option either as a concomitant agent with the quick-acting agents or via a fixed combination formulation. Regarding all pharmacotherapy, the additional maintenance therapy is based on asthma severity, and then adjustment of therapy is based on asthma control. So regarding maintenance therapy with controller agents, the stepwise approach to asthma treatment appears to be that core foundation in the asthma guidelines, which is basically where medications are escalated until good asthma control is achieved. This approach is based on the levels of severity and persistence of asthma, as I mentioned in the background section earlier. So Step 1 is for asthma that is assessed as intermittent and mild, and then Step 4 or higher is for asthma considered severe and persistent. So in adults and adolescents, maintenance therapy begins with Step 1, which is basically treatment as needed if pharmacotherapy is indicated. The National Asthma Education and Prevention Program Guidelines recommend only a quick-relief bronchodilator, so controller agents are not recommended by that organization, while the global initiative for asthma or GINA guidelines recommend combination therapy, so either as two agents used together or fixed-dose combination products. Corticosteroids plus a short-acting beta agonist or the newer fixed-dose combination product and corticosteroids plus formoterol, which is the LABA, such as Symbicort or Dulera. Step 2 is also treatment as needed where the National Asthma Education Prevention Program Guidelines recommend low-dose inhaled corticosteroids as monotherapy or in combination with short-acting β2 agonists while those GINA guidelines recommend the fixed-dose products of low-dose ICS plus formoterol agents. Leukotriene modifiers are recommended as alternatives when avoidance of inhaled corticosteroids is necessary because it has a little bit lower efficiency or efficacy. For Step 3 maintenance therapy, the guidelines recommend specifically the combination agents of corticosteroids and formoterol as preferred agents, -- and they also mentioned that tiotropium is appropriate for any patient intolerant to any LABA, such as formoterol. Step 4 or higher is for patients with severe and persistent asthma. This level of the condition is also called treatment-resistant asthma. Higher doses of inhaled corticosteroids plus formoterol or other LABAs are definitely recommended, and they also recommend to consider adding on an additional agent of leukotriene modifiers or utilize that new triple therapy product. It is also mentioned that systemic or oral glucocorticoids may be indicated in rare situations, but that the newer biologic agents may be a better alternative for severe asthma. For children, the overarching goals for those diagnosed with asthma are to maintain control of asthma symptoms

and reduce exacerbations with the least amount of medication and side effects. In general, the guidelines recommend "more intensive management for acute exacerbations in children, which can include oral glucocorticoids in children two to three years of age if they experienced these attacks more than two days per week and in children between four and 12 years if they experience those attacks throughout the day." The step care approach for pharmacotherapy is also used in this younger population for maintenance treatment, which is similar to adults. However, the corticosteroid formoterol product is not recommended in the guidelines until Step 3, and then Step 3 is also leukotriene modifiers maybe added as needed, where they were an option with Step 2 in adults. And also, I want to mention that the step care approach may include options to step-down in addition to stepping up, of course, and the guidelines recommend stepping down a level. It can occur if asthma control has been achieved for at least three months. So this last slide for guidelines here we have recommendations for exercise-induced bronchoconstriction. In general, they report that regular exercise actually improves cardiovascular fitness, which can actually reduce the risk for bronchoconstriction. So in the up-to-date guidelines, these recommendations are from the perspective that exercise-induced asthma is when exercise is a trigger for bronchoconstriction in patients with underlying asthma is not just an independent risk factor. So in patients with well-controlled asthma, the guidelines recommend individuals avoid triggers, such as cold air or dry air during exercise, and then if pharmacotherapy is indicated, a quick-relief agent like albuterol is recommended, or a combination of inhaled glucocorticoid and formoterol is recommended, and that should be taken about 5 to 20 minutes before exercise. For patients who require daily therapy for exercise-induced asthma with prolonged or recurrent exercise, they suggest regular use of a combined short- or quick-acting agent plus a long-acting product rather than a short-acting agent alone. And then they recommend if these pretreatments don't work and symptoms persist it is likely that the underlying asthma is poorly controlled, so they would refer to step-up therapy to be considered. So this is our final content slide for this report for controller agents for asthma. We list the relevant clinical practice guidelines for the treatment of asthma that were also referenced in the section for the guidelines in this report. They are also listed in alphabetical order, by author, or professional association, and the date of publication or guideline updates for these documents range from 2019 to 2023. So thank you for your attention.

Kavita Chawla: Thank you, Andrea. That was great. Kavita here. Nonye, any stakeholders for this section? I guess while we are waiting for that -- sorry, Committee, any questions for Andrea?

Peter Barkett: This is Peter Barkett. I have a question. Thank you for the presentation, very complete. I wanted to go back to the intraclass comparison of combination ICS/LABA products. I think what you had presented was that there was no difference between the different ICS/LABA products, but I thought that there was a difference with the formoterol-based products, and that was the basis for SMART therapy recommendations. Is that coming up in the rescue inhalers section? Or am I mistaken in the evidence?

Andrea Vintro: This is -- these were sort of the summary of Findings from the last DERP report. So exactly how that was translated, that would -- I could go back and look into that, but this is basically sort of extracted from the summary. If you could say that one more time for the intraclass.

Peter Barkett: Yeah. So, basically, it is my understanding that between 2016 and 2017, or whenever the last DERP report came out and now, the big change in asthma therapy is SMART therapy. And the basis of that was to accommodate the quick and long-acting effects of formoterol, which is why the formoterol-based ICS/LABAs get preferred treatment in most of the guidelines. And so I didn't hear mention of that in recent evidence, and so I am wondering if that evidence has been -- maybe I am mistaken and it is kind of overstated or -- and the reason I am bringing this up is because I am thinking that probably we want to include or require in our motion when we get to it that a formoterol-based ICS/LABA must be on the PDL because of SMART therapy. And so I was wondering where that was in the evidence for this report.

Andrea Vintro: It is possible that the newer evidence was not -- that there was newer evidence since that that has not been included in that last report. I don't know, Ryan, if you have anything else to add.

Ryan Pistoresi: Hi, good morning. This is Ryan Pistoresi. Yes, I am familiar with the new SMART therapy guidelines. I don't recall exactly where those recommendations were published and how that might have been within the scope of this presentation. As you know, this was a long overdue update in this class spanning from 2018 to recently, and I can just do a little bit of digging and see where that SMART therapy comes in versus what the guidelines were as part of the scope of this presentation.

Kavita Chawla: Kavita here. Thank you, Andrea and Ryan. And thank you, Peter, for asking that question because I think you are spot on about that. I did just post the last study that I am aware of as of last year, which compared salmeterol-based combo therapy versus formoterol. And I think you are spot on, Peter, that we try to -- whenever we review the motion, I, too, would like to ensure that we have a formoterol-based combo therapy that is listed as a preferred drug on the PDL. Great question. Other questions from the Committee? Any stakeholders, Nonye?

Nonye Connor: No, but I noticed [cross-talk] raised hands.

Ryan Pistoresi: This is Ryan. So before we would do the stakeholders, I do have the COPD portion to present, [cross-talk] and then -- yeah because this is together the asthma archive and the COPD are kind of one joint report. So let me go ahead and share my screen.

Kavita Chawla: I guess from the documents that we received in preparation for the meeting, I see that there are three different motions. There is one for control meds for asthma, there is one for quick-relief, and then there is one for COPD. So are we treating them as different motions, but we will just do them all together after you were done, Ryan? Is that what you would recommend?

Ryan Pistoresi: Right. So [cross-talk] --

Kavita Chawla: Okay.

Ryan Pistoresi: -- so this is Ryan. So for the Washington PDL, the asthma controllers and COPD controllers have always been treated as one evidence review, and as you saw in the reports, all of these COPD drugs were listed in red as being out of scope for the archive report. So in order for us to archive the asthma and COPD together as one class, we are providing some updated -- the most recent evidence that we have on the COPD Indications, which happens to be that last scan that we had from 2018. So as you saw from the recent presentation, that was all of the information updated on asthma since this scan, and because we didn't have COPD as part of that, we are including the COPD drugs as part of this, and then that way when we get to the motion, we can have all of those drugs together, and then we can do the archive together at the end of the P&T today.

Kavita Chawla: Great. Thank you for that, Ryan. All right, take it away.

Ryan Pistoresi: Okay. So, as I mentioned, this is the last scan that we had received for the asthma COPD controllers, and this was from 2018. And as you had seen with the previous presentation, the COPD drugs were excluded, so I am just going to highlight really the most recent evidence that we have seen for the COPD medications. So the last time that we had a full update for the asthma and COPD controllers as a class was in 2016. We had a previous scan in 2017 and a current scan from March of 2017 that looked through studies that were published through May of 2018. For those of you who are wondering about a scan versus a surveillance, a scan was a previous type of report that we received from DERP that looked at what type of evidence was being published to help states understand when to commission a new report. Surveillance documents are very similar, although they do have a bit more in depth looking at some of those studies that are being published. So if you are curious about the difference between a scan and a surveillance document, just know that these types of scan documents have since evolved into the current surveillance documents that we have been presenting over the last few years at our P&T meetings. The Key Questions for this scan, we are looking at the comparative Efficacy and Effectiveness within classes and across classes of the long-acting inhaled and long-acting oral medications used for asthma and COPD. The second Key Question was around Safety, so this was looking at within class and across class tolerability and frequency of Adverse Events of the long-acting inhaled and long-acting oral medications for asthma and COPD. And the third Key Question for this scan was around subpopulation, so looking at whether there were groups or subgroups of patients for which asthma or COPD controller medications differed in terms of their Efficacy or Safety. The populations that were included in this scan were for adults and pediatrics, so greater than or equal to 12 months for patients with persistent or chronic asthma and for COPD. They had to be 18 years of age or older. The included interventions are listed here on this slide. They were all previously mentioned in the asthma controllers. Just note that since this is from 2018, that the two underlined drugs are new to this scan but were previously mentioned in the asthma/COPD one, so that triple therapy that was bolded on that one slide with the new drugs. That is this one there, that is the Trelegy, and then the formoterol glycopyrrolate, that is a COPD only indication, so that one is new for this scan. Since our last report in 2016, as of 2018, these are the new Formulations and Indications. So this just highlights what happened mainly between 2016 and 2017. Regarding the Harms reported since the last report, there was a removal of a Blackbox

Warning for the ICS/LABAs around increased asthma-related hospitalizations and deaths. So in light of what Dr. Barkett mentioned around the formoterol being used in SMART therapy, there was that previous Blackbox Warning and just highlighting that that was removed in December of 2017. There was one comparative effectiveness review published by AHRQ that is part of the scope, but that was done in 2018. And I believe that that has then been evolved into those guideline updates that you had seen in the last presentation. So between the 2016 report and the May 2018 timeframe of when this scan was conducted, we identified 11 trials comparing the same drugs in different delivery devices, and we know that during this time they were changing a lot of the devices and formulations for these medications. In terms of the head-to-head studies that we are most interested in, there were 13, and 10 of them were identified in the period of the scan from 2017 through 2018, and then there were 18 secondary publications of previously included trials, and 16 were new in the scan. So on this slide, as you can see, we have some grayed out ones. The gray ones are new with this scan, so just highlighting that these are the new therapies that were published for asthma and COPD that were later incorporated into the guideline recommendations that you had seen, but just highlighting that for the ones with COPD, that I will highlight here, the Feldman from 2016, the Ferguson from 2017, the Kalberg from 2016, the Kerwin from 2017, our COPD-specific trials, and on this slide, the Lipson from 2017, the Papi from 2018, the Vestbo from 2016, and the Wedzicha from 2016 are also COPD specific, and so you did not get those with the asthma controller archive report previously. So the summary since the 2016 report is that there were six new formulations for the existing drugs, three were identified in the scan. One Blackbox Warning was removed for the ICS/LABAs in asthma. There was one new comparative effectiveness review, which was the AHRQ review that was completed in 2018. And in terms of new studies that were being published, there were 13 head-to-head trials that were identified. The 10 ones that were shaded were new from this scan, and there are 11 trials comparing different device types. So the different ways in which the drugs are delivered to the patient, and the 18 secondary publications with 16 that were new on this trial. So any questions on this scan highlighting what we had in terms of evidence around COPD? I am going to stop sharing because it is a little bit easier for me to see what is going on without the screen sharing.

Kavita Chawla: Thank you for that, Ryan. Questions from the Committee?

Ryan Pistoresi: Okay. If there are no questions, then I think the next thing is the stakeholders. So thank you for your attention this morning.

Kavita Chawla: Thank you, Ryan. Nonye, any stakeholders for either of these sections?

Nonye Connor: No, I don't see any stakeholders, no hands raised, and no questions.

Kavita Chawla: All right, thank you.

Nonye Connor: So I am going to go ahead and share my screen, and we are going to be doing -- going over the motions for both the COPD and the asthma controllers. So let me share my screen. There we go.

Kavita Chawla: Thank you.

Nonye Connor: Mm-hmm.

Kavita Chawla: Can I have you magnify it a little bit?

Nonye Connor: Oh, yes. Sorry.

Kavita Chawla: Thank you.

Nonye Connor: There we go.

Kavita Chawla: I guess I am curious what that last statement means. "All delivery systems and indications will be included for all drugs." [Cross-talk] Is that to say that all delivery systems will be available on the PDL?

Ryan Pistoresi: And so this is Ryan. So, no. This was to say that all the delivery systems for the drugs indicated on the column on the left are included within the purview of this study. [Cross-talk] --

Kavita Chawla: [Cross-talk] Oh, okay.

Ryan Pistoresi: [Cross-talk] So, for example, as I mentioned we changed from the CFCs to the HFAs, and now we have things like the RespiClick or the soft mist or the dry powder inhalers. So instead of trying to have these new delivery devices be considered new drugs and unstudied, we realize that the ingredient is the same between these different drugs and that because the ingredient had

been studied and reviewed as part of our P&T, that we didn't need to break out all of the different device types in the future. So this was more of a consideration that was made at the last meeting in 2018. Yeah. As you saw from that scan, we had some emphasis on the different device types that were just copied forward from the previous motion about that. So that is just saying that we don't need to study all of the different types of devices head-to-head between each other.

Kavita Chawla: Great. Thank you, Ryan. Questions from the Committee or comments about the motion? I guess the only thing I would wonder about is, do we need to say for treatment of asthma slash COPD in the motion? Or do we have a separate motion where we will call out COPD?

Ryan Pistoresi: So this is Ryan, and there are actually going to be seven of these motions for each of the [cross-talk] --

Kavita Chawla: [Cross-talk] Oh, okay. [Cross-talk]

Ryan Pistoresi: [Cross-talk] classes.

Kavita Chawla: Okay.

Ryan Pistoresi: The way that we had designed this is that because there is overlap between the asthma and COPD Indications, that we put that Block A or that Block C next to the drugs to indicate whether they are approved for asthma and COPD. So for the inhaled corticosteroids, these are all asthma only Indications.

Kavita Chawla: All right, Committee, expressions or comments.

Jon MacKay: This is Jon MacKay. I would move that the inhaled corticosteroids after considering the evidence of safety, efficacy, and special populations for the treatment of asthma, I move that beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone MDI aerosol, mometasone DPI powder, are safe and efficacious for the treatment of their approved indications. Inhaled corticosteroids can be subject to therapeutic interchange in Washington's Preferred Drug List. All delivery systems and indications will be included for all drugs.

Peter Barkett: Peter Barkett, I will second the motion.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Any opposed or abstained? Thank you. With that the motion carries.

Nonye Connor: Sorry for the scrolling. Next one.

Kavita Chawla: Great. Thank you. So this one is for the LABAs. And, yes, thank you for the background. A CNA now makes sense.

Jon MacKay: I think -- this is Jon MacKay. I would kind of second Dr. Barkett's concern that we had call out formoterol in terms of requiring that.

Ryan Pistoresi: This is Ryan again. I am trying to do some research about your question, Dr. Barkett. So looking at the GINA guidelines that were included as Slide 2 of 5 on the controllers, it looks like the recommendations are for the ICS/SABA, so the short-acting beta agonist or low-dose ICS/formoterol. So it does say ICS/LABAs. It looks like that recommendation is for ICS/formoterol. So I think that is what you were talking about as it relates to the study that Kavita mentioned. So I think that is included within the context of the report, it is just that it was on the clinical practice guidelines page.

Peter Barkett: Okay. Yeah, I think the concern would be -- well, the theory on SMART therapy is that if you give somebody a rescue inhaler and a separate maintenance inhaler, they may not have perfect compliance with one or both, and they are more likely to be more compliant if you give them a single inhaler for both. So for somebody with moderate persistent asthma, the evidence suggests that they do better on something like budesonide/formoterol as opposed to like a salmeterol/fluticasone product. And so the ICS/LABA combination products are my area of concern, and I assume we will have a separate [cross-talk] motion for the combination products.

Kavita Chawla: Yeah. That is right. I see that Page 7 is where we are going to be addressing the ICS/LABA, and I think that is where we can make sure to bring up this concern and word it is such that we incorporate the formoterol-based combo inhalers. So I think this one is -- so I think we are doing just ICS, we are doing just LABA, we are doing just LAMA, and [cross-talk], and then we are at the LK, and then we will get to the combo.

Nonye Connor: Yes.

Jon MacKay: Okay, then I am comfortable with this motion as is.

Kavita Chawla: Okay. So if no questions, if anybody would like to propose the motion.

Kevin Flynn: This is Kevin Flynn. After considering the evidence of safety, efficacy, and special populations for the treatment of asthma and COPD, I move that arformoterol, formoterol nebulizer, formoterol powder, indacaterol, olodaterol, and salmeterol are safe and efficacious for the treatment of COPD when used in combination with inhaled corticosteroids for the treatment of asthma. Long-acting beta agonists can be subject to therapeutic interchange in the Washington Preferred Drug List when the preferred drug is approved for the condition being treated.

Jon MacKay: This is Jon MacKay, I second.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? Okay. With that the motion carries. I suppose, Committee, the only question I have is the statement that we had at the very beginning, "All delivery systems and indications will be included for all drugs." Do we need that in every motion just to call it out? And maybe Ryan -- it is a question for Ryan.

Ryan Pistoresi: Yeah. So this is Ryan. For some of these other classes we are seeing different movement within the devices, so it could be prudent for us to include that statement going forward. I think for this class, we are okay not having that. I can just double check the Washington PDL and see for the [cross-talk] --

Kavita Chawla: [Cross-talk] And also because we are considering archiving these after, and so for future protection if we -- who knows what formulations are going to come out -- if we need to include that statement for all of these classes.

Ryan Pistoresi: Right. So it looks like for this one there has not been any new formulations that have been approved. It looks like most of these are actually nebulizers like the Brovana and Perforomist.

Kevin Flynn: There is inhaled -- there are dry powder inhalants in some of these.

Ryan Pistoresi: Yes, I do see that with the Serevent Diskus and the Striverdi Respimat.

Kevin Flynn: Yeah, like olodaterol has a Respimat [indistinct] to the point of future proof it because especially for generic, sometimes the device is different. Perhaps we should add that statement just to give the maximum freedom.

Kavita Chawla: I am seeing head nodding. So does the rest of the Committee agree with that?

Laura Beste: I agree.

Christy Weiland: I agree.

Greg Hudson: Yeah. [Cross-talk] --

Kevin Flynn: I just add that to my motion?

Kavita Chawla: Yes. Any opposed to that -- I know, reiterating the question. Sorry, I should have spoken up early on. Okay, cool. Thank you. Okay, great. We can go on to the next class, Nonye. Thank you so much. [cross-talk] We will keep adding it, I think, to each of the motions that is one statement, although this one, I don't think it matters. Is zileuton still a thing on the market?

Ryan Pistoresi: This is Ryan, and they may not be on the market, but they were included as within the scope of this study. So I think for this one, we will include it as a drug that is reviewed, but if you want to have it be in the motion that it is not -- I am just looking. It looks like they are all included on the market, but they may just not be widely used.

Kavita Chawla: Okay, thank you. Great. Comments from the Committee members?

Greg Hudson: I think in the past with drugs like zileuton we have -- in the left-hand column, we have sort of indicated that they are not preferred. Does that need to happen on this?

Ryan Pistoresi: Yes. And this is Ryan. So kind of in the middle of that zileuton shall not be a preferred drug on the Washington Preferred Drug List. So that was how we had always treated it as never being preferred but to the point that it is still

available, it looks like it still is technically available as an extended-release form.

Kavita Chawla: Great. Any other comments? And, if not, whenever we are ready for the motion.

Peter Barkett: This is Peter Barkett. I can make the motion. After considering the evidence of safety, efficacy, and special populations for the treatment of asthma, I move that montelukast, zafirlukast, and zileuton are efficacious. Montelukast and zafirlukast may be associated with a lower incidence of hepatic toxicity than zileuton. Zileuton shall not be a preferred drug in the Washington Preferred Drug List. Leukotriene modifiers can be subject to therapeutic interchange in the Washington Preferred Drug List for the indication of asthma.

Christy Weiland: Christy Weiland, [audio cuts out].

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? Okay. With that the motion carries. And I think the next one is the combination. That is the one we want to do work on. So should we propose somewhere in there after it says, "safe and efficacious for their approved indication," should we say at least one formulation of ICS/formoterol will be preferred on the PDL?

Peter Barkett: Yeah, I think that sounds good. Yeah, at least one combination of ICS plus formoterol must be included in the Washington Preferred Drug List, and then maybe a reference to that and that therapeutic interchange statement? Yeah.

Kavita Chawla: Okay.

Ryan Pistoresi: So this is Ryan. Is that true for both asthma and COPD?

Peter Barkett: No, it is just asthma.

Ryan Pistoresi: Okay. So then I think we would want to include that just given that we do have COPD [cross-talk] one of the -- yeah, the budesonide formoterol at the very top is a COPD indication as well.

Kavita Chawla: Okay, great. Yeah. So we can say at least one formulation of ICS/formoterol, F-O-R-M-O-T-E-R-O-L, will be included as a preferred drug for asthma on the PDL. This is my first run at it. Committee, go! Is that fair?

Ryan Pistoresi: I think the only suggestion I would have, Nonye, is to add Washington before PDL.

Kavita Chawla: Oh, yes. Thank you. And then I think, Peter, you were starting to say for the therapeutic interchange part, did you want to modify that somehow to [cross-talk] --

Peter Barkett: [Cross-talk] Yeah, I think so. So, I mean, if we want to include at least one formoterol product on the Preferred Drug List than the formoterol cannot be interchanged. [Cross-talk] But if we -- I don't know if we exempted formoterol from therapeutic interchange or if we clarified that the interchange was applicable to [cross-talk] non-formoterol product -- yeah.

Kevin Flynn: Well, you could technically interchange between the two, the mometasone and the budesonide one.

Kavita Chawla: Mm-hmm. [Cross-talk]

Peter Barkett: [Cross-talk] Yeah, like [cross-talk] --

Kavita Chawla: And so maybe the additional sentence can be formoterol/ICS can only be interchanged with another [cross-talk] --

Peter Barkett: [Cross-talk] Sure. Yeah. Symbicort or Dulera. It does not matter.

Kavita Chawla: Yeah.

Peter Barkett: It should be equally efficacious. It is just we don't want to -- I wouldn't want to interchange like a salmeterol product with a formoterol product. [Cross-talk] --

Laura Beste: [Cross-talk] [indistinct] --

Kavita Chawla: And so for [cross-talk] I guess we would have to say for asthma. Sorry, Laura. Go ahead.

Laura Beste: No. I wanted to say to make it less wordy you could just say, "formoterol/ICS for asthma may not be interchanged.

Kavita Chawla: How does that work, Ryan? What do you think?

Ryan Pistoresi: [Cross-talk] Yeah, so [cross-talk] --

Laura Beste: [Cross-talk] And then [Cross-talk] long-acting beta agonists can be.

Kavita Chawla: Yeah.

Ryan Pistoresi: Yeah. So this is Ryan. So that would be saying that if someone were to be prescribed a nonpreferred ICS/LABA that we would have to go to the other preferred, so that would be the fluticasone/salmeterol products. So if someone were to be getting the fluticasone/vilanterol, we would be switching to the salmeterol because we are excluding it from interchange. So if we are requiring that at least one formulation of an ICS/formoterol is preferred for asthma, that means any of the nonpreferred drugs could be switched into the ICS/formoterol. So I think my recommendation would be to remove that most recent line that says that it may not be interchanged because if it is preferred, it is not going to be interchanged. [cross-talk] --

Peter Barkett: [Cross-talk] how would [cross-talk] --

Ryan Pistoresi: [Cross-talk] applies to a nonpreferred drug.

Peter Barkett: What if we -- what if we changed it to formoterol/ICS product may only be interchanged with another formoterol/ICS product. So let's say, like, Symbicort is on the Preferred Drug List, but Dulera is not, if some someone gets prescribed Dulera, for SMART therapy, I wouldn't want that to get swapped to a non-formoterol preferred product, like, say Advair, if it were being prescribed. Does that make sense? Like, can we do like a positive inclusion, where we say, "formoterol/ICS products may only be interchanged with other formoterol/ICS products?"

Ryan Pistoresi: Yes. I think that is how you should phrase that because, to your point, Dulera and Symbicort are right now nonpreferred. Our preferred are the fluticasone, salmeterol, and the generic Symbicort, so potential interchange as of today

could be to either of those. If you change it to have that statement, then the Dulera or the Symbicort would be interchanged into the generic Symbicort.

Kavita Chawla: Great. That is helpful. Okay, so, Nonye, where you are at, I think formoterol/ICS for asthma may only be interchanged with another formoterol/ICS product. How does that look, Committee? Fair? Okay. Okay. Other comments? And, if not, we will proceed with the motion.

Kevin Flynn: This is Kevin Flynn. After considering the evidence of safety, efficacy, and special populations for the treatment of asthma and COPD, I move that fluticasone propionate/salmeterol DPI, fluticasone propionate/salmeterol MDI, budesonide/formoterol, fluticasone furoate/vilanterol, mometasone furoate/formoterol are safe and efficacious for the treatment of the approved indications. At least one formulation of ICS/formoterol will be included as a preferred drug for asthma on the Washington PDL. Formoterol/ICS for asthma can only be interchanged with another formoterol/ICS product. Long-acting beta agonist combinations with ICS products can be subject to therapeutic interchange in the Washington Preferred Drug List if the preferred drug is approved for the condition being treated. All delivery systems and indications will be included for all drugs.

Greg Hudson: This is Greg Hudson, and I second.

Kavita Chawla: Great, thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? All right. And with that the motion carries. Thank you, Committee. All right. Now LAMA/LABA combinations.

Kevin Flynn: Can we add our statement about the formulations?

Kavita Chawla: Yes, please.

Nonye Connor: Thank you.

Kavita Chawla: Thank you for the reminder, Kevin.

Ryan Pistoresi: So this is Ryan. So just down below, you will see that gray means that those were newer drugs that are not included in that review. So if you remember

from the scan that I presented that formoterol/glycopyrrolate was a newly identified one in the scan, meaning that it was not in the last report, meaning that we did not present evidence on it. And that new formoterol/aclidinium is also new and has not been reviewed by the Committee. So both of those are in gray, and they cannot be included in the motion or be preferred on the PDL without being reviewed.

Greg Hudson: This is Greg Hudson, Ryan. Is there any difference between the bolded and not bolded?

Ryan Pistoresi: Yes. So the bold means that it was new in this update. So because the formoterol/glycopyrrolate was reviewed in the scan in 2018, it would have been bolded back then, and since it is being carried forward in this motion, it is not a newly identified drug. It is just a drug that has not been reviewed yet, so that is the difference between the bold and non-bold.

Greg Hudson: Okay. Gotcha.

Laura Beste: And just for clarity, if a provider wanted to order those and prescribe those medications, they could still get them, they would just have to use a preferred -- two preferred agents before.

Ryan Pistoresi: So this is Ryan. It doesn't require two for the Washington Preferred Drug List. That is for the Apple Health Preferred Drug List. So when we get to the DUR portion, it is typically two for that. So for the Washington PDL, I believe we only have one preferred drug in this class, so they would have to try that one first, and then any of the nonpreferred could be used thereafter.

Laura Beste: Okay. This is Laura Beste. I will make a motion as long as no one else has any comments. No? For LAMA/LABA combinations, after considering the evidence of safety, efficacy, and special populations for the treatment of asthma and COPD, I move that in indacaterol/glycopyrrolate, olodaterol/tiotropium, and umeclidinium/vilanterol are safe and efficacious for the treatment of approved indications. Long-acting beta agonist combination with LAMA products can be subject to therapeutic interchange in the Washington Preferred Drug List if the preferred drug is approved for that condition being treated. All delivery systems and indications will be included for all drugs.

Peter Barkett: Peter Barkett, I second the motion.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? Thank you. With that the motion carries. On with the PDE inhibitors.

Laura Beste: Do you need to include the subject to therapeutic interchange when there are no other medications in the class besides roflumilast?

Ryan Pistoresi: This is Ryan. Technically, no, you don't. I think when they were making the motions in the past for the asthma/COPD, they continued to just have that in case there were other ones. As you know, this drug has been in a class of itself for many, many years. So I don't think having that makes any difference to how we would review and manage this class.

Kavita Chawla: Is roflumilast only approved for COPD, or is it also approved for pulmonary hypertension? And doesn't matter? Like, should -- do we need to include all the FDA-approved conditions in the motion, or it doesn't matter?

Ryan Pistoresi: So this is Ryan. So since this class is specific to asthma and COPD indications, we are only reviewing it for asthma/COPD.

Kavita Chawla: Okay.

Ryan Pistoresi: Like I mentioned with the medical provider prior, if it does have other indications and can be included in managing a patient with that disease state, it doesn't necessarily mean that it is being affected, it is just saying that as part of this motion for this class, we are only focusing on COPD and not some of the other indications that a drug may be used for.

Kavita Chawla: All right, thank you. Okay. Other questions from the Committee or comments?

Greg Hudson: [Cross-talk] Hi, this is Greg Hudson. I will motion that after considering the evidence of safety and efficacy and special populations for the treatment of COPD, I move that roflumilast is safe and efficacious for the treatment of COPD. Phosphodiesterase-4 inhibitors can be subject to therapeutic

interchange in the Washington State Preferred Drug List. All delivery systems and indications will be included for all drugs.

Jon MacKay: This is Jon MacKay, I second.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? Okay. With that the motion carries. Thank you. The LAMAs alone. I am wondering for some of these since we are seeing now "all delivery systems will be included," maybe we can clean up the motion a bit where, like, for example, after the tiotropium, it says DPI powder. Maybe we can just remove that. Tiotropium is basically listed twice because of the different formulations. So maybe we don't need that. Is that okay?

Ryan Pistoresi: So this Ryan. I would recommend keeping them separate [cross-talk] based off of what we see on the left where the DPI powder is COPD only and where the mist is asthma and COPD. So just I guess for for noticing that one device is approved for an indication that it is different than like we had prior in 2017/2018 with the other devices. So I would say because of that indication difference that I would prefer them to be separate.

Kavita Chawla: I appreciate that. Thank you.

Peter Barkett: This is Peter Barkett. I can make the motion. After considering the evidence of safety, efficacy, and special populations for the treatment of asthma and COPD, I move that aclidinium, glycopyrrolate, tiotropium DPI powder, tiotropium SMI mist, and umeclidinium are safe and efficacious for the treatment of their approved indications. LAMAs can be subject to therapeutic interchange in the Washington Preferred Drug List. All delivery systems and indications will be included for all drugs.

Kevin Flynn: This is Kevin Flynn. I second.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? Great. And with that the motion carries. Yay! Triple therapy! Is this the COPD one? Oh, okay. There was one for asthma.

Ryan Pistoresi: For this one, the gray one, it is still in the pipeline, so that is why it is listed there. Comments or suggestions from the Committee or questions.

Laura Beste: This is Laura Beste. I will make a motion that after considering the evidence of safety, efficacy, and special populations for the treatment of asthma and COPD, I move that budesonide/glycopyrrolate/formoterol furoate and fluticasone/umeclidinium/vilanterol are safe and efficacious for the treatment of their approved indications. Long-acting beta agonist combination with ICS and LAMA products can be subject to therapeutic interchange in the Washington Preferred Drug List if the preferred drug is approved for the condition being treated. All delivery systems and indications will be included for all drugs.

Christy Weiland: Christy Weiland, I second.

Kavita Chawla: Great All in favor, please say aye.

Multiple Speakers: Aye. Aye.

Kavita Chawla: And any opposed or abstained? Thank you. With that the motion carries. Ah!

Nonye Connor: That's it.

Kavita Chawla: We did it. Yay! Good job, Committee. And Laura gets the award for pronouncing the most number of drugs correctly at the first go round. Okay. So do we do the short-acting agents for asthma before we take a break? Are we okay with that, Committee, or do you want to take a break now? Technically, 11:10 is when we take the break. Take a break?

Laura Beste: I say push through.

Kavita Chawla: Push through!

Laura Beste: Push through!

Peter Barkett: Be bold.

Kavita Chawla: All right, let's do it. Where is my agenda? So I think that is Andrea again. Do we have her? There she is. Hi.

Andrea Vintro: It is me again.

Kavita Chawla: Welcome back.

Andrea Vintro: Great. Yes, hello everyone. Again, my name is Andrea Vintro. I am a Research Associate at the Center for Evidence-Based Policies. This is our third presentation today for this drug archiving project. For those of you who were with me during any of my previous presentations, as a reminder, I will need to repeat all the topics for this presentation because they are likely new audience members and specifically for this presentation it does include the background section and the clinical practice guidelines section because this report -- that last report was also for the condition of asthma. So for some of you, thank you for bearing with me. So this report is on the drug class of quick-relief or short-acting medications for asthma. So the aim of this work is for the Drug Effectiveness Review Project (DERP) to develop and present information to the Washington State Pharmacy and Therapeutics Committee on nine drug classes that are candidates to be archived from active review by the Committee. The list of the drug classes that are included in the archiving project are at the bottom of this slide with the drug class for this presentation highlighted in green, which is asthma quick-relief drugs. So for this presentation, we are going to review those topics listed in those darker green boxes on this slide. So starting on the left, I will first define the health condition of interest for this drug class, then I will review the key information in the most recent DERP reports for this drug class, including the PICOS, the Key Questions, a high-level summary of the Key Findings, and then general Findings of any surveillance that was completed after that last systematic review. Next, I will present any new actions by the FDA for this class since the last report, including any new drug approvals, new Boxed or Serious Warnings, and any new Indications. Moving on, and then I will report on any new pipeline drug Findings, and then also the generic status of those existing FDA-approved drugs for this class. And then, lastly, I will provide a high-level summary of recommendations and relevant clinical practice guidelines for the treatment of asthma, which includes recommendations about how and where these agents are used along the treatment pathway, and then we will have time for questions. So asthma is a chronic lung disease characterized by inflammation of the lining of the airway in the lungs, which causes the airways to narrow and the lining tissue to secrete extra mucus

that result in this reversible airway obstruction. Asthma also increases airway responsiveness, which is often called hyper-responsiveness. This is this predisposition for the airway to narrow excessively in response to stimuli that will produce little or no effect in otherwise healthy individuals. These stimuli are often considered triggers for asthma attacks. Those include things like tobacco smoke, pet dander, cold air, etc. Symptoms of asthma include wheezing, difficulty breathing or shortness of breath. There is also coughing, particularly at night or in the early mornings, and then also feelings of tightness in the chest. As with symptoms can also interfere with sleep or prevent individuals from doing activities of daily living that could affect overall health and increased risk for other health conditions. Individuals can die from untreated asthma attacks, but that is rare, but there are long-term risks in individuals with more severe forms of asthma, including worsening lung function over time and then side effects that come along with the long-term use of certain medications like oral corticosteroids. So according to the CDC recent statistics, nearly 25 million individuals in the US have asthma, 3% to 13% of individuals have the severe form of the condition, and those with that severe form have higher hospital utilization rates and higher medical costs. Of course, then those with the non-severe form. Asthma is the leading chronic disease in children. Male children are more likely to be diagnosed with asthma compared with female children, but this is reversed in adulthood, so more female adults are likely to have asthma. There are also racial disparities in prevalence with non-Hispanic black children being twice as likely to have the condition compared with white children. And then exercise-induced asthma is where exercise can trigger symptoms in individuals with asthma. There are some reports that people without a clinical diagnosis of asthma can experience exercise-induced asthma symptoms, but it is considered to be more rare. The exact cause of asthma is unknown. It is thought to be a combination of genetic and environmental factors. Common risk factors are in the green boxes at the bottom. So we have a family history of asthma, allergies, viral respiratory infections during childhood, also occupational environmental exposures, including dust, chemical fumes, or vapors, among others. And then obesity is also listed to as a risk factor, but the mechanism is the causal mechanism is less clear in the evidence. So the primary goal for treatment and management of asthma is the primary goals are to optimize controlling symptoms, reduce the risk of asthma exacerbations or attacks, and then reduce long-term complications. So clinically, asthma is typically classified into intermittent or persistent disease. Persistent asthma is when an individual has symptoms more than twice a week. And then with persistent asthma, it is further classified by the

severity of disease. Treatment typically starts with non-pharmacologic interventions, including breathing exercises or increased physical activity, and also to recommend avoiding environmental triggers, such as allergens or tobacco smoke and cold air. The more common medications used to treat asthma are categorized into first the two drug classes that we are presenting today at the top. Those are the top bullet points in the bottom light green box on the right there. So we have quick-relief medications, which is the class of drugs that we are reporting on for this presentation. Those are for acute symptoms, and also known as bronchodilators, of which all are short-acting β2 agonists or SABAs. And then controller medications help to prevent symptoms and slow the progression of the disease. Those include inhaled corticosteroids. Also sometimes oral systemic corticosteroids if the treatment continues to be challenging, and then also long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are also common maintenance or controller drugs for asthma. And then more recently, we have the combination quick-relief and controller medications together have become available. Also biologics are newer and are typically indicated for individuals with a more severe form of asthma. So four reports prepared by DERP on this topic. Last DERP systematic review for quick-relief products for asthma was presented in August of 2008, so that is over 15 years ago, and the search dates for that report were through May of 2008. And then since that last report, DERP prepared four surveillance reports -- or scans as they were called back then -- with the last surveillance presented in 2015, and sources for the surveillance were searched through mid-December of 2014. So the next three slides are the PICOS for the DERP products for the quick-relief agents. So the population included adults and children with asthma, including those with exercise-induced bronchospasm. The comparators were another listed intervention, so only head-to-head study comparators were included for study designs. They included randomized controlled trials, non-randomized controlled trials with at least 20 participants, and also observational studies for Safety or Adverse Event outcomes only. So for interventions, only two of the seven agents that were included in the most recent report are of interest for this archiving report, and those are albuterol and levalbuterol, both of which are short-acting beta agonists (SABAs). So those not of interest for this report are listed in red text that was included in the last report. For outcomes, the last report included symptoms, including cough, wheezing, shortness of breath, also changes in the treatment regimen for exacerbations or asthma attacks. Also, measures of healthcare use, also exercise tolerance and symptoms, and that is for exercise-induced bronchospasm only. Also mortality and several measures

for Adverse Events. There were three Key Questions in the last report. So Key Questions 1 and 2, asked about the comparative Efficacy and Harms of these agents for asthma and for the prevention of exercise-induced bronchospasm, and then Key Question 3 asked about differences in Effectiveness and Harms across patient subgroups. So for this summary of Findings from the last report on quick-relief agents for asthma, I only included Key Findings that were regarding the drugs of interest for this archive reports, only those Findings for albuterol and levalbuterol. So cumulatively since the original report, 10 studies were included comparing albuterol and levalbuterol for asthma, and there were no studies for these agents that were for exercise-induced bronchospasm. Four studies were in adults, and five were in children. So for adults with asthma, for the summary of those Key Findings, they found that -- so less rescue medication was required with levalbuterol, but there were no statistical analyses done for between group differences. So no significant -- no tests were done and, in general, there were no differences in number of symptoms between groups. In the emergency department setting, there were mixed results for hospitalization admission rates. However, there was some evidence for decreased admission with levalbuterol compared with albuterol in patients not using corticosteroids. For Safety outcomes, there was no difference in withdrawals due to Adverse Events, and most specific Adverse Events, although albuterol might show it has demonstrated some increases in heart rate compared with levalbuterol. They also addressed the limitations of the evidence reported that outcomes were not stratified by race, and studies that actually included mostly African American individuals, and there were no other studies that stratified results by different populations of interest. For children and adolescents the most recent report -- systematic review found that, in general, there were no differences in symptoms, rescue medications, or number of days of inadequate control between these two agents but that it may depend on the dose given. In the emergency department setting, there were no differences in symptoms and requirements for additional treatment, but there may be some benefit around fewer hospital admissions with levalbuterol. The report also noted that there was poor reporting of Safety data across all of the studies but, in general, it appeared that there were no differences in specific Adverse Events between these agents, but there may be some evidence for higher rates of overall Adverse Events with albuterol compared with levalbuterol, and then similarly, in studies of adults, outcomes were not stratified by populations of interest. So that Key Question about differences across populations was a challenge to answer -- remains a challenge to answer for Findings during the surveillance period. So after the most recent

report through -- this was up through December of 2014 -- they found no new FDA-approved drugs, no new Boxed or Serious Warnings, no new Comparative Effectiveness Systematic Reviews, but they did find two new published head-to-head trials of albuterol versus levalbuterol, which both were in pediatric populations. For FDA activity since the most recent report, this is including the surveillance and searches through the search dates for this archiving report. We found one new drug that was approved in January of 2023. This one is a fixed combination drug that includes both a short-acting and long-acting agent, so albuterol plus budesonide, the brand name Airsupra. Albuterol is the short-acting beta agonist, and budesonide is the inhaled corticosteroid, of course. So I included this drug as being in this class of quick-relief agents because its FDA-approved indication is for this class, as you will see on the next slide, but recognizing that it is somewhat of a crossover agent. Regarding the next bullet point, which is also of note, the epinephrine meter-based -- metered-dose inhaler, Primatene Mist, was also reapproved in 2018 for over-the-counter use through a new drug application after it was discontinued in 2011, and this was despite, likely, as you know, objections for physicians and medical organizations because of its potential to increase heart rate and blood pressure. And also of note, it is not listed as a recommended treatment in the NIH's guidelines for asthma treatment. Next, we have for new Indications, two brands of albuterol were approved for expanded use in children, who are at least four years of age -- this was in 2008 -- and the age was reduced from 12 years down to four years for this expansion. The FDA-approved Indications for albuterol, levalbuterol, and the new agent, Airsupra, are listed here on this table. All agents are approved for the treatment and prevention of bronchospasm with reversible obstructive airway disease. This is in patients in four years and older, and six and older with albuterol and levalbuterol, respectively, and then 18 and older with the newer Airsupra agent. So only albuterol is indicated for the prevention of exercise-induced bronchospasm. And then in the far right column, you can see that only the newer agent, Airsupra, is also approved for reducing the risk of exacerbations because it is that combination drug of both quick-relief and controller agents. So since the last report, there were no new Boxed Warnings or Serious Harms for quick-relief agents. We found one new pipeline therapy. This was a combination therapy of albuterol, which is the short -- SABA plus the inhaled corticosteroid, fluticasone propionate. This is a powder formulation that is inhaled, and it is currently in Phase III trials. So both albuterol and levalbuterol are available as generic agents and became newly available as generic since the last report. And then the exclusivity patent for Airsupra is expected to expire in 2030. So in the next five slides,

we are providing a very general summary of clinical practice guideline, recommendations for asthma in the population's interest, including those recommendations for how and when to use these agents along the treatment pathway. And just know, again, that the agents or the text in blue for this presentation are regarding the quick-relief agents, and again, this was done to differentiate from the guideline information for the controller agents for asthma that were presented at the last report. So, in general, the recommendations mentioned that all patients should receive patient education and an individualized treatment action plan when they are diagnosed with asthma. Education should be around self-monitoring and how to use these inhalers and medications and also how to avoid environmental triggers. And then pharmacotherapy is typically described in the, in the recommendations as the cornerstone of asthma treatment. So first here we have the inhaled bronchodilator, or quick-relief agents for asthma symptoms, where it is recommended that all patients with asthma should have access to albuterol levalbuterol. Those are common recommendations and, in general, the guidelines did not recommend one agent over the other. Then in patients with moderate or severe asthma or in those who have severe asthma attacks, adding low-dose corticosteroids was also a recommended option. Regarding all pharmacotherapy, the initial maintenance therapy is based on asthma severity, and then adjustments of therapy is based on asthma control. And then for maintenance therapy, the stepwise approach to asthma treatment appears to be the core foundation in these guidelines for asthma, which is basically where medications are escalated until good asthma control is achieved. This approach is based on the levels of severity and the persistence of asthma, as I mentioned in that background section. So Step 1 is for asthma that is assessed as intermittent and mild, and then Step 4 or higher as for asthma considered severe and persistent. So for adults and adolescents, maintenance therapy begins with Step 1, which is basically treatment as needed, and if pharmacotherapy is indicated, the National Asthma Education and Prevention Program guidelines recommend only a quick-relief bronchodilator, so no actual controller agents are recommended in this step. However, the Global Initiative for Asthma (GINA) guidelines do recommend combination therapy at Step 1, so either as two agents used together or a fixed-dose combination product that includes both a short-acting and a controller agent. Step 2 is also treatment as needed, where the National Asthma Education Prevention Program does recommend low-dose inhaled corticosteroids as monotherapy or in combination with quick-relief or short-acting β2 agonist. And then GINA Organization recommends the fixed-dose products of low-dose ICS plus formoterol agents,

and then leukotriene modifiers and other controller agents are recommended as alternatives. For Step 3 and higher, for maintenance therapy in adults and adolescents, the guidelines recommend a few different options for combinations of controller medications, while the quick-acting agents are recommended to always be available as needed for symptom relief. And then for children, the overarching goals for those diagnosed with asthma are to maintain control of asthma symptoms and reduce exacerbations with the least amount of medication and side effects. So, in general, the guidelines recommend more intensive management for acute exacerbations in children, which can include oral glucocorticoids in children 2 to 3 years of age if they are experiencing attacks more than twice per week or more than two days per week. And then in children between 4 and 12 years, if they are experiencing these attacks throughout the day, the step care approach for pharmacotherapy is also used in this younger population for maintenance and treatment. This is similar to adults; however, there is a more conservative approach to using some of the controller agents. And then it is also important to note that the step care approach can also include a step-down in addition to stepping up, of course. Stepping down a level can occur if asthma control has been achieved for at least three months. And then, this is our last slide for guidelines. We have recommendations for exercise-induced bronchoconstriction. So in general, they report that regular exercise improves cardiovascular fitness, which can actually reduce the risk for bronchoconstriction. So in those up-to-date guidelines, these recommendations are from the perspective that exercise-induced asthma is when exercise is that trigger for bronchoconstriction in patients with underlying asthma, so it is not just an independent risk factor. So in patients with well-controlled asthma, the guidelines recommend individuals avoid triggers such as cold air, cold or dry air during exercise. Then if pharmacotherapy is indicated that quick-relief agent like albuterol is recommended, or a combination of inhaled glucocorticoid and formoterol can be considered, and these should be taken approximately 5 to 20 minutes prior to exercise. And then for individuals who require daily therapy for exercise-induced asthma, they suggest regular use of combined short- or quick-acting agents plus a long-acting product rather than a quick agent alone. And they also recommend that if these pretreatments don't work and symptoms persist, it is likely that the underlying asthma is poorly controlled, so step-up therapy should then be considered. This is our final content slide for this report on quick-relief agents for asthma, here we list the relevant clinical practice guidelines for the treatment of asthma that were also referenced in the guideline section I just presented. These are in alphabetical

order by author professional association. The data publications are from 2019 through 2023. Thank you so much. So I take questions, maybe, of the other report and, of course, maybe I will direct the clinical questions to Ryan.

Kavita Chawla: Thank you, Andrea. That was a great comprehensive presentation. Questions for Andrea or Ryan? And, yes, if our Committee members can also come back on video, thank you. And if no questions, Nonye, any stakeholders?

Nonye Connor: No, there are no stakeholders and no hands raised.

Kavita Chawla: Okay. And so I suppose with that if we could share the motion. I think we have two motions, right?

Nonye Connor: Oh, just one motion.

Kavita Chawla: With just one motion, just the SABA, and then we also have something for the combination. Oh, no. Okay. It is all just included in this one.

Nonye Connor: Mm-hmm.

Kavita Chawla: Okay.

Ryan Pistoresi: This is Ryan. So as you see with the combination drugs in the past, we had previously said that the ipratropium albuterol did not have enough evidence for quick relief of asthma. So if you felt that you had enough information today on the new albuterol/budesonide, you would want to change that motion as it is written there, but that is carried forward from the last time this class was reviewed in 2018.

Peter Barkett: This is Peter. I mean, I am fine with the statement as it is. But, Ryan, were you anticipating putting Airsupra on the Washington Preferred Drug List? You know, I think there are other options for it. I don't think it is necessary, and I think it only recently got FDA approval here in the United States, right? Um, and my understanding is that it is very expensive. So I am just curious how you guys are thinking about Airsupra?

Ryan Pistoresi: So this is Ryan. Obviously, we would go through the cost analysis and look at whether it can be preferred and nonpreferred. But for the purposes of this P&T Committee, it is really just looking at the clinical aspects. So, if you felt that there wasn't enough evidence presented here at the meeting today to

say that it is on par with the tried and trued albuterol rescue inhalers, then that is fine, and we can leave that as is given that that was the recommendation from the P&T Committee back in 2018, but if you felt differently, we wanted to make sure that you knew that you could update that based off of what you saw today.

Peter Barkett: And do you know, when was -- when did the FDA approval go through? Because I think that is new since the last time this Committee would have reviewed the medication.

Ryan Pistoresi: Yes, it was really recently. Was it in these slides?

Peter Barkett: I think it has been in use in Europe for a long time, but we only got it over here very recently.

Ryan Pistoresi: Yes, I believe you are right. I believe it is used in Europe and elsewhere in the world, but to that point I am not sure how long it has been used. [cross-talk] --

Andrea Vintro: Sorry, [Cross-talk] 23 [cross-talk] --

Ryan Pistoresi: [Cross-talk] It looks FDA [cross-talk] Yeah [cross-talk] --

Andrea Vintro: 23. Yeah.

Ryan Pistoresi: Yep. Thank you.

Kavita Chawla: So I suppose it is one thing to have it preferred, and it is another to say, we shouldn't have it on the PDL at all for quick-relief of asthma, and I am leaning towards you can still be on the PDL, but the albuterol by itself remains the preferred agent. But I am open to being convinced otherwise, depending on the thoughts of the Committee.

Peter Barkett: Yeah, I would agree with you. I think instead of what it says now where we said there is not enough evidence, I would just change it to there is enough evidence, and I would leave that up to HCA to figure out if they want to have it on the Preferred Drug List or not. I suspect not because the cost effectiveness is terrible, [cross-talk] but I think there is reasonable evidence that it is not inferior.

Kavita Chawla: Other Committee members, any thoughts? Thank you for that, Peter.

Laura Beste: I would agree with Peter.

Greg Hudson: Yeah, I agree that keeping it on is fine.

Kavita Chawla: So then do we need to call out anything about it, like for I think other drug classes, even if it was more expensive, we did not necessarily call it out one way or the other. We just assumed it would not be a preferred agent, and providers would have to meet criteria to be able to approve it, prior auths, etc. So should we just remove that second paragraph?

Ryan Pistoresi: So this is -- oh, go ahead.

Christy Weiland: Oh, I was just going to ask, if we remove it, should we then specify that a single agent should be on formulary as a statement? Just not knowing when we will reevaluate this?

Kavita Chawla: Sure.

Christy Weiland: Knowing that we probably want albuterol, levalbuterol as an option, just in case at some point cost analysis did allow the combination therapy to be a preferred agent, it would be nice to actually spell out that there needs to be at least one mono agent.

Kavita Chawla: Mm-hmm.

Ryan Pistoresi: This is Ryan. The reason that I would say that you would want to keep that second paragraph is that the first paragraph is specific to just the SABAs and not the SABA combinations. So you could either add in the combinations in that paragraph and make it a bit longer, or to the point that was just made by Christy, if we wanted to have one of those preferred, you could have that be in that first paragraph, and then the second paragraph just say that after considering the evidence of safety, efficacy, and special populations for the combinations, I move that it is safe and efficacious and cannot be preferred on the PDL, or to whatever point you want to make for its structure.

Kavita Chawla: I guess the other thought then along those lines, Ryan, is as we did for the ICS and the LABAs and how we had different motions for each class. Should we have separate motions here? Because that is almost what we are doing in this

one motion, The first paragraph is a motion for SABAs, and then the second paragraph is a motion for the SABA/ICS combo. Do we need that with the understanding that for every motion I think we typically say at least one agent will be preferred, and maybe we don't do that. So I guess two questions. Do we need two separate motions? And then secondly, does that then end up requiring that a SABA/ICS combo has to become preferred, which, of course, I don't want either.

Ryan Pistoresi: Right. So this Ryan. We don't need to have it be two separate motions like this. I think in the past that is how the P&T Committee approached it just given that in the past the ipratropium bromide and albuterol was specifically that combination one, and they didn't want to have that be added. They wanted to focus more on using the albuterol single agent SABAs. So we could combine it into one motion. We would just have to draft it so that way we are talking about the SABAs and the combinations list of the drugs as they are and say whether it can be preferred or nonpreferred or must be preferred or must not be preferred.

Kavita Chawla: Okay, thank you, Ryan. Okay. So then coming back to the -- let's just start with the first paragraph if that is okay.

Zoe Taylor: So we could just add the albuterol/budesonide to the first paragraph.

Kavita Chawla: So what I heard was that Ryan is recommending keeping the two paragraphs separate, if I read that correctly, and so [cross-talk] --

Zoe Taylor: [Cross-talk] Okay. And so then we don't change the first paragraph, we just instead of saying that there is not enough evidence in the second paragraph, we change it to there is enough evidence? And then we just make the second one like approving same language as the first one?

Ryan Pistoresi: This is Ryan. I don't think you need to say [cross-talk] --

Peter Barkett: [Cross-talk] Makes that safe and efficacious.

Ryan Pistoresi: Yeah, I don't think you need to say that there is enough evidence because that is understood in every other motion. We don't have that language. It was mainly to say that based off of what the Committee saw back then, they did not feel that there was enough evidence and that was the basis for their reason on why it should not be added.

Kavita Chawla: So we would say, "I move that these products be added to the Washington PDL." Does that sound right? Christy, I think you are saying, but you are muted.

Christy Weiland: Um, if we make that statement, does it need to be preferred? It doesn't, right? If we say I move that it is added?

Kavita Chawla: No. Yeah, exactly. It won't mean that it is preferred. It just says that [cross-talk] --

Zoe Taylor: But we do have -- but we do put the safe and efficacious thing, right? Because it has to basically be the same as the first paragraph but about the combo medicine?

Ryan Pistoresi: So my [cross-talk] --

Zoe Taylor: [Cross-talk] Do you just copy and paste that or…?

Ryan Pistoresi: Yeah, my recommendation for the motion in order for it to be clear is "after considering the evidence of safety, efficacy, and special populations of using combination short-acting beta agonists for the quick-relief of asthma, I move that albuterol/budesonide is safe and efficacious." And that could be it.

Kavita Chawla: And be added to the PDL?

Ryan Pistoresi: Yeah.

Kavita Chawla: Okay. So I move that -- so I think we would come down to the fourth sentence there, Nonye. "I move that albuterol/budesonide is safe and efficacious" --

Nonye Connor: Whoop, sorry. Oh, sorry, sorry.

Kavita Chawla: You're okay.

Nonye Connor: Do you want me to move this part?

Kavita Chawla: Yeah.

Nonye Connor: Move this all the way to the Washington?

Kavita Chawla: Yeah.

Nonye Connor: Okay. And I will work on my spelling. Give me a quick second.

Laura Beste: Also, while she's working on that, pirbuterol isn't available anymore in the market. Is that correct?

Ryan Pistoresi: Ryan, and correct, yes. But because it was a reviewed drug in the past, we are carrying it forward, and that is why it is grayed out along with the ipratropium and ipratropium/albuterol.

Laura Beste: Right. Should we remove it then from the main paragraph?

Ryan Pistoresi: You could, yeah, from that top paragraph. If you do not feel that is safe and efficacious anymore, you could remove that from that top paragraph.

Laura Beste: Okay.

Nonye Connor: Okay. [Cross-talk] So I move -- sorry, go ahead.

Kavita Chawla: Safe and efficacious and, oh, comma, and be added to. Is that fair? Or any edits from the Committee, and then we can go up to the top paragraph and remove the pirbuterol. Is that -- uh, is the rest of the Committee okay with that, with what Laura suggested, that we remove the pirbuterol?

Ryan Pistoresi: Yeah. So in that case you do need to have a sentence about the pirbuterol just given that it is a reviewed drug. So you may have to say after that first paragraph, right at the end of that first paragraph that it cannot be preferred on the Washington PDL.

Kavita Chawla: Okay. Pirbuterol cannot be [cross-talk] --

Ryan Pistoresi: [Cross-talk] Well, you would have to say, "after reviewing the evidence of safety, efficacy, and special populations, I move that pirbuterol is not safe and efficacious for the treatment of quick-relief of asthma."

Nonye Connor: Over here, right?

Ryan Pistoresi: Yeah, so below that paragraph. No, no, no, no. As a separate paragraph.

Nonye Connor: Okay. Say that again.

Kavita Chawla: Yeah. [cross-talk] You would copy those three sentences. Start with the same first three sentences. Yeah, the first three lines I should say. Yeah. All the way through I move that --

Nonye Connor: Right there?

Kavita Chawla: Mm-hmm. Albuterol is not considered [cross-talk] --

Laura Beste: I guess I am a little confused. So wouldn't we have to do the same thing with ipratropium and ipratropium and albuterol, too? I mean, but we used DuoNeb all the time, so [indistinct] for asthma, though. Okay. Do we have to do the same with those two medications as well?

Ryan Pistoresi: So this is Ryan. So because the previous motion specifically was saying that pirbuterol was safe and efficacious, we will need a statement on why it is changing because we had reviewed but didn't make motions on the ipratropium, I don't believe that we need that here [cross-talk] let me just double check that.

Kevin Flynn: [Cross-talk] But how will this [cross-talk] available?

Laura Beste: Right, but you wouldn't use it for asthma or -- unless it is a combination asthma/COPD patient.

Kavita Chawla: Yeah. I guess here we are primarily reviewing for asthma. [Cross-talk] Then would we have to -- sorry, go ahead, Kevin.

Kevin Flynn: I was going to say we do use the nebs like on inpatient [indistinct] not that it would matter for [indistinct]. I know. That is what I was struggling with, too. But, I mean, primarily, it is our COPD patients with asthma or the combination. You wouldn't normally use it as a first-line agent, just for an asthma patient or asthma exacerbation.

Kavita Chawla: Yeah. Even though on the inpatient side I agree for pure asthma exacerbation.

Ryan Pistoresi: Yeah, and I think -- this is Ryan again -- so I think that's why we didn't have any inclusion. I think looking back to the 2016 motion, it didn't mention anything about the ipratropium, so I am assuming that in the past the P&T Committee decided that even though they reviewed it that it wouldn't be part of the motion and part of the PDL for quick-relief of asthma.

Laura Beste: Are these medications listed elsewhere for COPD?

Ryan Pistoresi: Let me check the Washington PDL on how this class is listed, so give me one moment. Looking at our Washington PDL, these drugs are not listed within the quick-relief class, but they would be on the UMP Preferred Drug List. So for the health plan, Uniform Medical Plan, those drugs would be available. They are just not under the purview of this Washington P&T Committee, but they would be available to members.

Kavita Chawla: So maybe for this specific purpose, we just stick with the pirbuterol and leave the ipratropium alone, just literally it is a gray zone as is the gray lettering. Would that be okay?

Ryan Pistoresi: Yes, that would be fine because, again, in the past we had not made any motions on those drugs.

Kavita Chawla: Okay. How does the Committee feel about having this paragraph about the pirbuterol?

Laura Beste: I like the paragraph just because it is not available. So I don't know. I wouldn't listed up above as safe and efficacious when it was removed because I had that -- was it [cross-talk] --

Kavita Chawla: [Cross-talk] Yeah.

Laura Beste: -- the fluorocarbon base.

Kavita Chawla: All right. So then let's continue to move that pirbuterol is not considered safe and efficacious for quick-relief of asthma. Okay. Other edits?

Christy Weiland: In the first paragraph, is it necessary that we say, "no single short-acting beta agonist is associated with fewer Adverse Events and special populations?"

Christy Weiland: Great point, Christy. I was wondering about that, too. You've not typically call that out? How's the Committee feel about that? And Ryan, does it serve any purpose by being there?

Ryan Pistoresi: This is Ryan. I think older previous P&T Committees, they would make statements like that kind of about the evidence or about what they saw, and maybe using that as part of the rationale for why they would make a decision. So I think in this case there were questions about the CFCs going to the HFAs. As you recall that was many, many years ago, and there may have been questions about the type of Adverse Events that may have been derived because of the different formulation in the propellants used for the quick-relief medications. So this was the P&T Committee's way of saying that they did not see any differences between the quick-relief products, and that is why they could say that there was therapeutic interchange. So in case if there was a provider that wanted ProAir instead of Proventil or something to that nature that the PNC Committee reviewed that and said there is no basis for there being any difference or variation in safety events. So, again, it doesn't necessarily add anything, but I think it just helped us know what the P&T Committee was thinking at the time when they were reviewing the evidence.

Laura Beste: This is Laura. I have a feeling, too, that originally when levalbuterol was released onto the market, their big push was that they had less tachycardia, and later on that really wasn't shown to be significant between albuterol and levalbuterol. So I know that we struggled in the hospital P&T with that decision, and there wasn't enough data to support it.

Donna Sullivan: So this is Donna. At the end of the day, your answer to do we need the sentence? No, we don't. You can delete it if you want to.

Kavita Chawla: I am good with that. The more succinct and clearer the better. Does the rest of the Committee agree? Yes. I see nodding. Okay. Um, Nonye, we can delete what you've highlighted right there. Great. Any other edits? And if not, we can proceed with the motion.

Kevin Flynn: Just do we need to get so descriptive about -- I'm sorry, just because technically ProAir and like Ventolin are different drugs. I guess for the healthcare it doesn't matter to you I would imagine.

Ryan Pistoresi: No. So this is Ryan. So for this we consider all the ingredients. I think in the past, we did make that, and if you look at some of the older motions, we

would try to call out some of the different newer formulations that were identified in the reports. But in the last five, six years, we have just been listing the ingredients and helping clean up because we do have some pretty long lists of drugs now in those drug reviewed columns.

Kavita Chawla: And that is a great point, actually. That also reminds me, should we have the statement that we had for the longer-acting agents in here, too, as in all of the formulations are included in this motion?

Laura Beste: I agree I think we should add it to be consistent.

Kavita Chawla: Look at that, she's ready to go. Nonye, thank you. Other questions, edits, or enhancements?

Kevin Flynn: This is Kevin Flynn. After considering the evidence of safety, efficacy, and special populations of using short-acting beta agonists for quick-relief of asthma, I move that albuterol and levalbuterol are safe and efficacious. The Washington Preferred Drug List must include a nebulizer and metered-dose formulation. The short-acting beta agonist can be subject to therapeutic interchange in the Washington Preferred Drug List for the quick relief of asthma -- After considering the evidence of safety, efficacy, and special populations of using short-acting beta agonists for quick relief of asthma, I move that pirbuterol is not considered safe and efficacious for the quick relief of asthma. After considering the evidence of safety, efficacy, and special populations of albuterol/budesonide for quick relief of asthma, I move that albuterol/budesonide is safe and efficacious and be added to the Preferred Drug List for the quick relief of asthma. All delivery systems and Indications will be included for all drugs.

Greg Hudson: This is Greg Hudson. I second.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? With that the motion carries. Thank you. Okay. So with an eye on the time, how are we doing, Committee? We are definitely long overdue for a break. And there are a couple more drug classes that need to be reviewed before we can do the archive -- the bulk archive motion. Should we take like a five-minute break? Or do you want to keep powering

through? Let's do like just a sanity/bio break for five minutes. How about that? [Cross-talk] And then just come back. Yeah? Okay. Five minutes, and we will come back, and we will keep soldiering on. Thank you.

[break]

Kavita Chawla: Welcome back, Committee. I think most of us are back. Nonye, I think we need -- what? -- eight for a quorum? Is that the deal before we get started?

Nonye Connor: We need six.

Kavita Chawla: Six. One, two, three, four, five, six, yay! Okay. Ready to get started. Okay, and we bring back Andrea for Overactive Bladder Agents.

Andrea Vintro: [Cross-talk] One more time. Hopefully, you are all -- won't get too tired of my voice. Let me share this with you. Very good. Okay, great. So yes, my name is Andrea Vintro. I am a Research Associate here at the Center For Evidence-Based Policy. This is the fourth out of five presentations for today for this Washington Drug Archiving Project. The first four drug classes were presented at the February P&T Committee Meeting. And then just as a reminder for those of you who were with me during any of my prior presentations, I will have to repeat all of the topics including the in general overview for this in the upcoming report because there may be new audience members, so thank you for bearing with me. So this presentation is entitled Drugs To Treat Overactive Bladder. So the aim of the work is for the Drug Effectiveness Review Project (DERP) to develop and present information to the Washington State Pharmacy and Therapeutics Committee on nine drug classes that are candidates to be archived from active review by the Committee, and the list of the drug classes that are included in the project are at the bottom of this slide, and you can see overactive bladder drugs is highlighted in green for this presentation. So we are going to review the topics in the darker green boxes on this slide for overactive bladder, starting on the left. I will first define the health condition of interest of this drug class it tends to address and summarize the general epidemiology and common treatments for the condition, then I will review the information that is in the most recent DERP reports for this drug class, including the PICOS, Key Questions, a high-level summary of the Key Findings, and then general Findings of any surveillance that was completed after the last systematic review. Then I will move to any new actions by the FDA since the last report including new approved drugs, any new Boxed or Serious Warnings and any

new Indications, and then on to report on a new pipeline of drugs in this class, and then also the generic status of the FDA-approved drugs in this class, and then finally, I will provide a high-level summary of relevant clinical practice guidelines for this condition of interest, including recommendations for how and where these agents are used along the treatment pathway. Then I will be available for questions. Okay. Background on Overactive Bladder. So overactive bladder is defined by the International Continence Society as a syndrome of urinary urgency often with urinary frequency and nocturia. and then nocturia is frequent nighttime waking in order to urinate. This is all in the absence of other conditions that could cause the symptoms such as obstruction or cancers. A subset of patients with overactive bladder may complain of urge or stress urinary incontinence. So this urge incontinence is this involuntary leakage of urine which is then accompanied by or immediately precedes the feeling of urgency, and then stress incontinence is defined as the inability to retain urine or leaking of urine when sneezing or coughing. This latter symptom occurs more often in females. In the clinical literature, overactive bladder is often included under the more nonspecific condition of lower urinary tract symptoms (LUTS) when discussing these issues in males, but LUTS can also be used to describe issues that are experienced by females. So this is going to be helpful to know as we walk through what the clinical practice guidelines say for the condition at the end of this presentation, since for the most part the recommendations are presented for each sex separately because of the different organ system physiology between males and females. So overactive bladder is common, and prevalence increases with age. So around 15% to 23% of US adults are diagnosed with overactive bladder, and the prevalence in males compared with females differs somewhat, depending on the resources that we looked at, but it was consistently reported that females are more likely than males to report the symptom of urge incontinence. Risk factors for overactive bladder include smoking, obesity, arthritis, depression, heart disease, and irritable bowel syndrome. Additional risk factors specific for men include a history of prostate disease. And then additional risk factors for females include certain neurological conditions, such as multiple sclerosis, also diabetes, pregnancy, urinary tract infections, uterine prolapse, hysterectomy, and menopause. There was a study in 2012 that reported evidence showing prevalence of overactive bladder was highest in African American individuals and lowest in white males. So in general, for treatments of overactive bladder first-line treatments include behavior modifications, such as pelvic floor muscle exercise. It is very interesting to learn that Kegels are preventive, too. Bladder training and also fluid management to achieving and maintaining a

healthy weight, and also having a healthy diet and exercise routine. Pharmaceutical agents are considered a second-line treatment. So for males, it is important to identify if the symptoms for an overactive bladder are caused by prostate enlargement, and if that is the case medications are first recommended to minimize -- or are commonly used to minimize blockage are the first-line treatments and then antimuscarinic agents are common treatments and they help to reduce bladder contractions, and then β3-adrenergic agonists are drugs that can promote bladder relaxation during the filling stage. Third-line treatments include peripheral tibial nerve stimulation, sacral neuromodulation, and botulinum toxin injections. The stimulation method involves electrical stimulation of nerves that are responsible for bladder control, and then the botulinum toxins can help to relax the bladder muscles. So regarding reports prepared by DERP on this topic. So the last DERB systematic review for drugs for overactive bladder was presented in June of 2018. This is just about six years ago, and the sources for that report were searched through February of 2018, and there has been no surveillance for this drug class since that last review in 2018. The next three slides are the PICOS for the most recent DERP systematic review for this drug class. So for population they included adults with urge incontinence or overactive bladder. For comparators, only [indistinct] intervention was included so head-to-head trials only. For outcomes, they looked at change in incontinence and urgency episodes, also the number of pads that would be used, patient symptom assessments, and then various measures for Adverse Events. For study designs, they included randomized controlled trials, systematic reviews that were considered good quality and published in 2013 or later. And then for Harms outcomes only, they allowed comparative cohort or case control studies that were eligible. So this table lists the interventions included in the last report. They are in alphabetical order by generic name. All of these drugs are considered urinary antispasmodics. So when we look at the far right column, the majority are muscarinic antagonists, except for mirabegron in that fifth row there, which is a beta adrenergic receptor agonist. So then back to the top there we have darifenacin then fesoterodine fumarate, flavoxate hydrochloride, which is the first drug approved for overactive bladder in 1970. It is now only available as generic, and then we have mirabegron, oxybutynin chloride and oxybutynin, and then next is solifenacin succinate in that eighth row, and then trospium chloride in the ninth row, and then tolterodine tartrate. So seven of these drugs have extended-release formulations: oxybutynin chloride with the brand name, Gelnique, is a transdermal gel, and oxybutynin with a brand new Oxytrol, is an extended-release transdermal film product. For the most

recently approved agent listed here is mirabegron, which was approved in July of 2012. The last report included two Key Questions. So they asked about the comparative Effectiveness and Harms between these agents for overactive bladder, and they also asked about the differences in the Effectiveness and Harms across patient subgroups. You can see those listed on this slide. With the 2018 report, being the sixth update from the original report, the cumulative number of studies included was 44, all of which were head-to-head comparative studies. So 42 were randomized controlled trials, of which some of the older trials were included only the systematic review, so not as independent publications, and there was also one cohort study that was included. So for the summary of Key Findings, we list here the number of the studies included for each identified drug comparison. There was only one study identified for six of these comparisons, but there were 15 trials, the most by far that compared tolterodine either as an intermediate or extended-release formulation with the intermediate or extended-release formulation of oxybutynin. So continuing on with Key Findings. For all of these mentions, while there were some statistically significant differences in the reported outcomes for some of these drug comparisons, nearly all were considered not clinically meaningful. I do want to point out the fourth sub bullet point there that mentions there were fewer withdrawals due to Adverse Events with solifenacin and tolterodine compared with oxybutynin, which may be of interest. For new FDA-approved drugs and actions since the most recent report, we identified one new drug approved for overactive bladder, vibegron, with a brand name, Gemtesa. It was approved in December 2020. This is a β3-adrenergic agonist it is delivered via an oral tablet. We also found new Indications for two of these agents. So both were approved for expansion to include the new indication of neurogenic detrusor overactivity. This is a type of bladder dysfunction where there is an increased or involuntary muscle contraction of bladder muscles. This is a common complication in patients with multiple sclerosis and injuries of the spinal cord. This is indication was added to fesoterodine fumarate in June of 2021 for pediatric patients at least six years of age, and then also added to mirabegron in March of 2021 in children at least three years of age. In April of 2018, the indication for mirabegron was also expanded to allow for combination use with a muscarinic antagonist, specifically solifenacin succinate, which is also included in this report, and just to confirm that there was no change to its approval for it to be used as a standalone or monotherapy agent. So we have the FDA-approved Indications for the agents of interest on this slide. All drugs are indicated for overactive bladder with symptoms of urinary incontinence, urgency, and frequency, as you can see

from all those checkmarks in that middle column there, and then three drugs have an additional indication that is on the far right column, and this is for neurogenic detrusor overactivity in pediatric patients. Those agents include fesoterodine fumarate, or Toviaz is the brand name. Also mirabegron, and then the extended-release tablet formulation of oxybutynin chloride. Since the most recent report in 2018, there were no new Boxed Warnings or Serious Warnings for any of the included drugs for overactive bladder. We did identify one new pipeline drug in Phase III trials for the indication of stress urinary incontinence. The drug is Iltamiocel. This is a stem cell therapy that is delivered via injection. If approved, it would be a potential option for females with stress urinary incontinence where prior surgery for this condition proved unsuccessful, and the approval outlook for that is in 2026. So on this slide, we show generic status for these agents. Seven of the included drugs appear to be available as generics. So darifenacin, flavoxate hydrochloride, oxybutynin chloride, trospium chloride, and tolterodine tartrate had formulations that were already available as generics with the last report in 2018. In that third row there, we can see fesoterodine fumarate is also now available as generic since the last report, and then row five, mirabegron is not yet available as generic, but appears to be losing its patent exclusivity status this year, and it appears that there are multiple applications submitted to the FDA for generic manufacturing. And then row seven, we see that solifenacin succinate was recently approved for generic manufacturing. And then in the bottom row, we have vibegron, which will likely not be available as generic for some time with its loss of exclusivity date out about 10 years from now. So on the next few slides, we provide the very general summary of clinical practice guideline recommendations for overactive bladder. This includes recommendations for how and where the agents of interest are to be used along the treatment pathway. For this section, we began with information from the up-to-date clinical decision support online resource and then cross-referenced that information with key practice guidelines from professional medical associations, which are listed at the end of this slide deck. The guidelines for overactive bladder were differentiated by sex because of the difference in physiology of the organ system, so the first two slides here were summarizing the practice guidelines for females. Nonpharmacologic interventions are recommended as first-line treatments, and those include education on pelvic floor muscle exercises and bladder training, also healthy lifestyle behaviors can help with these symptoms. If there is vaginal atrophy, which is often associated with one or more urinary symptoms, there are recommendations to treat with topical estrogens as needed, and then if these treatments do not provide adequate

relief of the symptoms, the next step would be to add systemic pharmacologic agents, so oral agents. So in addition to continuing with nonpharmacologic approaches as just mentioned, together, yes. So, in general, extended-release formulations were preferred, if available, and this is according to the American Neurological Association. And then the guidelines recommend that the medications be continued as long as there are improvements, and the patients do not experience any bothersome side effects. On this slide, we have more detail around the pharmacologic agents for female patients. So β3-adrenergic agonists are recommended first because of some evidence for increased risk for Adverse Events, including dementia, with the antimuscarinic agents, and they do acknowledge that the cost is greater, however, as these are newer agents. And for those who are prescribed antimuscarinic agents, trospium and darifenacin are preferred because there is more evidence, even though the volume of evidence is still considered weak and limited, however, that evidence did demonstrate that these agents are worse at penetrating the central nervous system, which is preferred, of course, compared with the other antimuscarinic agents. And so these guidelines recommended to start with the lowest dose and then reassess after two to six weeks and then adjust the dose as needed. And then if the symptoms continue while these individuals are still on these medications, the guidelines recommend to refer to a specialist where they may consider third-line options, including tibial nerve stimulation, botulinum toxin injections, sacral neuromodulation, and also laser therapy. So we will switch over now to the guideline recommendations for the treatment of overactive bladder in males. As mentioned earlier, in males this condition is often labeled as (LUTS), with lower urinary tract symptoms, which is a more sort of nonspecific term. It is recommended to first evaluate whether symptoms are due to an enlarged prostate with bladder outlet obstruction. This is the most common diagnosis when male patients present with these symptoms. So with overactive bladder, similar to females, should that be diagnosed the first-line treatments are nonpharmacologic interventions, pelvic floor exercises, bladder training, healthy lifestyle behaviors, achieving a healthy weight, and then if these initial treatments don't provide adequate relief, the next step would be to add medications. So for isolated overactive bladder, the recommendations are identical to females. So what we are seeing, β3-adrenergic agonists are recommended first over antimuscarinic agents, and then I've included what is generally recommended for enlarged prostate, including that bottom bullet point there which states if the diagnosed condition is mixed, overactive bladder with obstruction, which is supposedly quite common, it is recommended to treat the obstruction first.

So our final slide of content we list the key clinical practice guidelines that were also referenced for the guidelines section for overactive bladder. They are in alphabetical order, by author, or professional organization, and the date of publication for updates for these guidelines range from 2014 to 2020. Thank you so much. And, again, questions about the report from me and then any clinical questions likely to Ryan.

Kavita Chawla: Thank you, Andrea. I suppose just a question that I have is on the basis of these clinical guidelines for OAB in women, since vaginal estradiol is considered to be one of the first-line approaches. Is that something that we would include under DERP? Because the same theme as my questions before, and whether we would review that as part of the motion today.

Ryan Pistoresi: This is Ryan. Estradiol is actually a different drug class on the Washington PDL that has been previously archived. So, again, with a previous recommendation, these classes of drugs that we are defining with DERP and bringing to build the Washington P&T were identified because they were the more expensive and newer ones back in the mid-2000s. So that is why it doesn't include everything for the treatment of the disease state, just the newer [cross-talk] drugs that fit those criteria.

Kavita Chawla: Great. Thank you.

Peter Barkett: This is Peter Barkett. I have a question about the place in therapy of β3 agonists compared to the antimuscarinics. Which organizations or guidelines recommend the β3-agonist before the antimuscarinics? I guess I wasn't aware of that. And my understanding is they are equally efficacious but different side effect profile, and I thought that the cognitive side effects were more of a theoretical risk than something that has actually been proven out, so I wanted to do a little bit more digging into that.

Andrea Vintro: Yes. I mean, I will have to be doing a little bit more digging myself, I think. I don't know, Ryan, if you have -- I don't have them listed by which -- this was, again, starting from up-to-date, and so if there was anything that was specific to one of the guidelines that was listed -- on this last slide that might have been -- that would have been called out. So this was primarily in the up-to-date, and it was not otherwise stated in the other guidelines.

Ryan Pistoresi: This is Ryan. So it looks like one of the sources for the guideline updates was the European Association of Urology. So I am wondering if this may have

been preferred in Europe versus through an American guideline, like the ACOG. So I can look into that and see if I can find a little bit more information on the beta over the muscarinic.

Kavita Chawla: So Kavita here. I'm -- just the 2024 American Neurological Association guidelines it seems like. Yes, they are not really distinguishing one over the other in our AOA guidelines. Sorry, frog in throat.

Andrea Vintro: And that can be updated. I could update that if that is of interest.

Jon MacKay: This is Jon MacKay. I had a quick question for Ryan in terms of what antimuscarinic agent is typically preferred currently.

Ryan Pistoresi: Give me one second, I am pulling up our PDL. So for the short-acting, our preferred are the oxybutynin syrup, tablets. The tolterodine tablets, the trospium tablets. And for the long-acting, we have the darifenacin ER, the oxybutynin ER, the solifenacin tablets, the tolterodine ER tablets, and the trospium ER capsules. So quite are preferred on the Washington Preferred Drug List.

Kavita Chawla: Out of interest, Ryan, since you are already there, do we have any vaginal estradiol formulations that are preferred?

Ryan Pistoresi: That is going to be under the estradiol, so let me scroll there. And I believe those were archived a couple years to go, so they are not in this version. I could check the Washington PTL for that. I mean -- sorry -- the Uniform Medical Plan PDL because that will be the more current one on how it is applied to the health plan.

Kavita Chawla: While Ryan is looking that up, other questions from the Committee.

Zoe Taylor: Should the fact that Myrbetriq is going generic next year affect anything we do today? Or would that be more of like a DUR Board thing for next year?

Ryan Pistoresi: So this is Ryan. For the Washington P&T Committee, you are just going to be reviewing the clinical efficacy and safety aspects. So if a drug is going generic that will be handled during our cost analysis process, and that is separate from the DUR Board, which is Apple Health specific. [cross-talk] So you may get some more of that specific to Apple Health at the DUR, but for this -- your

P&T hat that you are wearing right now, you will just focus on the clinical safety and efficacy.

Kavita Chawla: I think that does bring up a good point. So, in general, we do see that the side effect profile is better with mirabegron. So I don't know if there is any kind of [cross-talk] --

Zoe Taylor: [Cross-talk] Yeah, it is much better [cross-talk], but I think we can look at the motion and just see one maybe when we get to the motion and decide if we want to do anything different.

Kavita Chawla: Are there any stakeholders before we get to the motion, Nonye?

Nonye Connor: Sorry, I was trying to unmute myself. Just looking. I don't see any hands raised, and there are no pre-registered stakeholders, so I will go ahead and share the motion now.

Kavita Chawla: Thank you.

Ryan Pistoresi: So Kavita, just to answer your question. So I am looking at the Uniform Medical Plan PDL, and we do have a few vaginal tabs for the estradiols. So it looks like there is the estradiol gel and another estradiol gel.

Kavita Chawla: Okay -- which are preferred?

Ryan Pistoresi: Yes, they are preferred, and they are on Tier 2.

Kavita Chawla: Okay. Thank you. Thank you for looking that up. Okay.

Jon MacKay: Ryan, this is Jon MacKay. Quick question. Does it take a failure of two antimuscarinic agents to get Myrbetriq approved? Or what does it take to get it approved?

Ryan Pistoresi: So that is a UMP PDL question, and also, I believe L&I participates in this class, too. So I believe that for Uniform Medical Plan, it would require trial and failure of two of those preferred that I had mentioned earlier. So typically, we see the oxybutynin being used and then either the tolterodine or the trospium as the second, and then from there the third could be the vibegron.

Laura Beste: This is Laura. So I have a question. So by saying that they are interchangeable within them, if you chose mirabegron because you had a patient that was elderly with dementia, and you didn't want to use an antimuscarinic, would you still have to use an antimuscarinic in that patient? Or can you just use your β3 and not have to jump through those hoops?

Ryan Pistoresi: You could send the PA to MODA and let them know that these other drugs are not appropriate because they are on the [indistinct] list, or there are other safety concerns that you've identified with the anticholinergics -- or antimuscarinics. So in that case, you could potentially get it approved without having to step through those, but for most patients, they would have to step through the preferred in order to get to a nonpreferred.

Zoe Taylor: It is not appropriate for them to have a therapeutic interchange between these classes, right? Like, that is something that seems like we really need to change on this resolution.

Laura Beste: I kind of feel strongly about that, too, just [cross-talk] because of that geriatric population.

Zoe Taylor: Yeah. Like, you wouldn't -- you couldn't have it be that you prescribed Myrbetriq, and instead of requesting a PA, the pharmacist just changed over to something else. Like, that would not be acceptable, so we should not allow that.

Kevin Flynn: [Audio cuts out] within its same class because it is a different class.

Jon MacKay: This is Jon again. I felt like there is a lot of clinical variability, too, even within the antimuscarinic class in terms of tolerability just with oxybutynin versus the more selective agents, so I probably wouldn't want to interchange one of the more selective antimuscarinics with oxybutynin.

Kavita Chawla: So I am hearing two concerns here. One is we don't want interchangeability between the β3-agonist antimuscarinics, and so we should have a statement to that effect, and then the second concern is the interchangeability just within the antimuscarinics. So why don't we tackle one at a time? Let's start with the β3 -- which was stated first. So should we say here, [indistinct] and subject to therapeutic interchange within the same drug class? I'm seeing nodding, yeah? Okay. Uh, interchange, yeah, right there, Nonye, within the same drug class.

Christy Weiland: Can we just remove the whole interchange in this class and remove that whole sentence?

Zoe Taylor: In general, I think that's a good idea, but I wonder, like, there are so many different ones. Like, if somebody failed oxybutynin, I might be like, okay, let's try trospium, and then the pharmacy doesn't have it. Like, I do kind of want them to be able to do, like, solifenacin or tolterodine instead, like, in that case, so, I guess, I felt kind of mixed about not allowing it at all, especially if we are just trying to step through two, and it doesn't really matter which two.

Kavita Chawla: So, Jon, along the concerns you were having, how would you phrase this so that it is best for the patients?

Jon MacKay: We didn't really go into terms of selectivity [cross-talk] --

Kavita Chawla: [Cross-talk] Mm-hmm.

Jon MacKay: -- that that in depth in terms of their tolerability, too. So I would be fine with leaving it just for open within the class, but I do think oxybutynin is probably less tolerated than the other agents in terms of dry mouth and just its anticholinergic effects.

Kavita Chawla: So which of the extended-release other agents are better? And if they are on the Preferred Drug List, then great it sounds like [cross-talk] --

Peter Barkett: [Cross-talk] Yeah, I think it would be trospium and darifenacin, right? And they are both preferred, I believe. We could exempt them in the language so that they stay preferred, or if they are no longer preferred at some point, then they wouldn't get changed to others. But I think, Jon, that would be probably the way to accommodate that request for the more neuroselective antimuscarinics would just be to exempt those two.

Jon MacKay: What do others think about that in terms of their experience clinically? Do they notice that a difference much within the class there?

Peter Barkett: I usually start with trospium for that reason, but I don't know if it always plays out the way I expect.

Kavita Chawla: I will be honest, I haven't seen it one way or the other, and I haven't seen our urologists call out one agent over the other. I could be missing something. Other experiences from clinical practice that would inform this? And I think as you said, the main thing is that there are already preferred. And since they are already generic, I doubt they will ever become nonpreferred.

Laura Beste: I like how Peter worded it and have the trospium and the two agents that are -- what's the other one that is less? Peter just said it.

Peter Barkett: Darifenacin.

Laura Beste: Yeah. And have those two separate that we can't interchange for those. Because, once again, you are back to that geriatric population as well where you wouldn't want to use oxybutynin if possible.

Kavita Chawla: So did I hear trospium and darifenacin? Okay.

Jon MacKay: That would be good with that approach.

Kavita Chawla: Okay. So how do we want to word that? Any of you want to dictate that out to help Nonye? I think that part, Nonye, is good. I would -- yeah, just do this spell correct there. Perfect. [cross-talk] And then be an additional statement. Go ahead.

Peter Barkett: Yeah, I think just like at the beginning of the sentence where it says, "Do you use drugs?" I just put comma, with the exception of trospium and darifenacin , comma, can be subject to therapeutic interchange within the same drug class in the Washington Preferred Drug List.

Kavita Chawla: All right, Great.

Laura Beste: We need to say why as far as, like, decreased CNS?

Peter Barkett: We could put in [cross-talk] like [cross-talk] due to greater neural selectivity.

Kavita Chawla: Yeah. Okay, so with the exception of trospium, T-R-O-S-P-I-U-M.

Nonye Connor: Sorry, uh. Right there with the [cross-talk] exception of this one?

Kavita Chawla: The one below it.

Nonye Connor: Oh, thank you.

Kavita Chawla: And the one that starts with D, darifenacin, the first one --

Nonye Connor: [Laugh] I missed it. [laugh]

Kavita Chawla: All fun drug names. With the exception of darifenacin due to their neuroselectivity.

Nonye Connor: I have a little -- did I capture that [indistinct]? Do I need to correct that?

Kavita Chawla: Yeah. So it's N-E-U --

Nonye Connor: Thank you. Thank you. Oh, is N-E -- okay?

Zoe Taylor: I put it in the chat. I don't know if you can copy from the chat or not.

Nonye Connor: There. Is that correct?

Zoe Taylor: There just needs to be a E after the L.

Nonye Connor: Yeah.

Ryan Pistoresi: E after L in selectivity.

Kavita Chawla: There we go. Beautiful.

Nonye Connor: Thank you.

Zoe Taylor: So then a comma after that long word, and then I think there should be a period instead of a comma after drug list and before immediate-release, just because I think it is a run-on sentence otherwise. [Cross-talk] So we could say, like, additionally, immediate-release formulations cannot be interchanged for once-daily formulations.

Kavita Chawla: Additionally. L-Y. Perfect. Immediate [mumbling].

Zoe Taylor: Can I just make sure it's clear that -- like, so what we're saying is that if you prescribe trospium or darifenacin, they cannot replace it with a different one. But if you prescribe oxybutynin, they still could replace it with trospium, which is something we would want them to do anyway. Or is it both -- bidirectional, I guess?

Ryan Pistoresi: I am reading the motion is that drugs, except for trospium and darifenacin, are subject to therapeutic interchange within their classes and that the trospium and darifenacin don't have any interchange within them. So if someone were to prescribe either of those drugs, there is no way to change to them [cross-talk] --

Zoe Taylor: [Cross-talk] Perfect.

Ryan Pistoresi: -- or from them.

Zoe Taylor: Okay, that's fine.

Kavita Chawla: And then the last sentence here is kind of just there for good measure given the number generic long-acting drugs we do have already on the formulary as preferred agents. Am I thinking about that right, Ryan?

Ryan Pistoresi: So this is Ryan, and yes. So I mean we do have five currently on it. I think it's fine to keep it as is just to reiterate that, but yes, we do want to make sure that we do have a once-daily version available in case. Who knows what happens in the future because this is a class that is being archived, so this motion would remain in perpetuity forever.

Laura Beste: For clarity, is it on the far left-hand column? Can we separate out antimuscarinics and β3?

Ryan Pistoresi: So this is Ryan. The way that we have it set up right now on the PDL is between long-acting and short-acting. I don't know -- I mean, we could divide it even further into for so long-acting and in short-acting for both the beta and the muscarinic. We don't necessarily need to do that for the column on the left, but if there is direction for us to split it out further, we could do that in the next update, which would be the October PDL update.

Laura Beste: I guess my only concern was just on that where it says drugs reviewed to put the β3-agonists separate from the antimuscarinics just because we have separated in here within the classes that they are not interchangeable.

Kavita Chawla: And so to call out what those classes are.

Laura Beste: Correct, which would have been a good point. I agree with that, just in the left-hand side.

Ryan Pistoresi: Okay. So can you help Nonye?

Kavita Chawla: Yeah.

Ryan Pistoresi: Yeah.

Kavita Chawla: On the leftmost column, Nonye, at the very top, if you could write antimuscarinics, so A-N-T-I -- and, actually, I can also drop it in the chat. That might be faster -- muscarinic agents. Then it would be β3-agonists, which I will also drop, and so we are going to make a separate section for the mirabegron and vibegron, so the one, two, three, fourth agent there, the mirabegron.

Nonye Connor: Mm-hmm.

Kavita Chawla: We will remove that for a different agent. Just that one, not the whole section.

Nonye Connor: And remove this one?

Kavita Chawla: Yeah, just that one. We will move it down to a separate section of its own.

Nonye Connor: So I just want to clarify this all stays together.

Kavita Chawla: Yeah, and the last agent, the vibegron.

Nonye Connor: That would be by itself?

Kavita Chawla: Along with the mirabegron.

Nonye Connor: Oh, thank you.

Kavita Chawla: Perfect. And then the name for that second section is what I dropped in the chat, which is the β3 agonist. Am I saying that right, my pharmacy friends? Please keep me accurate here.

Nonye Connor: Oh, great. It's not [indistinct], sorry. [Cross-talk] I'm trying to grab that. All right. It doesn't like it. Let me write it out. Okay. Like that?

Kavita Chawla: And put adrenergic. Kevin is making a [cross-talk] correction.

Nonye Connor: Oh, thank you.

Kevin Flynn: All right, trying to spell it out and I failed.

Kavita Chawla: Thank you.

Nonye Connor: Like that?

Kavita Chawla: Yes. Does that look good, Committee?

Ryan Pistoresi: For formatting, let's have those be underlined and not bolded.

Nonye Connor: Yeah. I'm -- that's what I'm doing next.

Ryan Pistoresi: And then not bolded. Thank you.

Kavita Chawla: Then I guess then the final question is for the last sentence, "A once daily formulation must be included as a preferred drug." Do we want to all out that should be one of those neuroselective agents, since this is for, as Ryan says, perpetuity. Do we want to call out those two agents here?

Zoe Taylor: I think we should, and I also just have a question about, like, if Myrbetriq is going generic next year, like, will there be an opportunity to put that one the -- to make that preferred if we are never reviewing this again? Or is that something that can happen with DUR even though we are not reviewing this again?

Ryan Pistoresi: This is Ryan. So the point of archiving these reports is that as you see that DERP states are not voting for these classes to be updated anymore, and so there has been a lot of time since we have been able to get new evidence, so

we are essentially archiving these, meaning we don't need to bring a new report to the P&T in order to conduct a new cost analysis.

Zoe Taylor: Got it.

Ryan Pistoresi: Because of this -- yep -- next time next year we could always do a new update without having to conform to the P&T schedule and get a new report. We could just go ahead and do that and then get it updated. So this would improve future generic entry for drugs like you had mentioned.

Kavita Chawla: Great, thank you.

Laura Beste: So if by us saying that -- this is Laura -- but us saying that we are not going to substitute for trospium and darifenacin, are we automatically saying that they are preferred or not? You might still have to get prior authorization for them?

Ryan Pistoresi: So they are both preferred right now on the PDL, and I don't imagine that we would, but there doesn't -- there isn't anything that would require us to always keep is preferred.

Laura Beste: Okay. The reason I was asking is because darifenacin is just once daily anyway, so I don't know that we need to call out those two necessarily because we have already said we can't interchange them.

Kavita Chawla: Okay.

Laura Beste: Unless I'm looking at that wrong.

Kavita Chawla: I think if they are already generic that wouldn't go un-generic, and so as long as we have them available, I think that then we don't need to make any adjustments to the last sentence. Other comments, edits, enhancements? And if not, we can proceed with this beautifully written motion.

Laura Beste: This is Laura Beste. I will make a motion that after considering the evidence of safety, efficacy, and special populations for the treatment of overactive bladder, I move that darifenacin, fesoterodine fumarate, flavoxate hydrochloride, mirabegron, oxybutynin and chloride, solifenacin, tolterodine tartrate, trospium chloride, and vibegron are safe and efficacious. These drugs, with the exception of trospium and darifenacin, due to their

neuroselectivity and can be subject to therapeutic interchange within the same drug class in the Washington Preferred Drug List. Additionally, immediate-release formulations cannot be interchanged for once-daily formulation and vice versa. A once-daily formulation must be included as a preferred drug on the Washington Preferred Drug List.

Peter Barkett: Peter Barkett, I'll second the motion.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye. Aye.

Kavita Chawla: Okay. Any opposed or abstain? With that the motion passes. Excellent. And I think we have one more review for long-acting opioids before we go for lunch. Is the Committee okay with that? Yes? All right, Andrea, whenever you are ready, take it away.

Andrea Vintro: Okay. Are we seeing that?

Kavita Chawla: Yes, we do.

Andrea Vintro: Perfect. Okay. Yes, hello one last time. I am sure you are all thrilled this is the final presentation today for this Washington Drug Archiving Project. My name is Andrea Vintro, and I am a Research Associate at the Center for Evidence-Based Policy. Just once again, I am going to -- I am needing to repeat some of the information around the aim, general overview of the project that I presented in the prior reports because there may be new audience members, so thank you for that. And this presentation is entitled Long-Acting Opioid Analgesics. So the aim of the work is for the Drug Effectiveness Review Project, also known as DERP, to develop and present information to the Washington State Pharmacy and Therapeutics Committee on the nine drug classes that you see below there, which are candidates to be archived from active review by the Committee, and the topic of long-acting opioids is highlighted in green for this presentation. So on this report, for the overview, I am going to review those topics in the darker green boxes on this slide. So at first I will define the health condition there on the far left for the drug class that this drug class is intended to address, summarize a general epidemiology, and common treatments for the condition, and I will review Key information in the recent DERP reports, including the PICOS and Key Questions in the last report, highlighting a summary of the Key Findings and

general findings of any surveillance since the last systematic review, then I will move to new actions by the FDA since the last report, including any newly-approved drugs, new Boxed or Serious Warnings and any new Indications, and they'll report on any current pipeline drugs and also the generic status of existing agents in this drug class. And then, finally, I will present a high-level summary of relevant clinical practice guidelines for this condition, which includes information about how and where these drugs are used on the treatment pathway, and then we will be available for questions. So this report focuses on the condition of chronic pain that is not related to cancer or cancer treatments. This is chronic pain that is typically defined as lasting at least three months. It is a common cause of major disability that can result in substantial healthcare costs and loss of productivity and, of course, poor quality of life. So here were the list the common example terms that people use to describe this kind of pain, such as aching or throbbing sensations. The condition of high impact chronic pain is defined as pain that results in serious restrictions to daily activities, and the types of non-cancer chronic pain include arthritis, joint pain, back or neck pain, also headaches among the other types listed here. So in adults, chronic pain is associated with other medical conditions, including depression, Alzheimer's, and other dementias, and also higher suicidal risks, worsening chronic disease, and substance misuse. It is also associated with poor quality of life, of course, and as mentioned earlier, there are societal concerns as well around reduced productivity and loss of wages. According to the CDC, the number of adults in the US with chronic pain has increased since 2016, with nearly 21% of all adults experiencing chronic pain in 2021. Also 2021, there is approximately 52 million individuals in the US that experienced chronic pain, and then 7% to 8% of adults are experiencing the high-impact chronic pain. There are disparities across populations for chronic pain. So our higher prevalence is seen in individuals who identify as non-Hispanic American Indian or Alaskan and Native adults, bisexual adults, and adults who are divorced or separated. So in children and adolescents, chronic pain is associated with depression and anxiety, also school absence, social isolation, and poor quality of life. It is also commonly attributed to headaches and GI disorders in youth. Factors that have been associated with the development of or risks for chronic pain in the scientific literature include some demographic factors including being of advanced age, also experiencing a lower socioeconomic status, lifestyle behaviors such as smoking, sedentary behavior, and poor diet. Also people with certain clinical conditions, including mental health conditions, surgical interventions, and being over or underweight, and also other factors such as a history of injury or abuse. So managing -- the management of chronic pain

often requires a multimodal approach that can include a combination of pharmacologic and non-pharmacologic therapy. So, in general, non-steroidal anti-inflammatory drugs or NSAIDs, such as ibuprofen are considered first-line treatments for musculoskeletal pain. This is often combined with non-pharmacologic approaches that include acupuncture, physical or exercise therapy, also massage among some others listed here. And then it also depends on the type of chronic pain that is being experienced. So for chronic neuropathic pain, initial treatment typically includes the drugs that are listed here. So selected antidepressants like serotonin or norepinephrine reuptake inhibitors, or anti-epileptic drugs like gabapentin or pregabalin. And then if the pain is localized, these drugs will typically be given in a combination with topical therapies. Of note, there is some evidence that cannabis can improve pain and function in adults with neuropathic pain. And, finally, only if these interventions prove to be unsuccessful would opioids be considered now for chronic pain because of the concerns for a variety of Adverse Events, including abuse and addiction? When opioids are prescribed, it is usually at the lowest effective dose and also for the shortest amount of time. And usually this is in combination with other non-opioid and non-pharmacologic therapies. So four reports prepared by DERP on this topic. The last DERP systematic review for long-acting opioids was completed and presented in September of 2015, so this is over eight years ago, and the evidence sources for that report were searched through February of 2015. DERP conducted three surveillance reports since that last report back when they were called scans, with the most recent surveillance presented in 2017, and the surveillance was through mid-November of 2017. Then next three slides list the PICOS for the DERP products for this drug class. So we start with the population, which included adults with chronic non-cancer pain, which was defined as continuous or recurring pain for at least six months. The comparators included another listed intervention, so any head-to-head trials and also short-acting opioids. For outcomes they included pain intensity and pain relief functions, such as cognitive function or physical or occupational fatigue or returning to work and also Adverse Events. For study designs, they included randomized controlled trials and Comparative Effectiveness Systematic Reviews. So this table lists the interventions included in the last report, and they are in alphabetical order by generic name. So we have buprenorphine, fentanyl, hydrocodone bitartrate, hydromorphone, levorphanol, methadone, morphine sulfate, morphine sulfate plus naltrexone, oxycodone, also oxycodone hydrochloride plus naloxone, oxymorphone, and tapentadol. That second column there provides the brand names with some different brand names for different formulations of the same drug, and you

can see the formulations listed in the third column. Then next, we have the mechanisms in column four all of our opioid agonists except for buprenorphine, which is -- so at the top, which is a partial opioid agonist, and then two agents are opioid agonists combined with opioid antagonists. In that far-right column, we have the FDA approval dates with the earliest drug approved in the 1940s. This was methadone. And then the most recently approved novel agent listed here is tapentadol, which was approved in 2011. There were six Key Questions in the most recent DERP report. Key Questions 1 through 4 asked about the Comparative Effectiveness and Harms between the long-acting opioids and between them individually as a group and between the long-acting and short-acting opioids in adults with chronic non-cancer pain. And then Key Questions 5 and 6 asked about differences in Effectiveness and Harms of these agents across different subpopulations. So the most recent report in 2015 was the seventh update of the original report, and cumulatively that report included 25 studies; 18 were head-to-head trials of long-acting opioids, and seven were trials comparing long-acting with short-acting opioids. For Key Findings in that report, we start with Effectiveness Findings. So its summary, tapentadol resulted in greater reduction in pain intensity in patients with knee osteoarthritis compared with oxycodone in two studies, and there was some greater improvement with back pain with tapentadol in one study. There was no difference in pain relief with hydromorphone versus oxycodone, and in general, there was no difference in effects between long-acting and short-acting opioids. However, they did conclude that the evidence was actually insufficient to determine whether there were differences between the long- and short-acting opioids, at least for the outcomes of interest for this report. So here we have the Key Findings for the Harms outcomes in the last report in 2015. So the extended-release formulations of tapentadol resulted in fewer withdrawals due to Adverse Events and fewer specific Adverse Events compared with oxycodone. They found that long-acting morphine resulted in fewer Adverse Events, withdrawals, compared with transdermal fentanyl, for the most part. There was a large cohort study that found a lower mortality rate with methadone compared with long-acting morphine. And then there were no differences in Safety or Adverse Event outcomes in studies that compared these drugs listed here. So we have hydromorphone osmotic-release oral system versus oxycodone sustained-release formulation, then also oxymorphone versus long-acting oxycodone, and then morphine extended-release formulation versus long-acting oxycodone as well as the morphine extended-release formulation compared with the sustained-release formulation. Also hydromorphone extended-release versus oxycodone, and

then finally the fixed-dose agent morphine plus naltrexone compared with the extended-release morphine agent. They also reported insufficient evidence to fully assess differences in Safety outcomes between the long-acting opioids themselves and between the long- and short-acting opioids. Surveillance after the most recent DERP report was through November of 2017, where they found one new drug. However, this is a different formulation of buprenorphine that was already included in the prior report, so whether that was actually new may be disputed, but this is how it was presented in this surveillance. And then they do report that there were five new formulations identified marketed as five new brands, and those are listed here. At the bottom of the slide, we see that they found six new studies during the surveillance period, four of which were systematic reviews, and two were new head-to-head trials. So during the surveillance period, they also found five new Boxed or Serious Warnings. They were all issued in December of 2016. The first Warning listed on this slide is for all of the included long-acting opioids except for levorphanol and methadone. It is stated that if these drugs are used concomitantly with benzodiazepines or other central nervous system depressants, Serious Side Effects, including profound sedation, respiratory depression, or coma, and even death could result. And then, additionally for buprenorphine, the Warning for neonatal opioid withdrawal syndrome was added. For the fentanyl patch, there was increased -- they Warned about increased fentanyl absorption with the application of external heat. And then for hydrocodone bitartrate, there was a Warning for Serious interactions with alcohol that was added. And then for oxymorphone, the Warning was for risks around addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, as well as interactions with alcohol. So now we will switch to the new FDA actions since the most recent report again, including anything that might have been in surveillance but up through the search for this archiving report. So for new drugs, we did not find any additional new drugs or formulations other than those identified during the surveillance, which included that one new drug, and then five new formulations, and those are are listed on the previous slide on Slide 13. There were no new Indications for these drugs. And for new Boxed or Serious Warnings, in addition to those Serious and Boxed Warnings found during surveillance -- and again, those are listed on the previous slide -- we did find one new additional Boxed Warning for all of the included drugs since the last surveillance, and this was added to drug inserts in September of 2018. And this Warning requires a risk evaluation and mitigation strategy program to try to help ensure that benefits of prescribing these opioids outweigh risks of

addiction abuse and misuse. So on this slide and the next, we have the FDA-approved Indications for the long-acting opioids of interest, including any new drugs that were identified. So in the top two rows, we have buprenorphine as both the extended-release transdermal film and the newer formulation of Belbuca, which is the buccal film. So both of these agents are approved only for moderate-to-severe chronic pain for when alternative treatments are inadequate. Hydrocodone bitartrate and levorphanol in those fifth and seventh rows also have this indication as their sole indication. In the bottom row, you can see that methadone as the Dolophine brand only. They also have this indication, and then both Dolophine and Methadose brands have two additional Indications, namely detoxification treatment for opioid addiction and maintenance treatment for opioid addiction in addition to other social and medical services. And, finally, we have fentanyl and hydromorphone in the fourth and six rows, which are indicated for severe pain and opioid-tolerant patients when alternative treatments are inadequate. So all drugs on this slide are approved for moderate-to-severe chronic pain when alternative treatments are inadequate. You can see that as you scan down that second column with the checkmarks next to all of those agents, and these include morphine sulfate, the fixed-dose product of morphine sulfate plus naltrexone, also oxycodone, and this is for adults only. And then also fixed-dose oxycodone plus Naloxone, oxymorphone and tapentadol. So oxycodone is also approved for severe pain in opioid-tolerant patients when alternative treatments are inadequate in patients 11 and older. And then tapentadol is also approved for Serious neuropathic pain associated with diabetic peripheral neuropathy in adults again, should alternative treatments be inadequate. So we have had one new pipeline drug that is said to likely compete with other long-acting opioids if approved. This drug is dinalbuphine sebacate. This was approved in Taiwan in 2017 and appears to show similar efficacy to morphine. However, respiratory depression is a concern. This is a kappa agonist partial new antagonist analgesic. It is currently in Phase III trials for post-surgery Indications, and the FDA approval timeline was uncertain at the time of our research. So next, we will move on to the generic status of these drugs. On this next slide. So for the most part, we found that all of these drugs with the exception of the new formulation of buprenorphine hydrochloride are available as generics. Some formulations of hydrocodone bitartrate and the drug hydromorphone became newly available as generic since the last report, and the estimated loss of exclusivity by the manufacturer of the buccal film of buprenorphine hydrochloride is the end of January 2027. So continuing on with generic availability. So we have at the top morphine sulfate was available as a generic

option with a prior report. And in the next row, we have row three. Also in row five, we see the fixed combination drugs, morphine sulfate plus naltrexone, and oxycodone plus naltrexone, they have been discontinued for the most part. And then in row four -- go back up -- we see that there has been at least one formulation of oxycodone that is available as generics as a generic option. And then in the bottom row, we see tapentadol is not yet available as a generic but may be soon with the estimated date of loss of exclusivity by the manufacturer in June of 2025. So on this and the next three slides we provided a very general summary of the clinical practice guideline recommendations for chronic non-cancer pain in adults, including how and when these agents are used along the treatment pathways. So for this section, we began with the information from up-to-date clinical decision support online resource and then cross-referenced to that information with key practice guidelines from professional medical associations, which are listed at the end of this slide deck. So, overall, the guidelines recommend a very individualized approach to chronic pain, with the first step being to determine the type or cause of the pain. So nociceptive pain is associated with the tissue injury or damage, including arthritis and joint pain. Neuropathic pain is when the pain comes from damaged or diseased nerve tissue. Diabetic neuropathy is an example. Then nociplastic pain is when pain receptors are activated despite any evidence of actual damage to the tissue or nerves. An example of this is fibromyalgia. So next, the guidelines recognize that problems with getting enough sleep are often a side effect of chronic pain, so it is important to address that first. And then non-pharmacologic interventions are recommended first for chronic pain, and those include exercise therapy and physical therapy. Tai Chi and yoga are examples. Also psycho educational interventions include CBT, patient education, my body therapies -- like mindfulness and stress reduction techniques. And then there are other physical interventions recommended like acupuncture and massage. And then the bottom bullet point there mentions that pharmacologic interventions are only recommended after these approached listed here have been tried and were deemed unsuccessful. So on this slide, we have the guideline recommendations for pharmacologic agents when non-drug interventions have been unsuccessful. So with chronic pain from musculoskeletal or tissue damage, the nociceptive pain, they first recommend adding NSAIDs like ibuprofen or aspirin. Second-line agents include antidepressants or antiseizure medications, including tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors (SNRIs), which have these analgesic qualities. Gabapentin and pregabalin, for example, were examples of antiseizure medications mentioned as effective

for diabetic neuropathy, as an example, and then opioids were only considered as third-line treatments if they were not successful with any of the above treatments. And then, if indicated, they should be prescribed at the lowest effective dose and for the shortest duration and then also combined with other nonopioid and nonpharmacologic treatments. The long-acting opioids most often mentioned included tapentadol and buprenorphine, but the caution that these should be reserved only for those patients who are anticipated to and informed that they will most likely remain continuously on opioids for the long-term. And I do want to mention that the guidelines do include tramadol as a third-line opioid treatment. This agent was not included in this report because it is considered a more of a pro-drug versus an actual opioid but in that its metabolite is where is most responsible for that opioid analgesic effect. However, most guidelines do list tramadol in the category of long-acting opioid. For neuropathic and nociplastic pain, or centralized pain, antidepressants and antiseizure medications are recommended first, and then a combination of these drugs, which they mentioned, may be particularly helpful in conditions like fibromyalgia. So opioids are considered, basically, as a last option, and there are no other opioid drugs specifically called out for this type of chronic pain. However, tramadol, tapentadol, and buprenorphine were mentioned more frequently. So here are the key recommendations in the guidelines specifically about long-term use of opioids for chronic pain. So, overall, long-term use is not recommended. If indicated, again, they recommend to use the lowest dose for the shortest period of time. Some guidelines also recommend immediate-release opioids or extended-release or long-acting opioids, and they caution that long-term use of opioids should be reserved for individuals with the with very low risk for substance abuse and those who demonstrate persistent pain despite a variety of other treatments that were tried first, and who are also expected to remain on these drugs for a long period of time. The VA guidelines really emphasize and pointed out to be cautious around the risks for abuse in younger population groups. And here are some general recommendations for the dosing of the opioids in the guidelines. And then also the VA recommends buprenorphine over full opioid agonist because buprenorphine is a partial agonist. And then methadone was recommended as a last option, and if it is provided should be delivered by trained staff only. And there was some mention that there was some but limited evidence for ketamine and lidocaine infusion but that these agents are likely options only for specific situations in certain patients. So, yes, we are at their final slide. These are the relevant key clinical practice guidelines that were also referenced for the guideline section above, and they are listed in alphabetical

order by author or professional organization, and then the dates of publication for these guidelines or guideline updates range from 2017 to 2022. So thank you so much. Questions about the report for me or any clinical questions we can pass to Ryan.

Kavita Chawla: Thank you, Andrea. You've been quite a trooper this morning.

Zoe Taylor: [Cross-talk] I'm sorry. [cross-talk] --

Kavita Chawla: Yeah, go ahead. Thanks.

Zoe Taylor: Sorry in advance for being super annoying on all of this before lunch, but I do a lot of addiction medicine. I prescribe a lot of buprenorphine, and I am not understanding a couple of things. One is, like, why are the categories long-acting versus short-acting opioids instead of full opioids versus partial opioids, just because buprenorphine has so much less in common with any of these other medicines than something like short-acting oxycodone does, and sublingual tablets and films of buprenorphine are just as long-acting as Oxycontin, so I am just -- I feel like there is a lot of stuff that is not correct clinically about the categorization, and that is sort of where we have to start, I think, when thinking through this.

Ryan Pistoresi: So this is Ryan. And, again, the way that these drug classes and reports are crafted is by the states, and when they were doing their selection, they want to emphasize that, yes, there are these different clinical considerations between these different opioid options. And so I think as part of the P&T Committee, your job is to interpret how these different types of medications can be used in the context of pain, so not necessarily with the addiction medicine side, but [cross-talk] --

Zoe Taylor: [Cross-talk] Right.

Ryan Pistoresi: -- in the context of pain.

Zoe Taylor: But even with pain, like the long-acting versus short-acting, like, we know now that Oxycontin isn't actually long-acting, right? That was a whole part of the lawsuits and everything. So is there any rule that we can have in this categorization? Or is that like forever done? [cross-talk] --

Donna Sullivan: [Cross-talk] This is Donna. The state, we decide on the categories. You can make recommendations, and we will take it into consideration. You know the long-acting opioids, the name came about back when Oxycontin was first introduced to market, and then there was a difference between long- and short-acting, and there was a lot of questions about -- that the states had at the time, so these are the drug classes that we that we provided, or that we created. We also use them in our opioid policy, whereas -- when you are treating pain, you can't just go to one of these long-acting opioids for acute pain. You have to start with what we call our immediate-release or short-acting medications, and we can debate where oxycodone or Oxycontin actually lands as far as is it long-acting or not? Define what long-acting means. So we are -- I don't see us changing the drug categories. They've been this way for 20 years.

Kavita Chawla: I think along those lines [cross-talk] --

Zoe Taylor: [Cross-talk] Okay.

Kavita Chawla: -- Zoey makes a great point about we can at least address that in the form of the policies that we put forth right in the motions, where we are able to call out the vast difference between buprenorphine and the other agents. But really good point, Zoey.

Zoe Taylor: And the buprenorphine, like, tablets and films, are those in a different category?

Laura Beste: Is it possible to bring up the motion? This is Laura.

Donna Sullivan: Yep. The buprenorphine products that are not approved for pain -- so you will see generic buprenorphine, naloxone, the suboxones, the Subutex, all of those are not considered part of this drug class.

Zoe Taylor: Okay, thank you.

Donna Sullivan: It's the patches, so we are only -- and they are addressed in a drug class. Like on the Apple Health PDL, they are actually in a Substance Use Disorder treatment category as a partial agonist. They are not considered long- or short-acting. They are different. But the transdermal film because the mechanism of delivery is a patch, which is, I think, at least a day long. I don't know the actual length the patch is good for. It is included in the long-acting

opioid category because we want to be able to compare buprenorphine transdermal the Effectiveness and Safety of it compared to some of the other products that were reviewed.

Kavita Chawla: So just to confirm -- Kavita here -- could the buprenorphine, we can not -- when we say just buprenorphine here at the top one, does that include both the sublingual and the buccal formula? [cross-talk] --

Donna Sullivan: [Cross-talk] No. It is just the [cross-talk] like it mentions here.

Zoe Taylor: [Cross-talk] I think the buprenorphine is just the buccal, and then the buprenorphine transdermal film is the Butrans patch, so Belbuca and Butrans separately, I think.

Ryan Pistoresi: Yeah. So this is Ryan. So the reason that it is bold is that in the report that you just received, they did mention that there was one new drug, the Belbuca, that was first approved in 2015, which just shows you know how old the last report was on this class. So that that bolded drug that you see there is a drug that was approved almost 10 years ago, but we haven't been able to add to date.

Kavita Chawla: So at this time, can you share with us which formulations of buprenorphine are preferred?

Ryan Pistoresi: Uh, on the Washington [cross-talk] PDL or the UMP PDL?

Kavita Chawla: I think the Washington PDL, and then if it is available, UMP as well [cross-talk].

Ryan Pistoresi: [Cross-talk] So for the [cross-talk] --

Kavita Chawla: [Cross-talk] Yeah.

Ryan Pistoresi: Yeah. So the UMP PDL is the buccal film, the patch, the sublingual tablets, so that is the Subutex, and the suboxone generic film, and the suboxone generic sublingual tabs. Those are all Tier 1, except for the buccal film, which is a Tier 2 drug.

Kavita Chawla: Okay. And for the Washington PDL?

Ryan Pistoresi: So it'll be the same. So the [cross-talk] --

Kavita Chawla: [Cross-talk] It's the same, okay.

Ryan Pistoresi: -- Butrans should be the preferred and then [cross-talk] hasn't been reviewed, it can't be preferred.

Donna Sullivan: So, Ryan -- can we update this to be buprenorphine buccal that it is not referring to monotherapy buprenorphine when [cross-talk] --

Ryan Pistoresi: [Cross-talk] Yes.

Donna Sullivan: [Cross-talk] the generic for Subutex? It is very important to -- and what Ryan just mentioned for UMP, the long-acting opioid class does not include buprenorphine products only approved for substance use disorder treatment. They are buprenorphine, but they are not part of this class, so [cross-talk] --

Kavita Chawla: Mm-hmm, mm-hmm.

Zoe Taylor: That's fair.

Donna Sullivan: -- so when you are making your decision, ignore them right now. They are not being impacted by this decision that you are making today.

Kavita Chawla: Mm-hmm.

Zoe Taylor: Makes sense.

Donna Sullivan: So coverage of those drugs for Medicaid, we have them, like I said, in a completely different class. For Ryan, they are in the lowest tier, but again, -- they are not used for pain, so they are not impacted by this motion.

Ryan Pistoresi: Nonye? On the bold buprenorphine at the top of that list, can you just add buccal film? B-U-C-C-A-L. And I can spell it. Great. Thank you.

Jon MacKay: Ryan, this is Jon MacKay. I was just wondering if you can give us kind of a high-level of what is preferred for all the opiates, not to kind of get off the buprenorphine but just what is preferred.

Donna Sullivan: Marissa, do you have the PDL?

Ryan Pistoresi: I can go over the Washington PDL, and Marissa can go over the Apple Health PDL [cross-talk] --

Marissa Tabile: This is Marissa. I don't have the AHPDL open, but I can open it while you discuss. It might take a little bit.

Ryan Pistoresi: Okay. So for the Washington PDL, it is the fentanyl patches, the hydromorphone ER tablets, the morphine sulfate capsules and controlled-release tablets, the morphine sulfate beads capsules, the oxycodone 12-hour tablets, the oxymorphone er tablets, and that is it for the Washington PDL.

Kavita Chawla: As I am reviewing this motion, I think right off the bat it seems like the statement says that "I move that buprenorphine and then all of the other medications are efficacious and have similar adverse effects. And so I think right off the bat we need to call out buprenorphine as separate and not [cross-talk] --

Zoe Taylor: [Cross-talk] Absolutely.

Kavita Chawla: -- comparable in their adverse effects.

Zoe Taylor: Yep.

Donna Sullivan: Why? What is your -- So this is Donna. What was the, I guess, reasoning behind that?

Zoe Taylor: So buprenorphine is a medicine that you can't overdose and die from, and so it is a very, very different medicine than the other ones. Like, I think in a non-palliative situation I would struggle to even say that a lot of these are safe, whereas buprenorphine absolutely is safe. And so I think it is just -- I get that we are working in the restrictions that we have, but I agree that we have to reword this in some way, or else we can't approve it.

Peter Barkett: I think this is a really tough one, and I've talked with Zoe about this before about there is this theoretical -- theoretically, buprenorphine should be safer. It makes sense that it would be. We don't have hard data and guidelines to back that up. It makes sense. The other P&T Committee of mine we set criteria for it for that reason, but if you look at that evidence -- like, we are

basing all of this on the pharmacokinetics and everything and not on clinical outcomes data, and so it is a really tough one to -- like, I think this is a little bit different than SMART therapy, where we have the studies and it is been worked into the guidelines. And I am still kind of thinking through this and how I would treat this in the motion. I am not sure I have -- I don't know that I've totally settled on how I think it should be addressed. But it definitely is a trend in pain medicine and management to use more buprenorphine, and a lot of that is based on the pharmacokinetics and everything and kind of believing that it is going to be safer but without the clinical outcomes to prove it.

Jon MacKay: This is Jon MacKay, again, and this might be a question for Ryan or Donna. But do we have any kind of clinical evidence or data to support the relative Safety within the opiate agonist group? I mean, a couple have jumped out to me as being less safe than others, maybe like methadone or fentanyl patches, and just in terms of maybe if policy can address those Safety concerns or if we need to [cross-talk] address those.

Donna Sullivan: [Cross-talk] Well [cross-talk] and this is Donna, I mean, I think the key to this motion is that they are efficacious when used appropriately. And it is up to the providers to use them appropriately. You know, methadone is a great drug at some point in time for treating chronic pain. It is also used for MOUD but when it is used appropriately and at the correct dose. Can people get too much methadone on Board and have Adverse Events? Absolutely. But there are studies that have shown that -- you know, there was a long argument we had methadone is preferred for a very, very, very long time, and at that time, there were a lot of methadone-related deaths due to illicit use of methadone, not necessarily methadone being prescribed appropriately. So -- there is a study -- I think it was Dr. Chow at OHSU -- specific to methadone, and it was a VA study. I would have to go back and pull the references, but it basically showed no difference in overdoses and deaths when using methadone or other opioids. And I think that is a lot of the basis of this particular motion, and it is a key. All opioids are dangerous when you take too much.

Zoe Taylor: Yeah.

Donna Sullivan: It doesn't matter if it is an abuse-deterrent formulation. I doesn't matter if it is immediate-release, long-acting, if you take too much, -- you can overdose and die. [Cross-talk] So that is why you say -- notice -- somebody needs to be on mute. I'm getting a lot of feedback there. I'm sorry. We don't come out and

say, "they are safe." The Committee at the time was not wanting to say, "these are safe and efficacious" like they often do in other motions. They are saying they are efficacious when used appropriately, and they do have similar adverse effects if you take too -- you know, they cause constipation. If you take too much, you can have depressed respirations and drowsy, sleepy. You know those Adverse Events are side effects, also, and they are similar, and that is what the Committee reflected in this motion.

Ryan Pistoresi: Jon, just to kind of address your question. So there are policy considerations, so we do have clinical policies that are not part of the Washington P&T process. So we do have the extra policies in place that go beyond this. So this is not just having kind of open access, this is just helping us understand which of these drugs is eligible to be preferred, and then from there we do have our clinical policies for both Labor and Industries and Uniform Medical Plan and Apple Health that do restrict it to appropriate use.

Jon MacKay: Yeah. I would definitely concur with you, Donna, that there are like class effects, and they all can result in overdose and death. But I do think there are additional, like, kinetic considerations and that prescribers should probably receive some specialty training in dosing methadone and sometimes fentanyl patches, or at least be [cross-talk] --

Donna Sullivan: [Cross-talk] I agree.

Jon MacKay: -- have extra additional training in their use when using them appropriately.

Donna Sullivan: Right. No, I mean -- this is Donna. I agree with you. We do have -- you know, fentanyl patches are on prior authorization as well as methadone, so you can't just prescribe it. There is very -- I think for methadone, you have to have tried every generic opioid in order to be considered for methadone for pain and let me qualify that. And with fentanyl, it is very strict to the indication, and I think it is only indicated in the treatment of cancer-related pain. And so that policy is pretty strict. So like, as Ryan was saying, we have -- the opioids are probably -- I want to say that the most policy to drugs we have, we have dose limits for acute, like kids can only get 18 doses per prescription for an acute prescription. We have then edits that say you can get your acute prescriptions filled up to a 42-day supply in a 90-day period, at that point in time, you are triggering that stepping into chronic opioid use. So we have an edit there where then the prescriber has to fill out an attestation saying that this patient requires chronic use, and that they are

following best practices, and it is all outlined in the attestation. And then we have a dose limit also. So you can't go beyond 120 mg of morphine equivalents. And once you get to 120, to go above it, again, there is another attestation where the prescriber has to pretty much say that it is a justifiable requirement. If you have somebody that is on -- you know, has chronic pain and they are on 120 mg of morphine, and they break leg, or they have surgery, they might need a higher dose than 120 mg for a short amount of time, and so we do require them to fill out that second application attestation. And then we have a hard stop at 200 mg, and then we require a full clinical review and a justification of why they need more than 200 mg. So there is a lot of policy around these drugs to make sure that they are being used appropriately.

Kavita Chawla: I would say as far as the motion goes, I think the background information about all of the policies in place for protection is fantastic to know about. I think my main concern about the wording is that we are seeing they have similar adverse effects in that I hear what you are saying that they are all working on opioid receptors, but if you look at the data that is available, the rate of accidental overuse or in general overuse deaths related to buprenorphine are, like, whichever studies you find they are all like [cross-talk] 2%-2.5% [cross-talk] of the overall opioid use deaths. [Cross-talk] And so I feel the adverse effects are not in that regard similar across all long-acting opiates and, hence, the comment about separating the buprenorphine agents into their own sentence.

Zoe Taylor: Like, could we put part similar to how we have broken out the left side in other ones? Can we break it out into partial opioid agonist and full opioid agonist? I think then [cross-talk] I could say [cross-talk] --

Donna Sullivan: [Cross-talk] This is Donna. Yeah. We are not -- it won't be considered a separate class. I am not sure if that is where you are trying to go. If you want to be able to say something different about buprenorphine, you can say whatever you would like in the motion, but for our cost analysis they will be all lumped together in as a single class.

Kavita Chawla: I think the spirit here, if I am hearing correctly, is that so we want to reword this a little bit to say, one, buprenorphine, the adverse effect profile of buprenorphine either is separate, and maybe we don't even need to call that out but have something in there that says that a formulation of buprenorphine is preferred on the PDL, is where I am leaning towards.

Zoe Taylor: I agree with that. Yeah.

Kavita Chawla: How about the rest of the [cross-talk] --

Zoe Taylor: [Cross-talk] And I think I would feel fine with saying buprenorphine is safe and efficacious, even if we can't say that about the rest of them. I wouldn't die on that hill, but I think it is really, really different than the other ones, and that is what I think everyone needs to understand.

Nonye Connor: Okay. So how do we want to word it?

Kavita Chawla: Sorry, I was just reading the post that Peter put in the chat. Um, I guess first comments from the rest of the Committee. Do you agree with separating out buprenorphine? And we are running low on glucose now.

Laura Beste: This is Laura. I don't see any problem with separating it out. I kind of see Donna's point, though, with this is that we are saying they are efficacious. We are not saying they are equally safe. The similar adverse effects are slightly different. But we are not interchanging them either, so we are not really blocking anything by adding that information. I think it is good to add it because the adverse effect profile is slightly different, but I don't know if we need to have two separate classes or anything.

Peter Barkett: Can we just add a sentence after the Adverse Effects to something because they the type of adverse effects are the same. We are saying the risk of is potentially less, so maybe just saying something like the statement is pasted in the chat, like, potentially has lower risk due to its partial agonist.

Laura Beste: Because I don't know that the morphine/naltrexone and oxycodone/naloxone combinations -- I don't know how they fall into those categories, either.

Kavita Chawla: That is a fair point, yes. [Cross-talk]

Peter Barkett: Those are all like a list of deterrents mostly there. I think those are what [cross-talk] --

Zoe Taylor: [Cross-talk] Buprenorphine [cross-talk] we are lacking some data for chronic pain for these exact formulations but, like, it is truly a miracle drug.

Like, you really, really can't overdose on it unless you are using it incorrectly or like using benzodiazepines and stuff with it. Like, I am not a scientist, but I do this every single day. So I do appreciate that we need more data, but it just seems like there is so much conflict about, like, which things -- it is, like, all about what the FDA says and which things. It is, like, only about what the guidelines say, and which is only about what papers we can find, but whatever. Anyway, I think I would love to have a sentence that says that buprenorphine -- like, a buprenorphine formulation needs to be preferred , and it would be great to call out in some way that buprenorphine is safer than the other ones, but I wouldn't die on that hill as much as I think the more important thing is actually just to make it preferred.

Kavita Chawla: So if we leave the whole -- well, number one, I think, yes, I do have hesitation in leaving buprenorphine in the list and saying, "similar adverse effects." As Zoe said, I am okay if we just want to leave that part alone, but in that final sentence I do think we need to say there should be at least one buprenorphine-based agent that is preferred on the PDL. How does the Committee feel about that?

Peter Barkett: [Cross-talk] This is Peter. I mean the trick -- so one other -- not to add more nuance and complexity to this but is the morphine equivalency dosing. Typically, you wouldn't go straight to buprenorphine because of the way that the dosage formulations are. Like, you would actually be jumping to a pretty high dose. And so, ultimately, I think the HCA should consider having buprenorphine on the preferred or a buprenorphine product, but I am comfortable leaving that to them because I don't think people should typically go straight to buprenorphine, and I would be fine with them going through another opioid.

Zoe Taylor: I disagree. I think it's much safer to go to buprenorphine first because then they have no risk of all of the risks of an initial opioid. I do it all the time. And I get that [cross-talk] there's an off-label thing.

Peter Barkett: [Cross-talk] There is a very high morbid equivalency.

Zoe Taylor: Yeah, but it can't cause respiratory depression.

Peter Barkett: Even if you cut the buccal films into quarters, which is still higher than I -- in terms of the MED, it is still higher than I would typically dose [cross-talk] patients [cross-talk] --

Zoe Taylor: [Cross-talk] I know I -- Yeah, I know that that is what the science would suggest, but I use 1 mg of the sublingual tablets twice a day all the time for chronic pain in people who are not opioid naive because they've been on and off of it, on and off of it, sometimes getting it on the street, sometimes getting it from a doc. Like, this is the real situation in the world, so I don't know. We don't have to talk about all of this now. Sorry.

Peter Barkett: Yeah.

Zoe Taylor: I know it is lunchtime. But it is a miracle drug. It is okay to start with it. It is going to save lives if people start with it more. And so I think whatever we can do, like, we have a very small role in this Committee in this, right? All of the policy stuff is more important. But if we can say that buprenorphine has to be preferred, I think that would actually save lives, and so that is why I think it would be great if we can do that. I think it would also be great if we could write a whole tome about how people should use it, but I guess that is not our role.

Laura Beste: So for what we are reviewing for this motion, that is not data that we have seen. Just a thought. Could we, as Kavita mentioned, add buprenorphine as a preferred agent in addition to another long-acting opioid, and then just remove the comment. Can we just leave it as efficacious when used appropriately and just remove the [cross-talk] have similar adverse effects?

Zoe Taylor: Yeah, that sounds good.

Kavita Chawla: I think that is reasonable. So, yeah, at the end of -- perfect. Just when used appropriately and [cross-talk] --

Nonye Connor: [Cross-talk] [Laugh] It's my mouse. [Cross-talk] My mouse has a mind of its own right now.

Kavita Chawla: The mouse is running away until lunch.

Nonye Connor: Yes. [Laughter]

Kavita Chawla: Okay, and then just, yeah, a period there, and there should be at least one buprenorphine agent that is preferred on the PDL. But I think, Laura, you were wordsmithing it more succinctly?

Laura Beste: No, I think what you have is fine. There should be at least one more. And did we say it -- and then and more than one oral preferred? Oh, I think I had said in addition to more than one or [cross-talk] --

Kavita Chawla: [Cross-talk] that is preferred. Oh, I see. So [cross-talk] --

Laura Beste: [Cross-talk] In a different opioid class, maybe? And yeah. [Indistinct] at least one --

Kavita Chawla: So after preferred --

Donna Sullivan: This is Donna. Can I make a suggestion? I would say [cross-talk] --

Laura Beste: Yes. [laughter] --

Donna Sullivan: [Cross-talk] there should be at least one buprenorphine agent and more than one oral preferred long-acting opioid in this class.

Nonye Connor: Oh, sorry. Say that again, Donna. Sorry. And more than one --

Laura Beste: I think if you just cut out the preferred in Washington PDL and put that in the end, you have it. Yay?

Multiple Speakers: Yeah. Yeah.

Donna Sullivan: Right.

Zoe Taylor: Ah, so here?

Laura Beste: So yep. So cut out preferred in Washington PDL. So cut, and then paste that at the end of the sentence, and then we will clean up the rest of the sentence.

Nonye Connor: Like this?

Laura Beste: Yep. And then cut out "that is more -- right? More than one, yeah. Then cut out "that is more than one" right there.

Kavita Chawla: Perfect.

Laura Beste: That's better.

Kavita Chawla: Yep, that looks satisfactory. Committee, edits? And, Zoey, what do you think?

Zoe Taylor: Um, yeah, I think that is fine.

Kavita Chawla: Okay, so we are ready for the motion whenever we are ready.

Kevin Flynn: This is Kevin Flynn. After considering the updated evidence of Harms, Efficacy, and special populations for the treatment of non-cancer pain, I move that buprenorphine buccal film, buprenorphine transdermal film, fentanyl transdermal film, hydrocodone bitartrate, hydromorphone, levorphanol, methadone, morphine sulfate, morphine sulfate with naltrexone, oxycodone, oxycodone with naloxone, oxymorphone, and tapentadol are efficacious when used appropriately. There should be at least one buprenorphine agent and more than one oral preferred drug in the long-acting opioid class preferred in the Washington PDL.

Laura Beste: I can second that.

Kavita Chawla: Thank you, both. All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstain? With that the motion carries. Well done, Committee. [Cross-talk] one more.

Nonye Connor: [Cross-talk] One more before we go.

Kavita Chawla: Oh, sorry, one more for the archiving.

Nonye Connor; Yes.

Kavita Chawla: Thank you, Nonye. I celebrated too soon.

Nonye Connor: [Laugh]. And then let me increase the font on this. Okay, can you guys see it? I'm sorry.

Kavita Chawla: No, we are still seeing the [cross-talk] --

Nonye Connor: Ah. Oh my goodness. I forgot I [indistinct], let me just [indistinct] out. I was, like, "Oh, okay." Everyone is quiet. [Laugh] Sorry about that.

Kavita Chawla: Breathe.

Nonye Connor: There we go.

Kavita Chawla: All right. Any comment and/or edits or enhancements by the Committee?

Nonye Connor: And if we can have all Committee members -- thank you.

Kavita Chawla: And hearing none. If we can have a proposal for the motion?

Greg Hudson: Hi, this is Greg. I'll do the motion. After considering the archive reports presented today, I move to archive the following drug classes from further regular review by the P&T Committee: Antiemetics, asthma/COPD controllers, asthma quick-relief, long-acting opiates or opioids, excuse me, overactive bladder as of today. The drug classes will remain on the PDL, and the Committee's last motion will remain in effect until changed by the Committee. The agencies may conduct updated cost analysis of these drugs without additional committee approval so long as any resulting changes in the preferred status of the drug remains consistent with the Committee's last motion for the drug class. The Committee may review the archived status of a drug class upon its own initiative or by request of the participating agencies at any time.

Laura Beste: [Cross-talk] This is Laura Beste, I will second the motion.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye.

Kavita Chawla: All right. Any opposed or abstained? All right. With that the motion carries.

Nonye Connor: Okay.

Kavita Chawla: And I believe with that the P&T Committee adjourns. Is that right, Nonye?

Nonye Connor: Let me take a look at the agenda, but that sounds right. Yes.

Kavita Chawla: And a very well-deserved lunch break for 30 minutes.

Nonye Connor: Okay.

Kavita Chawla: All right. See you at 2:30.

Nonye Connor: Thank you.

[break]

Kavita Chawla: Hello, Committee. Welcome back from lunch. More trickling in. And so I think we have a quorum. We have six of us. And so with this, we convene the Drug Utilization Board, and I think Ryan Taketomo and Marissa are going to start us off for the second half.

Marissa Tabile: This is Marissa. Yes. So let me just make sure I have everything teed up. Okay. So for this meeting and meetings moving forward upcoming DUR Board meetings, we are trying to do some utilization activities or present to you all some DUR Utilization, so letting you see what utilization is looking like for our Apple Health PDL and the products that are on it. So this is really our first introduction today that we have done in, I think, a long time or ever. As far as utilization that we are going to be presenting you, Ryan T. will pretty much -- I'm going to hand it off to him. He's going to do a really great job presenting it to you all, but it is going to be a very high-level type of presentation. And then moving forward our plan is to get a little bit more specific in future DUR Board meetings as far as maybe certain classes, certain products, things like that. So without further adieu, I will go ahead and hand this off to Ryan. Let me go ahead and just share the slides, as I will be driving for him. And let me get it all teed up. Hopefully, it is going to present well. Okay. You should be able to see the slides, Ryan. Let me know if they are not working, and you are good to go.

Ryan Taketomo: All right. Hi, this is Ryan Taketomo. Good afternoon, Committee. And as Marissa talked about, we will be starting off with the drug utilization review activity. This afternoon, we will be going over the top 25 drug classes and drugs by costs. Next slide. So just a quick overview. We will start off with just looking at annual utilization from 2021 to 2023, then we will be moving down to the top 25 classes, and then at the end the top 25 drugs. Next slide. So a little background for the annual utilizations and methodology. This data that we are presenting comes from our pharmacy point of sale claims. The

dates ranges from January 2021 to the end of December 2023, and the data includes fee-for-service and all our Managed Care Organization claims. Next slide. So on this slide, the top graph shows our actual paid amount and net paid amounts, and the bottom graph is adjusted to a per member per month basis. From just as a cost overview, we have about up to $2 billion of expenses annually. With rebates, it drops it down to about a billion dollars a year. Next to each of the year numbers if you see a YOY, that is the year-over-year percent change. And so focusing on the net pay, we have seen that it has been growing by about 9% to 10% every year. And then the bottom graph is, again, the per member per month adjustment, and we can see steady growth there as well with more growth kind of in the more recent year. Next slide, please. Yeah, and before I continue, I just want to let the Committee know if there are any questions, comments, or feedback, please feel free to raise your hand/or jump in and interrupt. Okay. So, on this slide, we are looking at the number of claims, the number of clients, and the annual number of member months. What member months is that for a particular month a member will be counted if they are enrolled in Apple Health Medicaid. So in 2021, there were 25 million total member months. And pretty much for all three metrics, we can see that there is growth over time, except in 2023, when there is a slight decrease in the number of claims and the number of member months. Next slide, please. Okay, that covers the annual utilization. Now we will go into the top 25 classes. So the way we defined what a class is for this presentation is using the Apple Health Preferred Drug Class name. For example, Antidepressants : Tricyclic Agents. The class for this presentation is the piece before the colon so that would be Antidepressants, and then there are 64 classes as of 2023. And then just for definitions, the subclass is what we are calling that piece after the colon, which would be Tricyclic Agents. And at the end of 2023, there were 494 subclasses. And then note like some classes such as Cytokine and CAMs don't have a subclass. Okay. And any class we will be discussing is based off of the cost inclusive of rebates, also referred to as net paid. Next slide. All right. So this just shows the top 25 classes sorted by the net paid amount. We can see that some of our most expensive classes are close to or even over $100 million in expenses in a single year, while the least expensive of the top 25 is $10 million, and so we see quite a big range in cost for these most expensive classes. And then for reference, we also have the per member per month as well. All right. Next slide. All right. On this slide, we will be looking -- focusing on the classes that had the greatest increases in PMPM, between 2021 and 2023. The way to read this chart is that each color represents a class, and they are stacked in order by their PMPM. So for example, in 2023, moving down from most

expensive and getting less expensive, we have Cytokine and CAM, then Diabetes, then Oncology, and asthma/COPD, and then antipsychotics, just as an example. When you see movement, it represents that a class has become more expensive than another class. So if we focus on antidiabetics, which is the yellow one, we can see it move from kind of the middle of the pack class to our second most expensive class in 2023. Next slide, please. Okay. And then here on this, we are looking again at the same classes that have had the greatest increases in PMPM, and this is looking at their actual changes. So for example, just the Antidiabetics between 2021 and 2023, the PMPM has increased by $1.16 per member per month. And to just name off like the top five biggest increases were the Cytokine and CAM Antagonists, the Antidiabetics, the Asthma and COPD agent, and the Atopic Dermatitis agents, and then the Endocrine and Metabolic agent. Next slide. So this kind of changes the data a little bit. It is looking at the same classes; however, this time, we are looking at what was the percent change in PMPM. So for example, the Antidiabetics, if it was $1.00 in 2021, it increased by 76% in 2023, so essentially going from $1 to $1.76 per member per month, and that is how you would read this graph. The top classes that had the greatest percent increase between the two timeframes include the Atopic Dermatitis agents, the Antidiabetics, the Neuromuscular agents, the Hematological agents, and the Asthma and COPD agents. Next slide, please. Okay. And then s now, we will be looking at the -- focusing on the classes with the greatest PMPM decreases between 2021 and 2023, so similar to the previous chart. The colors represent the order where the class with the highest PMPM is on the top, and then it goes down. So there weren't many changes between these class orders except between the GI or the Gastrointestinal agents and the Antidepressants, where they kind of switched. And the classes that had the greatest PMPM decrease include the Antivirals, the GI agents, the Antidepressants, the Analgesics, and then the Dermatologics. Okay. Next slide, please. Okay, this slide we are looking at kind of the absolute change in PMPM between the two years. Again, these are all the classes that had a decrease in their PMPM. Next slide. And then this looks at it from a percent change. So Contraceptives had the greatest percent decrease in the PMPM, then Dermatologics and then Antidepressants and so forth. Okay. Next slide. So in summary, just talking about the top 25 classes by cost, 15 of the classes had an increase in PMPM, and 10 classes had a decrease in their PMPM. Next slide. Okay. On this graph, we will be looking -- it is sorted by number of clients, so we are now going to be focusing on utilization. So we can see one thing that stands out is just the number of clients who are using these classes. It ranges from over a million Apple Health clients using antibiotics to a little

over 300 clients using respiratory agents. And I think what is interesting is when you look at the net paid per claim, obviously, the antibiotics with the sheer number is less costly per claim while when you get toward the bottom when there is a significantly less number of clients using these products, the cost for these therapies are very expensive. Next slide, please. All right. So here, we will just be looking at the percent change in clients between the years, and I only included the classes that had the biggest differences or the greatest percent difference. So looking at the ones with an increase in clients utilizing these classes, we have Atopic Dermatitis agents at the top increasing by 73%, almost 74% between 2021 and 2023. And then there is only one class that had a decrease in clients utilizing their class, and that was the Contraceptives class. Next slide, please. Okay. And then just in summary -- of the top 25 classes by cost, 24 of them had an increase in client utilization. Again, the Contraceptives class was the only class with a decrease in client utilization. And then the number of clients using a particular class ranges from 328 to as much as 527,000. Next slide, please. Now I will be shifting to be top 25 drugs by cost. So a little background. Drugs were identified using their, what we call, label name. So examples of what a label name would be include fluoxetine, Prozac, Humira, Humira Pen, and adalimumab-ADBM. And again, these top 25 drugs were included based on their cost inclusive of rebates or their net paid amount. Next slide. Okay. So here is the table with the top 25 drugs by cost. Every single one of these drugs came from one of the top 25 classes, and you can see and in each label name to the left list the class they come from, and they have also color-coded them. But we can see that there is a lot of representation from the Cytokine and CAM class. You can see quite a number of products from the HIV class and then the Asthma and COPD class. And then the topmost expensive drugs that we are paying for today include Stelara, Trikafta, Biktarvy, Dupixent, and Humira Pen. I think it is interesting when you look at the Cytokine and CAMs, that when you look at the net paid per client, Humira sits around $6000, while Stelara at the top is 73, almost $74,000, a big difference. And this is one of the reasons why we prefer that clients step through our preferred products before moving on to a nonpreferred agent. Next slide, please. Okay. Yeah. In this class -- I'm sorry -- on this graph, we again showed the drugs, and we are focusing on the ones that had the greatest PMPM increases between 2021 and 2023, but there are definitely some products that remain consistent as being the most expensive. Again, those are Stelara, Trikafta, Biktarvy, Dupixent, and Victoza being some of our most expensive products that we are paying for today. Next slide. And this graph, we are just looking at the what the absolute change in PMPM between the two years were for the same drugs on the previous slide. We can

see that Stelara stands out with a $0.68 PMPM difference within the span of two years. And next slide. And then here, we are changing it up and looking at which products had the greatest percent PMPM increase. So for this one, the biggest growing products, I guess, were the Skyrizi, Sublocade, Victoza, Jardiance, and Dupixent. Next slide. Okay. So in this slide, we are going to be focusing on the top 25 drugs that had a decrease in their PMPM between 2021 and 2023. You can see that there is quite a bit of movement between the drugs. For example, the methylphenidate kind of drops significantly in that difference in PMPM, while some drugs kind of go up and down in their rank, but all of these drugs do have a decrease in their PMPM between 2021 and 2023. Okay, next slide. All right. Again, this is just kind of showing the absolute changes in PMPM between the two years, and the ones with the greatest decreases include methylphenidate, hydrochloride ER, Mavyret, Genvoya, Cosentyx Sensoready Pen, and Descovy. Next slide. And this slide is just looking at it from a percentage decrease between the two years, the changes the ordering of it that gives you a different perspective of what might be going on. But the biggest percent decrease from the same group of drugs include the methylphenidate product, Genvoya, Mavyret, and the Cosentyx SensoReady Pen. Okay, next slide. So in summary for the top 25 drugs by cost, 18 of them had increases in PMPM between 2021 and 2023, and seven drugs had a decrease in their PMPM in this timeframe. Next slide. Now we are looking at the same top 25 drugs, but this is sorted by the number of clients utilizing these products. And I think similar to the class, I think it is interesting how the number of clients is so different. We have 63 clients using Uptravi all the way up to 157,000 clients using the albuterol sulfate HFA inhalers. And again, I have color coded the products to represent the Apple Health classes they come from. All right, next slide. Okay. So this slide we are just focusing on the drugs with the greatest percent change, whether it is an increase or decrease, by the number of clients. Between 2021 and 2023, you can definitely see some products having a lot of growth, such as the Skyrizi Pen, the Sublocade, the Rinvoq, and Dupixent, and Biktarvy, all of those drugs are having a lot more utilization over the past two years. And then at the bottom, we only see two drugs having a big percent change in their clientele, and those are the Mavyret and the Genvoya products. We can speculate that patients could be moving from one class -- or one product to another, but I will kind of be saving that discussion for a future P&T Meeting when we start to look at particular classes and all the drugs within that class. Next slide. Okay. So, in summary, for utilization of the top 25 drugs, 22 of them had an increase in client utilization, and only three drugs had a decrease in their use. And the number of clients utilizing a particular drug

ranges from 63 to over 157,000. Next slide. Okay. So just some takeaways. HCA uses utilization data to manage the pharmacy benefit and helps us kind of identify different trends and prescribing patterns. We use the data to develop management strategies for some of these classes with the supplemental rebates, and then we also use the data to kind of guide some of our clinical policy criteria. And just want to leave it that this is kind of the first presentation at least that I've done, but we plan to continue bringing more of these presentations to these meetings and provide additional detail for themselves. So, for example, we might be looking at all the different Cytokine and CAMs and how they might relate to one another. So I will leave it at that and open it up to the Committee for any comments, questions, or feedback. Thank you. [Cross-talk] --

Kavita Chawla: [Cross-talk] Please, go ahead, Jon.

Jon MacKay: Oh. Ryan, I just want to say that was outstanding. I really appreciate that. I am getting a high-level overview of the utilization that was great. But I was wondering in terms of the fee-for-service versus the MCO, can you kind of give us like a ratio of drug spend cost? And I guess why I ask is just like the rebate utilization, or the rebates are kind of dramatically different, like for 340Being passed through on the fee-for-service side, so I am just kind of wondering like what the drugs spend is on fee-for-service versus the MCOs.

Ryan Taketomo: Um, I'm not prepared to answer that question now, unfortunately, but I can take that feedback, and I think as we continue to bring these presentations, we can separate the data and split it up by each of the different MCOs and fee-for-service. So that is on the focus end, which I am not able to answer that question right now. In addition, I also want to say that when it comes to the cost of these products that we at HCA do have to be careful with how we present them, just because we are limited by law that states that we cannot give like the cost of a particular drug out. So that might cause some discussion, but I think in a lot of cases when you look at, for example, cost per client. If one drug is significantly more than the other, you can still reach the same conclusion that that drug is a lot more expensive, even though you might not have the exact price of the drug.

Jon MacKay: Yeah, thank you. I appreciate that. I think I just noticed that sometimes the 340B price when it is passed through to the fee-for-service, it can be a dramatically different price than like an MCO reimbursement, so you can end up with two dramatically different costs based on who is paying.

Donna Sullivan: And that is true, Jon, with 340B.

Kavita Chawla: For the sake of everyone on the Committee, including myself, can we clarify 340B pricing if we can just define that? Or is it more complicated than a one sentence definition?

Donna Sullivan: It is not a one sentence definition [cross-talk] but there are certain entities and [indistinct] by the way, there are certain entities that are federally recognized as being treating a disproportionate share of uninsured individuals, and so they have been granted this special, what we call -- it is called 340B because that is the paragraph within the federal regulation that contains this rule, but it allows -- it actually requires these entities to purchase drugs, when they purchase drugs, that they get a special discount from the manufacturer, which is better than the Medicaid best price. And so they -- because those 340B entities are getting this big discount from manufacturers, the Medicaid program is unable to collect rebate on drugs that were purchased at a 340B rate. So an entity could purchase Mavyret at the 340B price, but then it could also purchase Mavyret traditional costs that you would buy from your wholesaler. If they use their 340B stock, Medicaid can't get rebate on it, and if it is Mavyret, and it is a 340B entity, submitting a claim to fee-for-service Medicaid, then they have to -- the 340B entity has to submit to us their actual acquisition cost, so that 340B price, and that is what they get paid. That rule does not apply when they are billing to one of the Medicaid managed care plans. They can get reimbursed their commercial rate or whatever contracted rate they have with that pharmacy benefit manager who is running the claims for that Medicaid managed care plan. In either instance, Medicaid cannot collect rebate on that claim.

Donna Sullivan: Thank you for that explanation, Donna.

Kevin Flynn: [Audio cuts out] [indistinct] priced outpatient for a cost. It has nothing to do with the patient. For the -- your highest cost ones, there are a lot of biosimilars that are coming out in there but especially in the Cytokine and CAM class, particularly Humira. Do you anticipate that will help drive down cost? I mean, just looking at it, it looks like you get fairly significant rebates off that drug. So with that change what is preferred, are we going to stick with the brand for the most part?

Donna Sullivan: So this is Donna. The biosimilars are challenging for Medicaid because the way that they are approved, they are classified as a brand, a single-source product, and so they are no different from the Medicaid rebates themselves. They vary depending on if it is a brand name drug, if it is a generic drug, if it is a drug solely indicated for the treatment of children, and whether or not it is a hemophilia factor. I know the brands -- traditional brand name drugs are 23.1%, and that would include your biologics. A generic is only 13.1%, and that is the average manufacturer's price. So when a biosimilar comes out, the regulatory pathway, CMS considers it to be a brand, so it gets that 23.1% rebate. However, if a biosimilar is priced at a point where similar to the originator biologic -- so, like Humira has been on the market for a very long time, and they've had significant price increases over the years. There is a rule that requires the manufacturer if their price increases exceed the consumer price index -- the increase in consumer price index year over year, they have to add that to the rebate. So the price on a brand name drug, the net price after rebate becomes very small if it has been on the market for a long time, and the price has increased significantly over that time because of that rebate keeps just growing and growing and growing. So then when you get the biosimilar coming out, it is a brand. Its upfront price is the same as Humira, but it has not had those price increases because it is new. So we only get the 23% rebate, whereas with Humira we might be getting 65% or 70% off the drug net of rebate. So it is complicated. You know, they are cheaper upfront, they are cheaper for providers to purchase, but it is not necessarily the cheapest drug for Medicaid because of the way rebates work.

Kevin Flynn: Thank you [indistinct]. And it's also why a lot of them do their own authorized generics, right? [cross-talk] --

Donna Sullivan: Yeah. The same thing happens. Yeah, the same thing happens with generics, especially if there is not just an authorized generic, but if there is only a single manufacturer that comes to market, and they get that market exclusivity for, it might be six months. It could be longer, depending on if there was a lawsuit and what that resulted in. And so it is the same for generics. Sometimes the brand is cheaper from the generic until we have enough competition on the generic side for that price to really come down.

Peter Barkett: This is Peter Barkett. I wonder, Ryan or Donna, if you are able to speak to the pharmacy PMPM relative to other health plans. I imagine it is quite a bit lower because of some of the favorable pricing. But I am curious, what is the industry standard for other health plans?

Donna Sullivan: Ryan, did you -- did this include amount of rebate dollars? I forget.

Ryan Taketomo Yes.

Donna Sullivan: Okay.

Ryan Taketomo: This is Ryan Taketomo. Yes, it did.

Donna Sullivan: It is really hard. That is a really difficult question to answer because our rebates are so different from a commercial health plan. We have statutorily defined rebates. I get a rebate on a drug regardless of its preferred or not preferred with our federal rebate system. It is our supplemental rebates which are in addition to that federal rebate piece is where the preferred status would come in where, which is more like a commercial health plan. If it is a brand name drug, if it is going to get a rebate, the plan typically has to put it in a preferred position with limited or no restrictions, so couldn't be on prior authorization, or you couldn't require step therapy, that kind of situation. And every health plan is different. I don't have like what our Uniform Medical Plan PMPM numbers are off the top of my head, but the drugs, probably, when you look at the top 25 drugs and drug classes, I think the classes are very similar. You know, the specific PMPMs are probably going to be very different though.

Ryan Pistoresi: A good example is if we think about our UMP population. We have our Medicare population as well so we do see a lot more oncology there than we would here. Like today, looking at these top 25 costs, similarly, we are seeing a lot more HIV here in the Apple Health population than we do in UMP, so there are some differences. But for the Stelara, Dupixent, Victoza, those classes are all up there at the top for UMP but, unfortunately, we didn't prepare any information on UMP today.

Jon MacKay: This is Jon again. So just when you look at the drivers of future costs on a per member per month, it looks like it is primarily driven by specialty pharmacy. How do you contain that kind of growth, like, when they are so specialized and disease states?

Donna Sullivan: So my cynicism, Jon, is that there is no controlling that. There really isn't. You know, we are just like every other payer, we are at the mercy of the manufacturer setting really high prices, and the rebate system itself has

created kind of this mess that we are in because as manufacturers are pressured by pharmacy benefit managers to give them rebates to reduce their clients -- the PBMs clients prices, the manufacturers have to keep raising their price in order to keep their revenue streams. And so it is really a vicious cycle. So we put them -- that is why we have all of our clinical policies on prior authorization, and we take that into account -- the cost into account on deciding what gets put on prior authorization. That is why Victoza is our preferred GLP-1, it is relatively inexpensive compared to some of the other GLP-1s that we have, where there would be maybe $2.00 or $3.00 double the cost per member per month for the convenience of a weekly dose. And so, we do put policies in place and try to steer our members to the less -- the most cost effective drug in that class, but also maintaining access for those people that have a -- that really can't take the preferred drug and need to have that nonpreferred prescription filled.

Kavita Chawla: This is such a great discussion and a lot of what all the systems in the country at large are grappling with as far as the rising drug costs. Ryan, this is an excellent presentation. I think it is just so clarifying when we see some of these numbers in the context of the decisions that we make. I completely respect keeping the clinical decision-making separate from cost discussions, but I mean, to an extent, the awareness of these drug costs. And the comparisons are really valuable in us thinking about our policies more effectively. Committee, other comments, questions for Ryan? If not, Marissa, did you have anything else to add?

Marissa Tabile: This is Marissa. No, I don't have anything to add besides the fact that moving forward for the upcoming DUR Board Meetings we do plan on presenting more of these utilization data analyses to you all as we tweak it and get a little bit better at them. So we -- you know, this is not -- this is really just an introduction as far as introducing you all to what that data looks like, how we are presenting it, but we can get a little bit more specific moving forward as far as drilling down to specific drug classes, drilling down into specific drugs, drilling down to specific MCOs. So that is just more to come. We do have one planned, I believe, in August. We are still working on that. But yeah, we welcome -- we do welcome any feedback that you all might have as far as what you were presented today, so just feel free to let us know things that you might be interested in improving the presentation or, like I said, just things that you might be interested in seeing overall.

Kavita Chawla: Thank you, Marissa. Yes, we have been craving this drug utilization data, so this is a great start, and we are looking forward to more. Peter, did you have something to say?

Peter Barkett: Yeah, thanks. Yeah, I have one other question. As like a percentage of the medical loss ratio, what does the pharmacy spend doing over time? Is it trending higher as a percentage of overall spend relative to other buckets like professional services or hospitalizations or elective surgeries? Or has it stayed pretty steady?

Donna Sullivan: Hi, Peter, this is Donna again. You know, that is a great question, and I hate to try to guess. I think it is holding its own, and it is probably growing. It makes it challenging in what we are presenting to you today is just drugs that are dispensed at a community pharmacy or possibly mail order pharmacy but is an outpatient benefit versus drugs that are administered under the physician -- you know, physician-administered drugs. So I know that -- I think the data that we get from our actuaries includes both, and that is something that we can maybe start looking at is some of the data that we actually do get from the actuaries looking at. I don't know if they are really looking at the medical loss ratio, per se, but they are looking when we are setting our capitated rates, we could be looking at how much of that capitated rate that we pay to the plan is attributed to drug cost.

Peter Barkett: Thanks. So this is fascinating. It is often difficult to get this level of insight.

Kavita Chawla: Thank you. Any other final comments, Committee before we move on to Nina at Magellan? Okay. Hi, Nina. We're [cross-talk] ready for you. Welcome [cross-talk] --

Nina Huynh: [Cross-talk] Thank you. [Cross-talk] Yes [cross-talk] I am [cross-talk] --

Marissa Tabile: Let me go ahead and get your slides pulled up.

Nina Huynh: Okay. And DUR Board, just doing a time check. It does look like we only have about 45 minutes left in our meeting. [cross-talk] I think the best plan is just to kind of see what we can get through moving forward. It might only be, like, one or two classes or two agenda items. We will do a time check kind of -- I will be mindful of the time after every motion and then determine from there if we should proceed or not. So I will just go ahead and have Nina present. I don't know if some of the DUR Board if everyone was there at the last

meeting or not, but Nina Huynh when is our new Magellan Account Manager. She is slowly transitioning, it is from Umang to her, so this is her first meeting presenting for us here at our DUR Board. So I just wanted to welcome her and then formally introduce her to you all you all haven't met her yet. But Nina, I will go ahead and let you take it away, I think I should be able to present here in a minute. And your slides should be showing, so whenever you are ready, I think you are good to go.

Nina Huynh: Okay. Thank you for the introduction, Marissa. We will go ahead and start my presentation. So on the next slide, you will see the agenda topics for the classes that will be reviewed. We will be going over the disease states, any recent updates in the past 13 months, including Indications, Dosage, Formulation, and Guidelines. On the top in blue are the prime therapeutic market baskets, and the words below in black are the Apple Health drug classes. So for the first Apple Health drug class we will be going over is Antidiabetics : Cellular Therapy which falls under the prime therapeutic market basket Disease Modifiers, Type 1 Diabetes. So the first disease state we will be going over is Type 1 Diabetes. It is estimated that over 37 million Americans have diabetes. Diabetes is responsible for increased morbidity and mortality, and achieving adequate glycemic control is crucial to minimize chronic microvascular and macrovascular complications. Misclassification of Type 1 Diabetes in adults is common and over 40% of those diagnosed with Type 1 Diabetes after the age of 30 years were initially thought to be Type 2 Diabetes. Distinguishing features of Type 1 Diabetes include younger age at diagnosis, so less than 35 years old, a lower BMI of less than 25 kg/meter square, unintended weight loss, ketoacidosis, and glucose greater than 360 mg/dL. A family history of Type 1 Diabetes or a history of autoimmune disease may also be present. The 2023 American Diabetes Association advises that most adults and children with Type 1 Diabetes be treated with multiple daily insulin injections of prandial and basal insulin or continuous subcutaneous insulin infusions. Rapid-acting insulin analogs are typically used to reduce hypoglycemic risks. Continuous glucose monitoring (CGM) should also be considered in most patients. Automated insulin delivery systems are recommended to improve glycemic control and reduce hypoglycemia. The rapid-acting insulin, insulin aspart, insulin glulisine, insulin lispro, insulin lispro-aabc, and insulin lispro/protamine lispro combinations are approved for use with insulin pumps. Okay, here we have Lantidra (donislecel-jujn). So in June 2023, FDA-approved donislecel, the first pancreatic islet cellular therapy made from deceased donor cells for the treatment of adults with Type 1 Diabetes, who are unable to approach target

hemoglobin A1C because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. There is a Warning or risk from concomitant immunosuppression, which includes increased risk of severe infections, including opportunistic infections, malignancy, and severe anemia. There are also procedural complications such as liver laceration, hemorrhage, and intra-abdominal bleeding with portal administration. The dose is individualized based on tissue volume. The recommended minimum dose is 5000 equivalent islet number (EIN)/kg for initial infusion and 4500 EIN/kg for subsequent infusion in their same recipient. The maximum dose per infusion is dictated by the estimated tissue volume, which should not exceed 10 mL per infusion, and the total EIN present in the infusion bag, which is up to a maximum of 1 x 10^6 EIN per bag. The second or third infusion may be performed within one year of the previous infusion or within one year of losing independence from exogenous insulin. Pre-infusion induction immunosuppression is required, is available as a cellular suspension administered as an IV infusion into the hepatic portal vein. Each infusion uses one lot of Lantidra, which consists of islets manufactured from the pancreas of a single deceased donor. The dosage strength is represented by the total EIN in a single preparation and varies between product batches. And that is it for disease modifiers. I will go ahead and pass it back to the Committee.

Kavita Chawla: Thank you, Nina. Questions for Nina from the Committee.

Peter Barkett: This is Peter Barkett. I have a question. So before Lantidra, patients would get immunosuppression, and then presumably they would stay on immunosuppression indefinitely? Or if they got to a treatment failure, would they come off of immunosuppression? Would that be safe?

Umang Patel: Peter Barkett, its Umang. I believe there is a phase where the patient was taken off. But if you give me a few minutes, I can double check that for you.

Peter Barkett: Thanks. Yeah, I guess a simpler way of stating the question is, are patients committed to lifelong immunosuppression after the treatment?

Umang Patel: It does, actually. I stand corrected. It does require lifelong immunosuppression.

Peter Barkett: Okay.

Kavita Chawla: Other questions? Any stakeholders, Nonye? Or Marissa.

Marissa Tabile: This is Marissa. I will ask Nonye if there are any stakeholders. But for my end, I will just go through our PDL just so you all are aware. It is pretty straightforward for this class. For this one, we just have the one product that Nina had mentioned, which is the Lantidra, and that is preferred with PA on our AHPDL. So I can answer any questions about the AHPDL, and then, Nonye, I'll kick it off to you if there are any stakeholders that we need to take into account.

Nonye Connor: No problem.

Kavita Chawla: Okay. Any questions? And I don't see the stakeholders listed here.

Nonye Connor: And there are no stakeholders' hands raised.

Kavita Chawla: Okay. Thank you for loading the motion. Kavita here. My question is for like a new agent, and there is only one option in this drug class. When we make a motion like this, would a policy be reviewed at the same time? Because, you know, a lot of the things in here don't really apply to this agent. There is no nonpreferred, and there are no alternatives.

Marissa Tabile: No, so we don't have a policy that would be reviewed just because, one, we don't have one created at this time. We do try our best to align if there are policies that do fall within a drug class you are reviewing, we do try to make it aligned with like when that drug class is being reviewed. But in this current state, no, you don't have a policy. You are just kind of doing the same motion that you usually do when you do these reviews. If we do have a motion, we will bring it to the DUR Board Meeting in the future.

Kavita Chawla: Got it. So this motion is primarily whether this agent enters Apple PDL or not.

Marissa Tabile: Yes.

Kavita Chawla: All right.

Marissa Tabile: It is currently on there, yeah. It's just a formality as far as reviewing it. This product has never been reviewed ever to my recollection on our AHPDL before because it is a brand new product. So we do want to just make sure we bring it all to you first so then it has gone through our normal DUR Board

process. And then, of course, moving forward it will keep coming back as often as we would like it to if there are any policies, anything that might change, we will definitely bring it back.

Kavita Chawla: Okay. Okay [cross-talk] with that, Committee, [cross-talk] any questions? Yeah.

Peter Barkett: Sorry. So if there were other drugs in this class, which I imagine eventually there will be, then it would come back.

Marissa Tabile: This is Marissa. Yes, it would come back. Yeah.

Christy Weiland: So just to clarify. So without a policy and just needing a PA, this can be submitted. And are there certain criteria they are having to meet then? Because normally our policies that we have reviewed in the past as specified seems like a very specialized medication that would require several things to qualify for the medication. How is that evaluated then without a policy?

Marissa Tabile: Yeah, This is Marissa. So typically when we have new drugs that come to market and that get placed on our PDL, and we don't have a policy for them, we do review them generally. We do review them by their FDA labeling for medical necessity per their labeling, We can as we do those reviews because sometimes labels can be very broad, we can ask providers for specific clinical information that we might be interested in. So for example, in this case, we could request A1C labs, and we could request looking back at clinical trials, maybe kind of monitoring those things and asking for those specifics. But generally, that is our rule of thumb of just reviewing it per the labeling. And then on special circumstances, we can request additional information and then take that into consideration as we do the reviews.

Kavita Chawla: Great question. Any other questions before we proceed with the motion? I kind of thought I think the verbiage here is pretty much our standard boilerplate language for the agents.

Laura Beste: This is Laura Beste. I make a motion that I move that all products and the Antidiabetics : Cellular Therapy class are considered safe and efficacious. -- Oops, I can't read it [indistinct] smaller -- safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred

products require a trial of at least two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Zoe Taylor: This is Zoe Taylor. I can Second.

Kavita Chawla: Thank you. All in favor, please say aye.

Multiple Speakers: Aye. Aye.

Kavita Chawla: Any opposed or abstain? Great. With that the motion carries. Our next set is Cardiovascular agents. Back to you, Nina.

Nina Huynh: Thank you. So next we have Cardiovascular Agents : Miscellaneous. Between 2013 and 2019, the American College of Cardiology and the American Heart Association in combination with National Heart, Lung, and Blood Institute released four new consensus guidelines regarding cholesterol management, cardiovascular risk assessment, obesity, and lifestyle. Obesity is associated with increased risk in cardiovascular disease mortality. In 2018, ACC and AHA emphasizes lifestyle modification, including a reduced-calorie diet and aerobic physical activity as a critical component of atherosclerotic cardiovascular disease risk reduction both prior to and in conjunction with cholesterol-lowering drug therapies. In June 2021, AHA published a scientific statement on physical activity as a crucial component in the first-line treatment for increased blood pressure and cholesterol. The statement detailed mild-to-moderate risk patient groups appropriate for lifestyle only treatment of increased cholesterol as well as a description of the recommendations, usual effects, and consideration for lifestyle management with physical activity. In 2023, AHA also published a scientific statement, which reports that resistance training has a favorable but modest effect on total cholesterol, triglycerides, and high-density lipoprotein cholesterol. Evidence for the effect of resistant training on low-density lipoprotein cholesterol is more variable. So here we have Lodoco, which is colchicine. So in June 2023, FDA approved colchicine 0.5 mg tablets to reduce the risk of MI, stroke, coronary revascularization, and CV death in adults with established as atherosclerotic disease, or with multiple risk factors for the disease. This medication has multiple Warnings, including blood dyscrasias, such as myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia, and aplastic anemia. It can also cause neuromuscular toxicities, such as myotoxicity, including rhabdomyolysis, especially in

combination with other drugs known to cause this effect. Consider temporary interruption or discontinuation of this medication if that occurs. There are contraindications for a patient with pre-existing blood dyscrasias, renal failure, and severe hepatic impairment. The recommended dose is 0.5 mg once daily, and it is available as a 0.5 mg tablet. And that is it for Cardiovascular. I will pass it back to the Committee.

Kavita Chawla: Thank you, Nina. So to be clear, I think the only one we are looking at is colchicine, then, for this section? Yeah? Okay.

Marissa Tabile: This is Marissa. Yes. Looking at the drug class, it looks like that is the only product that is there, so it is preferred on our PDL.

Kavita Chawla: All right. Under this class, would the -- well, I'm guessing like the other newer agents like the bempedoic acids and all those come under way? But -- or those who be more specific for lipids?

Marissa Tabile: This is Marissa. Um, if it is not in this class, it probably -- it most likely lives in another class. The name of the class, however, escapes me. And unfortunately, what you all have, as far as like the AHPDL Excel document is only really a snapshot of the classes that are being reviewed, so I'm not sure exactly where that falls. I know it is under a PDL for sure, I just don't know what class it is. But we do try to separate them by their mechanism of action. This product is just for reference, it is so much different than the other cardiovascular agents that we have on our PDL. Even though it is colchicine, the indication of it is not for gout. It is for another indication, which makes it a little bit more special; hence, why it has its own class. So that is kind of why it is separated from everything else.

Kavita Chawla: Thank you, Marissa. [Cross-talk] --

Laura Beste: Hi, this is Laura. You know, I had a question for you. Did you use -- is, like, the release mechanism of this colchicine product different than --- I am not that familiar with it so kind of curious. Is it just plain colchicine that we use for gout?

Marissa Tabile: This is Marissa. Nina and Umang, I don't know if you all have insight into it, but from what I can recollect when I was looking at it -- it has been a while since I looked at this class -- but when I did see it, it didn't strike me as any different than regular generic colchicine that has been out on the market. So

to my knowledge it is the same, just a little different brand name. But I don't know, Nina or Umang, if you all know any nuance differences between it or if it is different. I didn't see any, so I'm not aware of any.

Nina Huynh: I didn't see any as well. Marissa.

Kavita Chawla: In a Lodoco trial they just use this dosing of colchicine. I don't if it is because it was not out of US because I thought that the only one we had access to was the 0.6 mg tab. But, yeah, there was no delayed-release or anything like that in that study. Um, okay. [cross-talk] --

Zoe Taylor: [Cross-talk], like it's purposeful [cross-talk]. Like, you know?

Peter Barkett: You're trying to [cross-talk] --

Zoe Taylor: [Cross-talk] Yeah. [Cross-talk]

Multiple Speakers: [Cross-talk] [indistinct] [cross-talk] --

Kevin Flynn: [Cross-talk] Yeah, which the 0.6 came about because we used to have 1 mg tablets, and then -- the drug was so old [audio cuts out] approved, and when they went and got approval, they didn't want you to split 1 mg tabs, so they didn't -- well, providers were already using one-half a mg, and they chose 0.6 on purpose because it doesn't make a significant difference, right?

Kavita Chawla: Fascinating. Oh, golly, but not surprising. Thank you.

Kevin Flynn: All the gamesmanship on these old drugs. Like alcohol got approved for cardiac ablation updated that was ancient for cardiac, too, because the drug is pre-1932 so it's old.

Jon MacKay: It looks like this one is 0.5 mg versus 0.6.

Kavita Chawla: Mm-hmm.

Zoe Taylor: Exactly, yeah.

Kavita Chawla: Other questions or any stakeholders, Nonye? I didn't see anything listed.

Nonye Connor: And they are none who raised their hands at this time. Thank you.

Kavita Chawla: Thank you. There is the motion. [Cross-talk] --

Jon MacKay: This is -- oh, go ahead.

Kevin Flynn: Go for it. You started first.

Jon MacKay: This is Jon MacKay. I move that all products in the Cardiovascular Agents : Miscellaneous class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products require a trial of at least two preferred products -- with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Kevin Flynn: This is Kevin Flynn. I second.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstained? Thank you. With that the motion carries. And back to you, Nina.

Marissa Tabile: This is Marissa. So Nina, I believe we have allotted about 25 minutes for your next section, and we have 20 minutes left. Do you think we will be able to get through it in 20 minutes? Or do you think you will need the full 25? Not to put any pressure on you or anything? [laughter]

Nina Huynh: I think we can get through it.

Marissa Tabile: Okay, I will go ahead and set up the next section for you then.

Nina Huynh: Okay, thank you. Okay, so next we have Stem Cell Mobilizers. Okay. So the disease state of multiple myeloma is a malignant neoplasm of plasma cells that accumulate in the bone marrow leading to bone destruction and marrow failure. In addition, patients with symptomatic multiple myelomas must have greater or equal to one myeloma-defining event, which may include hypercalcemia, renal insufficiency, anemia, or lytic bone lesions. Multiple

myelomas account for approximately 1.8% of all malignancies and 18% of all hematologic malignancies in the US. The median age of diagnosis is 69 years. Multiple myeloma is sensitive to a variety of agents, but the disease is not considered curable with currently available drug therapies. The clinical course of multiple myeloma usually involves initial responses to chemotherapy, but these responses may be transient. Thus retreatment with multiple rounds of therapy with different agents may be required to treat relapse. The 5-year relative survival rate is 57.9%, and overall survival now is estimated to be 8 to 10 years among patients with standard risk disease, but it is significantly lower in patients that exhibit high-risk features. Here, I included the overview of the 2022 NCCN guidelines. Since they are well over one year old, I have just included it here for completeness' sake and for your review during your leisure. So the medication we are going over today for this class is Aphexda (motixafortide). So in September 2023, FDA approved Aphexda, a hematopoietic stem cell mobilizer indicated in combination with filgrastim to mobilize hematopoetic stem cells to the peripheral blood for collection and subsequent otologist transplantation in patients with multiple myeloma. There is an anaphylactic shock and hypersensitivity reaction Warning, so all patients should be premedicated with the combination of an H1 antihistamine and H2 blocker and a leukotriene inhibitor prior to each dose. Aphexda should be administered in a setting where personnel and therapies are available for immediate treatment. It can also cause injection site reactions, so the addition of an analgesic premedication such as acetaminophen is recommended. It can also cause tumor cell mobilization in patients with leukemia, therefore, should be avoided in those patients. It can also cause leukocytosis, so we make sure to monitor the white blood cell count during use. Aphexda is initiated after filgrastim has been administered daily for four days. The recommended dose is 1.25 mg/kg of actual bodyweight subcutaneously 10 to 14 hours prior to initiation of apheresis. A second dose can be administered 10 to 14 hours prior to a third apheresis, and it is available as a 62 mg lyophilized powder in a single-dose vial for reconstitution. And that is it for Stem Cell Mobilizer, and I will pass it back to Committee.

Marissa Tabile: Hey, Nina, this is Marissa. It does look like we have the Stem Cell Mobilizers in the TPO Stimulating Proteins on one motion. So would you mind just going through this section so then we can do the motion for both of them at once?

Nina Huynh: Yes. I will go ahead and [cross-talk] --

Marissa Tabile: [Cross-talk] Okay, thanks.

Nina Huynh: Okay. So next is thrombopoiesis stimulating proteins. So immune thrombocytopenia is an immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system. In children, ITP is usually an acute self-limiting disease that often occurs weeks after viral infection or immunization. Spontaneous remission in children typically occurs within less than or equal to two months in 80% of usual cases. Although treatment does not impact the likelihood for chronic ITP, it can shorten the duration of thrombocytopenia in some patients. In adults, ITP has an insidious onset, with no preceding viral or other illness and typically has a chronic course. A complete blood count shows isolated thrombocytopenia. If anemia and/or neutropenia are found, it indicates the potential for other conditions. Signs and symptoms of ITP are highly variable and range from asymptomatic, with mild bruising or mucosal bleeding to frank hemorrhage from any site. Severity of ITP in adults is dependent on the presence of active bleeding as well as platelet count, patient age, patient lifestyle, related to risk of bleeding, and presence of additional risk factors for bleeding, such as uremia or chronic liver disease. Secondary causes of ITP include drug-induced autoimmune disease, such as systemic lupus erythematosus and viral infections, such as HIV and Hep C virus. Here I included the overview of the 2019 ASH guidelines. Since they are well over one year, I've included it for completeness' sake. Okay, the next disease state is Aplastic Anemia, which is caused by bone marrow failure. Most cases of aplastic anemia have an acquired cause. This can include idiopathic factors, infection, exposure to ionizing radiation, toxic chemical, pregnancy, and other conditions. Initial presentation is often related to anemia or bleeding; however, fever or infections may occur. Symptoms include dyspnea, fatigue, swelling of the feet, gingival bleeding, petechial rashes, infection, headache, and pallor color. The major causes of morbidity and mortality from aplastic anemia include infection and bleeding. Severe or very severe aplastic anemia should be treated properly. Nonpharmacologic treatment includes blood transfusions and hematopoetic cell transplant. Pharmacotherapy includes immunosuppressant agents such as cyclosporine, methylprednisolone, equine or rabbit antithymocyte globulin, cyclophosphamide, and alemtuzumab. All off-label use, except for the antithymocyte globulin, which is indicated for the treatment of moderate-to-severe aplastic anemia in patients unsuitable for bone marrow transplant. Approximately 25% to 30% of patients fail to respond to immunosuppressant therapy. Another pharmacotherapy agent used is the

hematopoietic growth factors, eltrombopag and sargramostim, which is off-label. Filgrastim, also off-label, and the antineoplastic agent, fludarabine, which is also off-label. Monotherapy with hematopoietic growth factors such as recombinant human erythropoietin granulocyte colony-stimulating factors is not recommended for newly-diagnosed patients. Chelating agents, such as deferoxamine and deferasirox may be required in patients chronically transfused due to elevated serum ferritin levels. Okay. Here we have Alvaiz, which is eltrombopag. So in November 2023, FDA has approved a new formulation of eltrombopag (Alvaiz), a thrombopoietin receptor agonist indicated for 1.) the treatment of thrombocytopenia in patients greater or equal to six years old, with persistent or chronic immune thrombocytopenia, who have had an insufficient response to corticosteroids, immunoglobulins, or a splenectomy. This should be used only in a patient with ITP whose degree of thrombocytopenia and clinical condition increase the risk of bleeding. It is also indicated for treatment of thrombocytopenia in adults with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be only used in patient with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of the interferon-based therapy or limits the ability to maintain the INF-based therapy. Treatment also is indicated for the treatment of adults with severe aplastic anemia, who have had an insufficient response to immunosuppressive therapy. There is a Blackbox Warning for risk of hepatic decompensation in patients with chronic hepatitis C and a risk of hepatotoxicity. Safety and efficacy have not been established in combination with direct-acting antiviral agents use without interferon treatment of chronic hepatitis C infection, and it is not indicated for treatment of patients with myelodysplastic syndrome, as it increases the risk of death and progression of MDS to acute myeloid leukemia. For Dosing for persistent or chronic ITP, it is recommended to initiate the dose at 36 mg daily. Dose reductions are needed for patients with hepatic impairment and some patients have East and Southeast Asian ancestry. Adjust the dose to maintain platelet count greater than or equal to 50 x 10^9/L, not to exceed 54 mg per day. For chronic hepatitis C-associated thrombocytopenia, it is recommended to initiate dose at 18 mg daily for all patients, adjust the dose to achieve a target platelet count required to initiate antiviral therapy, and not to exceed a dose of 72 mg per day. For refractory severe aplastic anemia, it is recommended to initiate at the dose of 36 mg daily. Again, reduce initial dose in patients with hepatic impairment or patients of East and Southeast Asian ancestry and then adjust the dose to maintain platelet count greater than 50

x 10^9/L, not to exceed 108 mg per day. It is available as 9 mg, 18 mg, 36 mg, and 54 mg oral tablets. And that is all I have for the last two drug classes.

Kavita Chawla: Well done, Nina. Questions for Nina from the Committee as Marissa pulls it up.

Marissa Tabile: All right. This is Marissa. So I did pull up the AHPDL for you all. It is pretty straightforward. These classes are not very big. So for the stem cell mobilizers, we do have Aphexda as preferred. The other products are listed here, but I believe since they are probably medical and probably carve-outs, they don't have specific statuses here, but we do include them on our PDL just for completeness' sake and communications' sake for MCOs and our stakeholders. And then for the TPO-stimulating proteins, our preferred products are the Alvaiz that Nina had mentioned, and then we have Promacta tablets preferred. And I can take any questions from the Board.

Kavita Chawla: Any questions from the Committee? While we wait there, Nonye, I don't see any stakeholders listed on the agenda. Do we have any with their hands raised?

Nonye Connor: No. I don't have any with their hands raised.

Kavita Chawla: Thank you.

Marissa Tabile: This is Marissa. I kind of alluded to it in the middle of Nina's presentation, but we will just be doing one motion for both the Stem Cell Mobilizers and the TPO-Stimulating Proteins onto one slide. So it is similar to what you all have done before, but just wanted to be transparent about that.

Kavita Chawla: Great. And if we could look at the next slide so we could review the motion. Great, thank you. Questions from the Committee or edits or comments, or the motion?

Peter Barkett: I can make the motion. Peter Barkett. I move that all products in the drug classes listed on Slide 4 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in these classes may require prior authorization to determine medical necessity. All nonpreferred products require a trial of at least two preferred products with the same

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

Christy Weiland: Christy Weiland. I'll second.

Kavita Chawla: All in favor, please say aye.

Multiple Speakers: Aye. Aye. Aye. Aye.

Kavita Chawla: Any opposed or abstained? Great. With that the motion carries. [Cross-talk] -- I hand it over to you, Marissa.

Marissa Tabile: Yeah, we are -- I think we have five minutes left, which I don't think is going to be anywhere close to the amount of time that we will need for the AHPDL classes, so we are good to go as far as the DUR Board Meeting things that we need. As far as the other classes that are scheduled -- that were scheduled for this meeting, I will look into the upcoming schedule to see if I can accommodate scheduling them for other DUR Board meetings or future DUR Board meetings this year, so you might see these come up. The ones that we didn't get to, you might see them come up again at the future meetings. The dates, I don't know why that -- I don't know the exact dates. I will have to shuffle things around, but just wanted to put that out there for you all. I have everything I need. So Nonye, I will go ahead and pass it back to you. Thank you, DUR Board.

Nonye Connor: Yeah. Thank you, Marissa. I think we have everything we need so far. So Kavita, you can join the meeting whenever you're ready. Excellent. Well, thank you for a fantastic job today, DUR Board. I know we had an especially long first half of the day, so with that, we adjourn the DUR Board, and have a lovely evening.

Multiple Speakers: [Cross-talk] Thank you. Bye. Thank you, Bye. [Laughter]

Laura Beste: Hey, a little one. [Laugh].

Nonye Connor: I know [laugh].

[end of audio]