Drug Utilization Review Board

November 15, 2017

Michael Johnson: Good morning. It's 9:00. We're going to go ahead and get started. Welcome to the Washington State Pharmacy and Therapeutics Committee and Drug Utilization Review Committee. This is a recorded meeting so before any of the speakers speak please introduce yourself. With that we're going to go ahead and introduce the committee and all the members up here at the table starting with Frances on my left.

Frances McGaugh: Hi. Frances McGaugh, Community Health Plan of Washington.

Petra Eichelsdoerfer: Petra Eichelsdoerfer, United Healthcare.

Susan Flatebo: Susan Flatebo, committee member.

Dale Sanderson: Dale Sanderson, committee member.

Catherine Brown: Catherine Brown, committee member.

Jordan Storhaug: Jordan Storhaug, committee member.

Lisa Chew: Lisa Chew, committee member.

Michael Johnson: Michael Johnson, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Po Karczewski: Po Karczewski, committee member.

Nancy Lee: Nancy Lee, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Michael Johnson: All right. This convenes the Drug Utilization Review Board and I think we'll start with some announcements.

Leta Evaskus: I just wanted to let the committee know that at the December meeting you're going to be selecting a new chair and traditionally the vice chair moves up, if she wants to, but think about who you want to nominate and then we'll need a new vice chair, as well. So we'll be doing that in December.

Michael Johnson: Thank you, Leta. I think Stephanie… are you on the line, Stephanie?

Stephanie Christofferson: I am. Good morning.

Michael Johnson: All right. We have your slide up and we're ready for you to start.

Stephanie Christofferson: I think you can just go ahead and advance to slide 2. This is just a brief overview of what we'll be talking about in general today on the different topics, which will be indications, dosage and formulations and then any guideline updates for the various disease states.

The first group of medications that we'll discuss today is the colony stimulating factors. Next slide.

So myelosuppressive chemotherapy can induce neutropenia and actually febrile neutropenia, which can be a dose limiting toxicity of chemotherapy. Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations and then also increased use of antibiotics which can cause chemotherapy dose reductions, treatment delays and ultimately compromise the health of patients and treatment outcomes. So colony stimulating factors are growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and also of course improve

chemotherapy dose intensity. Prophylactic use of these medications can reduce the severity, risk and duration of febrile neutropenia and also decrease the risk of infection. There's two different groups of classifications of the medications. There's the granulocyte colony-stimulating factors, which include Neupogen… or the filgrastim products and the pegfilgrastim. And then there's also the granulocyte-macrophage colony stimulating factors which includes the Leukine product. Next slide.

This slide here just lists the different indications that the medications have. As you can see from the chart many of the medications share the same exact indication. And then of note the filgrastim-sndz that was approved in March 2015 as the FDA's first biosimilar product in this class. The reference product to this medication is Amgen Neupogen. However, currently the medication is not considered interchangeable once dispensed. Next slide.

This just rounds out the rest of the medications and their indication. Next slide.

So the next three slides I'll just kind of speak to as a whole which includes the dosing and formulations of the products. All the products except for leukine can be… provided as sub-q injection either once or twice daily depending on the condition in which the patient is being treated for. Leukine, which is on the next slide is approved for IV infusion most often except for when it is indicated for peripheral blood progenerator cell collection and therapy in which case they can be used as a sub-q injection. The dosing for the medications is really weight-based and most of the products come in pre-filled syringes which make it a bit easier for patients to self-administer. I did want to note that within probably the last year or so there was a new pegfilgrastim product that came out and it is actually an on-body injector that the health care provider may initiate administration and actually they apply it to the body the same day the administration of chemotherapy. However, once it is applied it does not dispense the medication until approximately 27 hours after the on-body injector is applied and

then the medication is infused over 45 minutes. However, that device has not been studied in pediatrics. So at this time it is only available or indicated for adult patients. There's kind of some nuances to the product such as the injector must be at least 4 inches away from electrical equipment including cell phones and cordless telephones and microwaves and other common appliances. Because actually it can alter the dosing of the medication or have an incomplete dose. It also shouldn't be used in hot tubs or saunas or anything like that. Patients should not sleep on the on-body injector. It's kind of a novel approach and it helps administration of the production because it used to be that even though it wasn't ideal patients would receive the medication on the same day as chemotherapy and really that was just kind of for logistical purposes, but this device is allowed for next-day administration of other medication which is better for the medication and the patient. Next slide, slide 10.

This is the clinical considerations. There are a lot of warnings about these products. Some of the select ones I've just listed here on this page or this slide. But the granulocyte colony-stimulating factors for this one if the patient is hypersensitive to E. coli-derived proteins they shouldn't use this product. Also, there's an increased chance of splenic rupture including fatal cases, acute respiratory distress syndrome, alveolar hemorrhage, sickle cell crisis. And with these patients some deaths have been reported and they really suggest only doctors qualified in treating sickle cell disease patients prescribe this medication. Growth factors for any tumor type if that's an issue. However, data is limited. Cutaneous vasculitis, thrombocytopenia, capillary leak syndrome and glomerulonephritis. For the granulocyte-macrophage colony stimulating factor warnings include excessive leukemic myeloid blasts. The medication does contain benzyl alcohol, which of course you have to be concerned with in pediatrics. Also there's a warning on fluid retention, respiratory symptoms and then also again the… it has a tendency to be a growth factor for any tumor. Next slide, please.

So for guidelines updates. In 2017 the National Conference of Cancer Network updated guidelines. Just like the previous guidelines they still stratify patients into three different risk groups based on chemotherapy regimens and patient-related risk factors. The three groups are high-risk, which there's a greater than 20% chance of developing febrile neutropenia. There's an intermediate risk which is 10 to 20% chance and then low risk. In patients that are in the high risk they do recommend the colony stimulating factors. Intermediate risk is kind of geared, you know, based on patients… the specific patient and how they responded to in the past and other various factors and then the low risk really did find that there is no benefit to these products. The guidelines are derived mainly from the green light colony stimulating [inaudible] studies and in adult patients with solid tumors or non-amyloid malignancies the guidelines state that safety data appears similar between the filgrastim products and also that the subcutaneous route is preferred for all the agents. However, they do note that there really is insufficient head-to-head comparative studies on the clinical benefits between the products. The subcutaneous filgrastim products have high level evidence from randomized controlled clinical trials and there was uniform consensus from this group that they prophylactically reduced the risk of febrile neutropenia. They also suggest that the filgrastim products can be administered the day after chemotherapy up to 3 to 4 days after therapy and through post [inaudible] recovery. And then based on clinical trials the pegfilgrastim products should be administered the day after chemotherapy. However, they did say, again, just like the other filgrastim products, administration up to 3 to 4 days after chemotherapy is also reasonable. As we discussed earlier the same day administration of pegfilgrastim that used to be I guess… it wasn't recommended, but it was deemed okay to do the same day as the chemotherapy products due to logistical reasons. However, with that new on-body injector product the guidelines have changed for 2017 due to that and now that they… if you're going to use that product they do recommend that the medication be used the next day and again for logical purposes if the patient can't be in there to receive the medication then they

recommend the on-body injector since it can do self-administration 27 hours after the injector is applied. [inaudible] is no longer recommended for prophylactic use and they also state that the biosimilar products, the filgrastim-sndz can be used in the same instances as the reference products, the filgrastim. However, they do not recommend switching between the biosimilars and their corresponding reference product during treatment. So they recommend either, you know, one or the other, but not switching back. Not in the guidelines, but just as an overall comment as far as patient preference and things like that, the pegfilgrastim in clinical studies might have shown a slightly higher rate of reducing febrile neutropenia and it could be viewed as more favorable since administration is less than the other products. But again head-to-head trials are extremely limited between the products.

So with that I'll go ahead and end what I planned on sharing today.

Michael Johnson: Thank you, Stephanie. Any questions from the committee? Okay. Seeing none there is one stakeholder. I'll remind you, you have a three-minute time limit and if you could please come up to the podium and use the microphone. We only have one stakeholder for the topic. It's Dr. Maria Agapova.

Maria Agapova: Good morning. My name is Maria Agapova. On behalf of Teva Pharmaceuticals I would like to bring your attention to and consideration of two recently published studies of Granix, tbo-filgrastim. Granix was approved by the FDA in 2012 and is a short-acting granule [inaudible] colony stimulating factor or GCSF indicated for reducing the duration and severe neutropenia in patients with non-malignancy receiving myelosuppressive anti-cancer drugs that are also associated with clinically significant incidence of febrile neutropenia. Now you may already be familiar with the clinical studies associated with Granix so I'll update you on two studies.

The first, in 2015 the efficacy of Granix in mobilizing peripheral blood cells or PBSCs or accelerating [inaudible] of [inaudible] stem cell transportation were evaluated using retrospective analysis. In this study 185 patients with lymphomas or plasma cell disorders receiving Granix were compared to retrospective filgrastim controls. Patients on Granix demonstrated similar CD34 yield compared to the filgrastim immobilization and post transplantation settings with no clinical meaningful differences in secondary efficacy and safety endpoints. [inaudible] was the study to show that expansion of indications is possible given that Granix was not driven through the regular biosimilars approval process, but the BLA.

In a second single-institution study filgrastim was replaced by TBO filgrastim for all clinical settings. So all indication with filgrastim had received FDA approval, a total of six indications. Although at this time its indication from the FDA is only for febrile neutropenia. Following the hospital-wide formulary conversion this efficacy of Granix was compared with… in 182 multiple myeloma patients in the [inaudible] stem cell transplantation setting. Two retrospective controls of filgrastim. Although the overall time to neutral full recovery was similar for both groups [inaudible] less than 12 days occurred more often, P level of .05 and [inaudible] less often, that's the more than 14 days P level of .09 in filgrastim treated patients. The number of documented infections was significantly less in the Granix group. Day 100 mortality and [inaudible] hospital stay were similar for the two groups and this data indicates that there's no material difference [inaudible] filgrastim and Granix in this particular clinical setting. This was at North Western Memorial Hospital.

So I ask for favorable placement of filgrastim… tbo-filgrastim or Granix on the Washington state formulary. Thank you. I'll take any questions.

Michael Johnson: Thank you. Any thoughts from the committee? Any discussion with the motion proposed up above?

Diane Schwilke: I just have one little concern from the NCCN guidelines recommending not switching between any kind of biosimilars. That's a little bit concerning. If somebody is already on it, I don't know if we're going to talk about grandfathering at all. That's the only thing I was… that kind of caught my attention from this presentation.

April Phillips: HCAs recommendation is that all products are safe and efficacious and therefore eligible for preferred status at the discretion of HCA. And that all non-preferred products try and fail a… I'm sorry, two preferred products and if you would like to add in "grandfathered" since you discussed it just a moment ago.

Donna Sullivan: I would like to… if you are going to do grandfathering, what does that mean? I don't know how frequently patients might be getting these medications if they get a medication let's say in January and then they don't need another one until March. Is that okay to change medications or would that… would you consider that, that that patient should be grandfathered? So that's just my question to you as clinicians of how you would expect it to be seen. Usually grandfathering is when patients are on a continuous medication and you wouldn't want to switch them. I'm not sure that these are used in that fashion.

Susan Flatebo: What is the preferred product? I mean it says they are non-preferred products. Which one is preferred?

Donna Sullivan: At this point in time we don't have a preferred product. So we'll be selecting one after we do the financial analysis with Magellan.

Susan Flatebo: I think when the speaker was talking about interchanging one product to another I'm assuming that's with each cycle of chemo. So if they're getting five days of a colony stimulating factor, whether it be Granix or the new Zarxio or the Neupogen that the… those five days it would remain the same. Maybe the next cycle would be different. I'm not clear either on what she meant by that, but that's what I would assume was if they…

Stephanie Christofferson: Yes. It would be like that current therapy.

Susan Flatebo: Within each cycle, I'm assuming. Is that what you said?

Stephanie Christofferson: Yes, ma'am.

Susan Flatebo: Okay. Thanks.

Michael Johnson: Having said that I think it would be easy to vision, you know, if you're on one cycle you wouldn't switch during that cycle, but if a new product became preferred I wouldn't see a problem for that next cycle using a preferred agent.

Susan Flatebo: I agree with that.

Michael Johnson: Okay. Any other discussion? So I move that the Apple Health Medicaid Program implement the limitations for the colony stimulating factor drug class listed on slide 2 as recommended.

Donna Sullivan: That would be slide 12.

Michael Johnson: Is it 12? Okay. That would be with the caveat of not switching in the middle of a cycle, which is kind of standard.

Susan Flatebo: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Amber Figueroa: Do we want to put verbiage in there based on… during that cycle?

Donna Sullivan: Leta, you can just put that patients shall not…

Michael Johnson: The product is not changed within a cycle. Is that how you say it? Or during a treatment cycle.

Diane Schwilke: I can't really see that issue. I can't see that becoming an issue unless they are in the middle of a cycle on New Year's. You know? It was cleared up for me. I'm not concerned there anymore.

Michael Johnson: Okay. All right. That brings us to erythropoiesis stimulating factors. We're ready for you, Stephanie.

Stephanie Christofferson: Okay. So with this drug class disease states such as chronic kidney disease, cancer, diabetes and heart disease and other disease states can cause anemia and actually, you know, chemotherapy drugs themselves can cause anemia as well. So erythropoietin is a glycoprotein produced in the kidneys that stimulates red blood cells and from production in the bone marrow and recombinant human epoetin alfa is a glycoprotein manufactured by recombinant DNA technology and has the same biological effects as endogenous erythropoietin. Epogen and Procrit are identical recombinant products that contain identical amino acid sequences and then Aranesp has two additional N-glycosylation sites that actually slow its clearance compared to Epogen and Procrit and then Mircera also has a slower clearance due to additional conjugated PEG polymer on the medication compared to Epogen and Procrit. Next slide.

As you can see in this chart the medications, here with the indications, and a lot of them have of course the same indications and Epogen and Procrit do have the widest variety of FDA approved indications. We've also included in this chart instances where the medication should not be used, which is… sort of the main ones is essentially where anemia should be managed by transfusion or there's immediate need for anemia correction in which case of course you would not want to use these products. Next slide.

The medications are indicated for either subcutaneous or IV infusion and the dosing and frequency of dosing is specific to the disease state and whether or not the patient is on dialysis. IV infusions are usually reserved for patients that are on dialysis and

really subcutaneous route of administration is the method of choice and different clinical studies, cost, safety and lower dosages were seen with the subcutaneous route. So it is the route of choice for administration. Next slide.

On this slide you'll see the different formulations that are listed here. They are both single-dose and multiple dose vials, as well as some pre-filled syringes that the products are available in. The Procrit and Epogen products do contain albumen. That might be something to consider for dosing patients. And then the multiple dose vials do contain a preservative. When you look at the package inserts or prescribing information for these products there are conversion tables to aid prescribers in determining appropriate dosages for the medications for each of their patients. Next slide.

There are several warnings about these medications. The few that we have highlighted here – it is contraindicated in patient's uncontrolled hypertension or patients that have a hypersensitivity to albumin. Mammalian cell-derived products and instances where there's Pure Red Cell Aplasia that begins after treatment with any of these products. The multiple dose vials do contain benzyl alcohol, which of course is contraindicated in [inaudible] symptoms and also pregnant women and nursing women. In these populations it is recommended that the medications be used at the single-dose vials be used. There is also increased risk of mortality, MI, stroke and thromboembolisms, especially in patients who have had previous risk factors for thrombosis. The risk of all dose-dependent for the products. There's increased risk for DVT in patients receiving the products. So they do recommend that patients receive prophylactic anticoagulation in order to decrease that risk. Patients with uncontrolled hypertension and chronic renal disease should not begin therapy with these products. And if therapy is started monitoring is needed and an increased dose of hypertension for products might be needed for patients. There's increased risk of seizures, particularly in the first 90 days of therapy and Pure Red Cell Aplasia and severe anemia with or without other cytopenias have

been reported with the products. As you can see on the list there are several boxed warnings. Some of them we have already kind of touched base on, but these include increased risk of death, MI and stroke and thromboembolisms and tumor progression or reoccurrence. Patients with chronic kidney disease have actually experienced a greater risk of death, serious cardiovascular reactions and strokes when administered these products to target hemoglobin levels of greater than 11 grams per deciliter. However, there have been no trials that have identified target hemoglobin level. A dose of product or dosing strategy that does not increase these risks. So the recommendation is just to use the lowest dose possible in order to prevent any sort of transfusions. In cancer patients another blocked… boxed warning is that they can shorten overall survival and/or increase the risk of tumor progression or reoccurrence. So the same take home message is included with these, which is use the lowest dose possible in order to avoid red blood cell transfusions. And then also the medication they recommend the… be stopped once there is a completion of the chemotherapy course. And then perisurgical patients have an increased risk, like we discussed, of DVTs when they're not receiving prophylactic anticoagulation. So they do recommend that can be considered in this patient population. Next slide.

The medications are categorized as a pregnancy category C and in pediatrics for the Epogen and Procrit there's pharmacokinetic profiles that are similar in adults and children. So the FDA has approved the medications for the treatment of anemia and chronic renal failure patients, peer required dialysis and this was FDA approved in ages 1 month to 16 years and patients ages 5 to 18 years there's an indication for treatment of anemia due to concurrent myelosuppressive chemotherapy. And then data does exist to support the use of Epogen and Procrit in patients 8 months to 17 years old with zidovudine-treated HIV induction patients. Aranesp and [inaudible] for this the safety and efficacy has not been established for initial treatment of chronic kidney disease or in transition from another erythropoietin in chronic kidney disease in patients less than 1 years of age and safety and

efficacy has not been established for chemotherapy-induced anemia for the pediatric population. Next slide.

Again, referring back to the NCCN guidelines for 2017 the guidelines state that the agents are associated with an increased risk of thrombosis, decreased survival and shortened time to tumor. They advise that physicians use the lowest possible dose of the product in order to maintain hemoglobin levels sufficient to avoid blood transfusions and to prescribe according to the FDA guidelines and also to obtain patient consent. And then they also state that there's not enough evidence to support the use of the products for treatment of anemia related to mild suppressive chemotherapy with curative intent. Patients receiving non-myelosuppressive therapy or patients with cancer not receiving therapy. The American Society of Clinical Oncology considers all the products really to be equivalent with respect to effectiveness and safety. So I just wanted to add that in there, as well, even though it's not part of the NCCN guidelines.

With that said I'll go ahead and wrap my portion up.

Michael Johnson: Thank you, Stephanie. Any questions for the committee? Having said that there are no stakeholders for this topic. We'll jump right up into the motion.

April Phillips: Our recommendation is that all products are considered safe and efficacious and are eligible for preferred status at the discretion of HCA and that all non-preferred products try and fail two preferred products prior to…

Susan Flatebo: My only issue is they're safe and efficacious if they are prescribed according to the FDA guidelines, you know, with chronic kidney disease patients. They shouldn't be treating a patient with an ESA agent if their hemoglobin is above 11 or approaching 11 and then with patients with cancer only those that are not considered to be cured with their chemotherapy… I mean I don't know if we need to add verbiage in like that or not. Is that kind of already…?

Donna Sullivan: I mean often times what we've done with the Washington PDL classes is inserted the… they are safe and efficacious according to their FDA labeled indications into the motion. If you would like to do that you could. These drugs we haven't really talked about limitations, but if you want them on prior authorization for their, you know, for us to make sure that they are actually being used on label according to labeling, you know, that's something you could do as well.

Susan Flatebo: The ESA class are rarely used in patients with cancer anymore. So I would think that it would need a prior authorization for that diagnosis if they do have cancer so that they can make sure all the criteria are being met.

Donna Sullivan: It just occurred to me one challenge we might have is often times these are administered in the doctor's office or pursuant to dialysis. So if they are being billed under the medical claims that is a little bit more challenging for prior authorization, but on the outpatient side it definitely is something we could do.

Susan Flatebo: I would think especially for the indication for anemia for patients… chemotherapy-induced anemia indication. That one should have criteria.

Michael Johnson: Any other discussion?

Susan Flatebo: This probably isn't the right arena to talk about what the prior authorization would… or what criteria would need to be in for that or is that another discussion at another…?

Donna Sullivan: What the criteria actually is? Is that what you're asking?

Susan Flatebo: Yeah.

Donna Sullivan: We could bring it back to you. At this point in time I'm thinking it would be just to our… to ensure that it is being used according to label. I'll give a shout out to my colleagues from the health plans.

Do you know if you have these on prior authorization? What are your policies around anemia?

David Johnson: I am actually not sure. I don't ever see these so I don't know that we actually have a PA on these.

Petra Eichelsdoerfer: I would concur with the same thing, but I would add that when we have PA criteria related to this type of agent it almost invariably is ensuring that they are matching up with the FDA guidelines or with national guidelines that are widely accepted.

Michael Johnson: I think most of these are, like Donna said, being used either in infusion centers or offices… oncology offices, etc. So I think it is probably really rare to receive a prescription for one of these.

Donna Sullivan: Right. And so I don't know what the volume is either on the utilization of these particular products. It is possible that it could cause a lot of disruption putting them on prior authorization. We could look into it, maybe pull some utilization and then bring it back as far as… allow us to select preferred products today and then we'll come back with some more specific limitations on this class at a future meeting. Okay. Great.

Michael Johnson: To do that do we have to make a motion now?

Donna Sullivan: Yes. If you could make a motion now that way we can continue our work with setting the preferred drugs. That would be great.

Dale Sanderson: I just have a point of grammar with this. Is it, "I move *that* the Apple Health Medicaid Program implement the limitations"? Or you could say, "I move the Apple Health Medicaid Program to implement the limitations". It's a point of grammar.

Lisa Chew: Going back to slide 22 then do we want to remove the statement about the prior authorization right now or keep that for this motion?

Donna Sullivan: We can remove it.

Lisa Chew: Then we would re-look at the prior authorization criteria based on utilization.

Donna Sullivan: Yes, thank you.

Jordan Storhaug: I move that the Apple Health Medicaid Program implement the limitations for the erythropoiesis stimulating protein drug class listed on slide #22 as recommended.

Amber Figueroa: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. The motion carriers. That will bring us to neuropathic pain. So give us a second.

April Phillips: I wanted to let you guys know that we do plan in the future to bring back and let you know what our preferred products are. So we just don't know them at this time, but it's our intention to let you know.

Michael Johnson: Thank you. I think we're ready for you, Stephanie.

Stephanie Christofferson: Okay. Great. So next we'll jump over into the neuropathic pain portion. So neuropathic pain can of course be caused by a number of different disease states. In this review we primarily concentrated on post-herpetic neuralgia, diabetic peripheral neuropathy, neuropathic pain and fibromyalgia. In addition to these drugs there are a lot of different other treatment options or medication classes that treat these conditions such as PCAs, antidepressants, muscle relaxers, opioids, tramadol, and so on. As you can see from this first slide on indications. There are different generic options available in the class, as well as different convenience kits with gabapentin and menthol which we didn't list here, but those existed well. Next slide.

As far as availability there are both oral and topical options for patients within this category. As you can see in the availability column most formulations are either capsules or tablets, but there are some solution products for perhaps patients that are unable to swallow different products. There are once-daily options which include Cymbalta, Irenka release and then also the topical therapy Lidoderm. But multiple dosing is needed for Neurontin, Horizant, Savella and Lyrica. Next slide.

With the clinical considerations table here safety and effectiveness in the pediatric population has not been established for these products when it comes to the treatment of neuropathic pain. For pregnancy the lidocaine patch is considered a pregnancy Category B and duloxetine and Savella are pregnancy Category C. However, to note that neonates exposed to SNRIs during the third trimesters have developed complications prolonged hospitalization and so that might be something to take into account for pregnant patients. Lyrica is actually… the labeling has been revised recently to comply with the pregnancy and lactation rules, but previously it had been categorized as a pregnancy Category C. Although as classified as a pregnancy Category C we did want to mention that the gabapentin has not been evaluated for [inaudible] during pregnancy. And as you can see in the table there are some hepatic and renal impairment dosing adjustments and contraindications for these products which might, again, need to be kept in line when product selection for patients with those different disease states. Next slide.

We tried to select some of the more pertinent information as far as warnings and major drug interactions, but ones to note are… there have been reports of suicidal behavior associated with the antiepileptic drugs including gabapentin and pregabalin. Patients have been found to be at twice the risk for suicidal behavior or ideation. However, the frequency is very low so that is something to note. And then there is a boxed warning for duloxetine and Savella regarding the risk of suicide. Just like any other

depressants, including SNRIs these agents have increased… have an increased risk compared to placebo of suicidal thinking or behavior in children, young adults and adolescents. However, Savella has not been approved for use in pediatrics and duloxetine is not actually indicated to treat neuropathic pain in pediatric patients. For major drug interactions SNRIs are contraindicated in patients using or who have used within the last two weeks the MAOI products. There is a risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions with SNRIs and there is also an increased risk of bleeding when the SNRIs are used in combination with anticoagulants. Then finally when using lidocaine patches it really should be used… or I'm sorry, avoided in any patients who have a class 1 arrhythmia due to additive toxicity. SNRIs, gabapentin and pregabalin should be tapered over one week whenever possible when discontinuing any of the medications. There has been an increased risk for seizure potential. To note is that Lyrica is a controlled substance. It's a schedule 5 and I'm sure, you know, probably in the news like other states have been hearing, gabapentin is beginning to be a drug of abuse with different medication cocktails. So that might also be something to keep in mind. When prescribers are prescribing the medications, patient history and drug abuse history should be taken into consideration when prescribing these products. As far as professional guidelines – professional guidelines suggest different first and second-line therapy treatments based on the indication of the patient. And really they state that any of these medications could be considered first line options for patients. For postherpetic neuralgia the American Academy of Neurology treatment guidelines advise that TCAs gabapentin, Lyrica, opioids or lidocaine transdermal patches could be used as a first option and then for diabetic peripheral neuropathy the American Diabetes Association in 2016 stated that there is limited clinically-significant evidence to suggest that one product is superior to another when choosing therapy for the individual patients. But for patients with neuro… diabetic neuropathic pain they recommend Lyrica or duloxetine as initial therapy and have also stated that gabapentin can be used in select patients. They did note that TCAs are effective, but should

be used with caution due to their adverse effects and then opioids are not recommended for first or second line due to addiction risks and then also the adverse effect profiles. And then for fibromyalgia the American Pain Society recommends amitriptyline or cyclobenzaprine as the initial pharmacologic options and then if that doesn't work SSRIs, tramadol or opioids are recommended after that. But they note that there's not… there are no studies available to compare the evidence to suggest that one product or one therapy is superior to another. But I did want to note that these guidelines come out prior to any of the products that actually have an approval for this condition coming to market such as duloxetine, Savella and Lyrica. In general, factors that could impact selection of the product are FDA approved indications or comorbidities, adverse effect profiles, drug interaction or contraindications, and then also something to keep in mind, especially with the opioid epidemic is, you know, drug abuse and misuse. Any questions?

Michael Johnson: I see no questions from the committee. We do have one stakeholder. Dr. Dave Gross.

Dave Gross: Good morning. I'm Dave Gross from the medical affairs division of Pfizer. I'm here on behalf of Lyrica. I know this isn't your typical P&T Committee where you look at the clinical efficacy and all the studies and stuff. I applaud Stephanie for pointing out the guideline, but I do want to add one thing that she did not mention. In addition to the ADA in their January issue of Diabetes Care recommending Lyrica as a first line agent for painful diabetic peripheral neuropathy, the 2011 AAN guidelines state "Lyrica is the only therapy recommended as a Level A medication for the treatment of PDPN and Level A indicates strong evidence on a scale of strong, moderate, weak or insufficient." So I just wanted to point that out, one of the guidelines that weren't mentioned were the most recent AAN guidelines for the treatment of PDP.

The last thing I'll say is that Lyrica is one of the drugs that is approved across… has an FDA approval across all of the

indications that were mentioned today. Thank you for your time and consideration.

Michael Johnson: Thank you.

Amber Figueroa: Can you guys discuss or remind me what a trial looks like? Is that two days and had reaction to it or they have to have tried it for 30 days? Or they have to have gotten to the max? Or what does that look like clinically when you're trying to determine if they have failed something?

April Phillips: For us it is usually considered if they try it and have, you know, like an allergic reaction that's instant we don't make them try it again, clearly. But we would like them to try it potentially more than a week before they decide it's not working for them. But usually we take the word of the prescriber if they're like…

Donna Sullivan: I mean it's always a challenge for us when we do this because the other thing is, you know, what does stable mean? If they are stable on it they don't have to change or if they've… a lot of the times if drugs don't take they might take four to six weeks or longer before they really meet their maximum therapeutic value. And so I would ask you to possibly give us some guidance around what you think a trial should be. Again, with colleagues with the health plans, if you have standard trials when you have tried and failed what does that typically look like.

David Johnson: At least for Lyrica, which is by far our most commonly requested one of this, I say you've got to be on 900 mg for 30 days.

Donna Sullivan: Is that 900 mg of gabapentin for 30 days?

David Johnson: I'm sorry, yes. 900 mg of gabapentin for 30 days before you can call it a therapeutic failure.

Diane Schwilke: So my question is, you said you say that. So is that you? And then if somebody else were to be involved in the prior auth they would have different standards?

David Johnson: That's our criteria and I'm the one who reviews these. So, yeah.

Diane Schwilke: For Molina in general that's the Molina criteria?

David Johnson: Correct.

Diane Schwilke: And that's where we see the biggest variation at the pharmacy level dealing with different plans and how they interpret it. And so that creates a lot of administrative burden. At the pharmacy level and for the providers… or for the prescribers trying to figure out which plan requires what and is this going to be eligible for prior auth and all of that. Because even though we're going to have this list, the issue still becomes we have multiple plans carrying out the list and they all sort of have different rules and how they interpret it.

Donna Sullivan: Going forward as we develop any PA criteria they will be all the same. So they will be rolled out across the plans. Initially for January 1st classes it's not going to be quite like that, but once we kind of get the PDL classes approved and preferred products established then we'll go through and start consolidating the clinical policies across all of the plans and you'll see those meetings in the next year we'll be focusing more on the clinical policies as opposed to the preferred drugs. The idea is that if we have PAs for these drug classes that they will be the same and that's why it's… it's helpful for you to give us guidance so that we can, you know, try to make sure that we're reducing as much burden as we possibly can, but still making sure that there's appropriate utilization.

Diane Schwilke: That's great.

Amber Figueroa: Are we… we're going to be looking at that in the future and right now we should keep it generic in the motion?

Donna Sullivan: I believe so, yes.

Michael Johnson: I was going to say that, you know, we should do the motion. But this would bear… once we know what the preferred agents are going to be we should spell out what a trial would look like dosing wise and [inaudible] the therapy.

Donna Sullivan: And we can bring that back to you next year when we start going through the clinical policies. By then we should have the preferred products selected. My expectation is, is all these classes that you have not actually said this drug is going to be preferred and these are non-preferred. We'll bring them back to you kind of as a packed deal and let you see what the final selections are and then give a final approval on that. So you'll definitely be able to see that. Thanks.

Diane Schwilke: Before we move on to the motion can we just move back to the recommendation slide for a second? I would sort of like to see something in there about having preferred oral and topical. Because there are both options and there's not great coverage for topical at this moment. For some patients that really is a better option. What does the committee think?

April Phillips: Since this meeting is recorded I will say the recommendations that we have it. Our recommendation is that all products are considered safe and efficacious and are eligible for preferred status at the discretion of HCA and that all non-preferred products need a trial of two preferred products.

Donna Sullivan: If topical, I'm assuming you mean like the diclofenac gels or the lidocaine patches? As long as they are being used on label I think that's the biggest concern with those is that there is not a lot of evidence around their efficacy other than their labeled indications, which can be specific to certain body areas… areas on the body.

Amber Figueroa: So Diane, what would you propose that looks like?

Diane Schwilke: I don't know if we would put it in the recommendation then. Is that kind of where we are at? Where we would say and must include both oral and topical options?

Donna Sullivan: Yes. So if you want to ensure that there is a topical product that is preferred you would have to call it out and say that there is a topical product preferred.

Diane Schwilke: That's kind of my goal.

Donna Sullivan: I guess the question too then is, do you go straight to a topical or is it appropriate to have them try, you know, an oral product first that might be less costly before they actually get qualified for a topical?

Amber Figueroa: So just coming from a clinical perspective I've spent lots of time with patients trying to create a Lidoderm patch with Tegaderm and some lidocaine gel. That's a big time waster for me. It may be, you know, I recognize that it is an expensive medication, but we're trying to go around it to get it for the patient as best we can. I don't know, just kind of a tid bit.

Diane Schwilke: Just with this class that we're talking about there's a lot of different contraindications. There are a lot of things to consider when choosing a product and sometimes topical is just the way to go and I know you're putting more trust in the hands of your prescribers in being thorough and choosing the right product for the right person and not just choosing a topical because they want to, but I just think it is important to have that as an option. I see the creativity in prescribing at the pharmacy level and trying to get there. And if they really want it they are going to figure out how to do it. But if we just make it an option… I don't know, I come from 340B world. Maybe I don't have a good feel for the actual cost of those items, but they aren't that expensive for us. But I truly don't have real-world perspective on that.

Donna Sullivan: We can share that with you.

Diane Schwilke: Even at that though they aren't widely prescribed anyway. There are certain patients that they are really the right product for and I feel like they should be available for those patients.

Michael Johnson: I think that… I like the modification for oral and topical, but I think this is also a topic that next year we should bring back to the DUR to look at the criteria for when to go to that and what somebody would need to do to get to that point.

Diane Schwilke: I would be okay if it is really cost prohibitive, truly, to require a prior auth, I suppose like it is now for a topical product, but I'd prefer it like it is.

Lisa Chew: I see actually both sides of it. The cost, but I think in our current climate are we really trying to diminish the prescribing of opiates. I think having a topical product as an option is a good thing.

Amber Figueroa: Exactly. I also think with the current climate of minimizing polypharmacy that the fewer systemic drugs that we can have, the better. So I also think that is a step in the right direction to offer a topical product.

I move the Apple Health Medicaid Program implement the limitations for the neuropathic pain drug class listed on slide #29 as recommended.

Diane Schwilke: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

Dale Sanderson: Just a point of grammar on all these motions going forward, that.

Michael Johnson: All right. The motion carries. So give us a moment, Stephanie. We just need to get your slide up. All right. You can go ahead and start.

Stephanie Christofferson: The next class we'll be discussing are the ophthalmics, anti-inflammatory/immunomodulator. Really there's only two different medications that we'll discuss here in this class, which is the cyclosporine or Restasis products and lifitegrast or Xiidra product. So keratoconjunctivitis sicca is defined as a dry eye syndrome related to either a decrease in tear volume or a rapid evaporation loss the tears, which lead to poor tear quality. It impacts anywhere from 10 to 30% of the U.S. population and usually occurs in patients that are over the age of 40 and also more prevalent in post-menopausal women. Many times it is idiopathic in nature, but it can be secondary to damage to malfunctioning [inaudible] glands or other autoimmune conditions. In general, treatments really just aimed at preventing cranial ulcers or scaring. The OTC rewettening agents are often used for symptomatic treatments. However, prescription cyclosporine and Xiidra are prescription products that provide treatment aimed at the cause of the dry eye symptoms rather than just symptomatic treatment. As you can see in the indication section both are listed above to help decrease dry eyes. Both medications are taken twice daily and are available in emulsion formulas. The onset of action is kind of delayed with the medication. For Restasis it can take anywhere from 4 to 6 weeks before benefit can be seen and Xiidra can take up to 12 weeks to work. Some of the more common side effects have been listed here and the medications can be used in young adults and older. The cyclosporine product is categorized as a pregnancy Category C where Xiidra, in the package insert, there's no data available… no data has been published. Next slide.

No new guidelines have been published since 2016. But in 2016 the American Academy of Ophthalmology stated that specific treatment recommendations depend on the severity and source of the dry eye. They do recommend artificial tear substitutes for mild conditions and they do recommend that preservative-free

formulations be used. Anti-inflammatory agents including the cyclosporine topical corticosteroids or systemic omega-3 fatty acid supplements are recommended along with the rewettening drops or other non-pharmacological methods such as warm compresses, increased blinking, increasing the humidity levels in the environment. They recommend those treatment options for patients with moderate dry eyes. And then for severe dry eye, in addition to the things that we just mentioned, that's when they start recommending systemic therapy with like cholinergic, anti-inflammatories, [inaudible] agents, and then some other procedural type interventions such as permanent punctual occlusion, and [inaudible], again, procedures that are done at ophthalmologists or at the doctor's office. With that said I'll go ahead and end my discussion on these agents and open it up to any questions.

Michael Johnson: Thank you, Stephanie. I see no questions. I think with you we'll see you back at 10:40 if you want to take a short break.

Stephanie Christofferson: I'll see you in a few minutes. Thank you.

Michael Johnson: There are no stakeholders so we'll look at the motion.

April Phillips: Our recommendation is that all ophthalmic anti-inflammatory/ immunomodulatory products are considered safe and efficacious and are eligible for the preferred status at the discretion of HCA. And that all non-preferred products require a trial of two preferred products… I say two preferred but there's actually only two. So at least one preferred product prior to approval of a non-preferred.

Amber Figueroa: I move that the Apple Health Medicaid Program implement the limitations for the ophthalmic anti-inflammatory/ immunomodulator drug class listed on slide #34 as recommended.

Catherine Brown: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

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

We're going to get started again. We have your first slide up whenever you're ready.

Stephanie Christofferson: Okay. So the next class I'll talk about are the ophthalmic antibiotics. Just so the committee is aware I've been asked for the remaining therapeutic classes that will be reviewed is a very short two- to three-minute overview of the medications. I think primarily because, you know, they are older classes and probably everyone is pretty familiar with the medications. Just in case you're wondering why they are really short compared to the other ones.

So for the ophthalmic antibiotic indications as you can see in the first two slides there are many generic products available for the medications in this class. There are actually a wide variety of different medications and different subcategories of the medications, including the aminoglycosides, fluoroquinolones, macrolides and then what we've kind of grouped as the other group. Most of the medications have the same FDA approved indication for the treatment of bacterial conjunctivitis and almost all of the medications are indicated in very young children and then of course all the way through to adulthood. Skip to the next slide.

Again, this rounds out the rest of the medications in the class including the macrolides and what we consider the other medications in the class. Next slide, please.

The most burdensome thing about these medications is the frequency in which the patient has to administer the medication. For instance, some of these medications have to be administered every two hours. I can imagine compliance is probably difficult in

a certain… with the various medications. The medications that require the least administration is ofloxacin which is approved for twice daily administration. And then azithromycin is approved one drop into the affected eye twice daily 8 to 12 hours apart for the first two days and then after that is one drop daily for five days. Three times daily includes gentamicin ointment, Besivance, Ciloxan ointment, which is three times a day and then it decreases two twice a day. After that the medications go up from there. The medications are available in a variety of different formulations, including solutions and ointments and suspensions. So product selection, again, there's a lot of things for patients to choose from. Next slide.

That just rounds out, again, the dosage and formulation of the products. Next slide.

Again, the rest of the dosing and administration directions. Next slide.

These are the guideline updates. There are really no new guideline updates for this class of medication. A meta-analyses found that antibiotics are associated with beneficial effects early in therapy days 2 through 5 and then after that the benefit drops off, but it is still persistent. In [inaudible] studies the fluoroquinolones, such as gatifloxacin, moxifloxacin appear to have better coverage for grant positive products and there is resistant organisms to the levofloxacin and ciprofloxacin and ofloxacin. Then the Besivance is a relatively new ophthalmic fluoroquinolone indicated for the treatment of bacterial conjunctivitis and is reported to be non-inferior to moxifloxacin in clinical studies. The guidelines did note that clinical data was azithromycin and gatifloxacin are limited at this time. Any questions?

Michael Johnson: I see no questions. I think we're going to keep going.

Stephanie Christofferson: The next one we have is the ophthalmic antibiotic steroid combinations. This first slide that we have here, all the products

are indicated for corticosteroid responsive inflammatory ocular conditions in which a corticosteroid is indicated and whether it is a bacterial infection or risk of bacterial infection exists. Again, like we just discussed with the previous class, all the medications require frequent dosing schedules and there's a wide variety of products available—solutions, suspension ointments, and again there are a lot of generics available in the class. Next slide.

This just looks at the, again, the rest of these medications discusses the availability and generic availability. Next slide.

There are no new guidelines and information states that there are not enough published comparative trials to distinguish if any of these products are actually superior to one another. So selection really comes down to the individual patient cost and patient preference for the condition in which they are being treated. Any questions?

Michael Johnson: I see no questions. We'll go ahead and continue.

Stephanie Christofferson: Okay. The next one we have is the ophthalmics for allergic conjunctivitis. The first slide reviews the indications. As you can see nearly all the medications have the same indications. Again, there's a lot of generic products available within this class and the age range goes down to the very young pediatric patient population with Pazeo having the youngest… indicated at two months and older. Next slide.

Azelastine, Bepreve, Elestat, Zaditor, Alocril and Patanol require two or three times daily administration versus other products within this list that require four times per day dosing. Lastacraft, Pataday and Pazeo are actually administered once daily. All the products you see here are available in a solution formulation. Next slide.

There are no new guidelines. The 2016 American Academy of Ophthalmology recommend over-the-counter antihistamine benzo constrictors or the use of a more selective second

generation topical histamine receptor agonist for the treatment of mild allergic conjunctivitis. They do not recommend any certain product over another. For persistent or frequent symptoms the guidelines suggest that a mast cell stabilizer be used. They do also recommend that shorter courses of therapy between one to two weeks of ophthalmic corticosteroid at the lowest potency and frequency based on response and tolerance be used for the disease state. Numerous comparative trials have been looked at or studied for this condition. However, based on the outcomes it was difficult to declare one drug being superior to another. So, again, patient preference and costs are probably some main concerns or selection of the products for this class. Any questions?

Michael Johnson: I see no questions. We'll go ahead and continue.

Stephanie Christofferson: Okay. The next one we have is the ophthalmic anti-inflammatories. The first slide here… actually, I'll talk about the first three slides. For the indications I'll just talk to as a whole. There are three classes in this review including the corticosteroids. The corticosteroid intravitreal medications and the NSAIDs. The corticosteroid and NSAIDs are of course self-administered and have similar indications for the treatment of inflammatory conditions of the eye or pain associated with it and there are several generic options available in the class. I did want to mention that BromSite, which is on the third slide of indications, is a newer product in the class. It is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. It does contain a preservative and the most common side effects are headache, floaters in the eye, eye pain and ocular hypertension. And the safety in pediatrics has not been established.

On the second slide of indications this starts the corticosteroids that are actually injected into the eye. The indications for this are a little bit different than the other medications that we discussed during this class and that they include indications for macular edema, and some other more serious eye conditions compared to

just your, you know, regular inflammatory diseases. But Ozurdex is actually injected in the eye and it lasts up to six months wherein it fully dissolves. Cataracts can develop with the medication though. Then you have Iluvien which is a single implant that delivers steroids into the eye for up to 36 months, and again it fully dissolves in the eye, as well. Then we have Retisert that can deliver up to 30 months of continuous treatment and then the last one is Triesence, which is a suspension that's injected into the eye and doesn't last as long as the other ones. Again, the major side effects of many of these drugs is that they have a high prevalence of causing cataracts in patients. Again, these medications are for, you know, eye conditions in which there is a more severe disease state. Next slide.

That just rounds out the NSAIDs and their indications. Next slide.

This talks about the dosage and formulations. Again, like many of the eye drops, administration burden. It can be high with having to place eye drops in the eye up to every four hours, if not more. Some of the medications that are indicated for postop have less administration though. Again, the newer products, BromSite is applied one drop into the affected eye twice daily starting one day prior to surgery and then continue the day of surgery through two weeks post surgery. Next slide.

This just finishes off the dosage and formulation of the products and then the next slide does as well.

And the last slide for this section there are no new guidelines to report. However, the American Academy of Ophthalmology did report that postoperative topical regimens following cataract surgery they vary among practitioners and there's no controlled studies that establish optimal regimens for the various products, including the topical corticosteroids and NSAIDs following cataract surgery. But in general ophthalmic corticosteroids have been used for a very long time for first line therapy for these conditions, but they also note that ophthalmic NSAIDs offer equivalent anti-inflammatory effects post surgery. There's no

data to suggest any advantage over one product or another. Any questions?

Michael Johnson: I see no questions from the committee and I think we'll just continue on.

Stephanie Christofferson: Okay. The next one we have are the glaucoma agents. There are six different classes in this review for the topical treatment of glaucoma for the reduction of intraocular pressure. This includes the miotics, sympathomimetics, beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs and then there are combination products. The reduction of intraocular pressure is achieved by either decreasing the rate of production of [inaudible] tumor or increasing the outflow of the aqueous humor. As you can see from the chart, I mean nearly all the medications have the same indication and there really are a lot of different generic products available for physicians to choose from. Next slide.

This just finishes off the rest of the medications in this class. Next slide, please.

Same thing. Administration, again, frequency of which you have to do it is high up to four times daily depending on the product that's selected. Prostaglandin analogs do require the least number of administration times with once daily dosing, which may help increase compliance in a class that is known to have some compliance issues already. Next slide.

This just finishes off the rest of dosing information for these products. Next slide.

Again, there are no new guidelines to update. But again, referring back to the American Academy of Ophthalmology they do state that prostaglandin analogs and beta-blockers are the most frequently used initial treatment for open angle glaucoma. The 2015 guidelines state that the prostaglandin analogs are the most effective drugs at lowering intraocular pressure and can be

considered the initial medication therapy of choice. The beta-blockers, carbonic anhydrase inhibitors and prostaglandin analogs really are the main stays of therapy with beta-blocks and the carbonic anhydrase inhibitors decreasing pressure in a range from 15 to 25% with the prostaglandin analogs decreasing the pressure the most by up to 33%. With that said I'll go ahead and close out this section unless there's any questions.

Michael Johnson: Thank you, Stephanie. There are no stakeholders for this topic. Give us a moment, Stephanie. Shall we just keep going? Okay. So we'll just go ahead and keep going at this time.

Stephanie Christofferson: Okay. Sounds good. Now we'll transition into otic antibiotics. The first slide reviews the indications. The medications on this slide are of course for topical otic antibiotics, which are used for otitis externa and otitis media. As you can see most of them have the same indication for the treatment of acute otitis externa and Coly-mycin S and Cortisporin also have indication for the treatment of infections with mastoidectomy and fenestration cavities in adults and also pediatrics. The Ciprodex, Otovel and ofloxacin are indicated in ages that go all the way down to six months. As you can see there's some generic options available in this category, as well. Next slide.

The next slide looks at the dosage and formulations of the product. The neomycin products do require more frequent dosing than other medications in this review, but most of the fluocinolones, as you'll note in here, are indicated for twice daily dosing. But ofloxacin when it's used for otitis externa can be used once daily. The duration of therapy ranges anywhere from one week to two weeks and of course you can see the ages in which those dosages are appropriate, as well. Next slide.

Again, there are no new guidelines that have been recently published. However, the standard of treatment for otitis media has been the use of systemic antibiotics while the topical therapy has generally been used for otitis externa. The American Academy of Otolaryngology Head and Neck Surgery Foundation,

the 2014 guidelines for the management of acute otitis external in patients over the two years of age recommend topical preparations for initial therapies when it's uncomplicated. They don't recommend systemic antibiotics unless there is an extension of infection outside of the ear canal or there is other factors that would be present… that would require a need for systemic. Topical aminoglycosides combined with a second antibiotic and a topical steroid is commonly prescribed for otitis externa. However, caution should be used when prescribing the neomycin products and otic toxicity from aminoglycosides are a concern. In general, again, the fluocinolones are not associated with any otic toxicity so in cases where the… there's a concern for [inaudible] membrane perforation they actually recommend the fluocinolone products. Any questions with that?

Michael Johnson: I see no questions from the committee. We'll go ahead and continue.

Stephanie Christofferson: Okay. The next one we have is the otic anti-infectives and anesthetics. Not too many medications in this class. As we discussed the standard treatments for the otitis media is the use of systemic antibiotic. These medications are reserved for otitis externa. The American Academy of Otolaryngology recommendations apply here with the use of topical preparations for initial therapy when it is uncomplicated. Again, systemic therapy should not be used unless there's reasons for systemic therapy. As previously discussed the management should include an assessment of pain and whether or not analgesic therapy should be prescribed based on pain severity. Effective topical treatments include otic antibiotics, otic steroids and low pH anesthetics such as the aluminum acetate or the acetic acid. The choice of therapy should be based on efficacy. The low incidence of adverse events, patient preferences and the likelihood of adherence to therapy. The medications listed here include the low pH anesthetics, which again is the acetic acid in aluminum acetate and hydrocortisone, which is of course the topical corticosteroid. Again, administration is high. It's generally recommended that the drops be given for three days beyond the

[inaudible] of therapy just to ensure that the infection is taken care of and up to 14 days may be required. All products in this review are also contraindicated in patients with a perforated tympanic membrane. Any questions?

Michael Johnson: I see no questions from the committee. Actually, we do have a question.

Amber Figueroa: I haven't seen these used. Can you clarify when you… when clinically these would be used as opposed to an antibiotic?

Stephanie Christofferson: I agree with you. I don't think… I can't even remember the last time they were prescribed. I think it's when they feel like the anesthetic is needed to help with pain in the ear. Otherwise, I don't see them used very often.

Amber Figueroa: Okay. Thank you.

David Johnson: I'll comment on that as far as because the antipyrine products have all been removed from the market… there essentially isn't much of anything so if they do think they want some [inaudible] or that kind of thing, this is pretty much all that's left. Before, everybody used to just throw a [inaudible] at everybody. That's not an option anymore.

Michael Johnson: There are no stakeholders for the otic products. With that we'll go ahead and start the antihistamines.

Stephanie Christofferson: Okay. The first slide reviews the indications. Actually, the first two slides. The indications include seasonal allergic rhinitis, perennial allergic rhinitis and urticarial. The intranasal corticosteroids and oral antihistamines are the primary treatment for patients with allergic rhinitis. The oral antihistamines are particularly effective in severe rhinorrhea, sneezing, itchiness and conjunctivitis associated with allergic rhinitis. Although they are less effective for nasal congestion symptoms. The second generation antihistamines are the minimally-sedating antihistamines and are associated with a lower incidence of side

effects and are generally considered before first generation antihistamines; especially in older adults and school age children. Again, just due to the adverse side effect profile. For patients with more significant nasal congestion, as you're probably aware, there are a variety of different products that are available out there with the pseudoephedrine… nasal decongestant combinations. There are several medications that are available in this class as generic and there are several that are now available as over-the-counter products. The newest over-the-counter product that is out there is the Xyzal Allergy 24. However, it's not approved for use in children less than six years of age. And also it's noted that a doctor should be consulted for use in patients 65 years and older. Next slide.

This just rounds out the rest of the products that are available along with their indications. Next slide, please.

This slide looks at the dosage and formulations of the products. Most of the products are taken once or twice daily and again there are formulations with the pseudoephedrine included. Most medications are indicated in the pediatric community with cetirizine, desloratadine, levocetrizine, going to… down to six months of age and older. There are a wide variety of formulations available including tablets, solutions, chewables, orally-disintegrating tablets and so on. Again, lots of different options available for patients to choose from. Next slide.

This just finishes off the rest of the dosages and formulations of the products. Next slide.

There are no new guidelines that have been published. However, the 2008 guidelines from American Academy of Allergy, Asthma and Immunology states that oral antihistamines are considered to be the most effective treatment for seasonal or perennial allergic rhinitis when used continuously. Due to rapid onset of action antihistamines dosed when needed can be appropriate when it is for episodic allergic rhinitis. They also state that second generation antihistamines are preferred over the first generation

due to the more favorable side effect profile, as well as safer options that can be used in pregnancy. They also state that all agents really are similar in efficacy. Some studies do indicate that cetirizine may be more effective than loratadine at providing symptomatic relief. However, cetirizine can cause significantly more sedation in many patients compared to other products. But current data suggests that the less likelihood of sedation is with the fexofenadine products or Clarinex. And that the fexofenadine products appear to have the fewest CNF effects just because of the absorption into the brain is minimal. Any questions with that?

Michael Johnson: Any questions from the committee? I see no questions from the committee. We'll go ahead and do the H2 receptor blockers.

Stephanie Christofferson: Okay. Histamine2-receptor antagonists. The first table we have are the indications. They have been used for many years to treat peptic ulcer, disease and symptoms of gastroesophageal reflux or GERD. Doses are often increased to two to four times normal when treating more severe cases of GERD and for patients who fail to achieve adequate acid suppression with these products a lot of times then they move on to PPIs or proton pump inhibitors that have even greater acid suppressing capabilities. As you can see here as far as indications, they are indicated for a wide variety of GI conditions including duodenal ulcers, gastric ulcers, GERD, esophagitis and so on. All the medications are available in a generic formulation, again, due to the length of time in which these products have been out. Next slide.

The next two slides actually have the dosage and formulations that are available. I'm not going to read through all of those, but all the products are available in OTC formulation except for Axid, which is still the… is only available by prescription. Of various formulations that are available in [inaudible] solutions, suspensions and tablets and so forth. Again, a lot of different availability for the product. Next slide.

That just rounds out the dosage of formulation.

Then finally, again, there are no new recent guidelines. According to the American Gastroenterological Association H2 antagonists improve health outcomes in patients diagnosed with GERD. The guidelines state that in [inaudible] therapy it is appropriate initial management for uncomplicated heartburn and that these medications are more effective than placebo, but again they are not more effective than the PPIs. Data supporting the prescribing of these agents at high than standard dosages are weak. However, dosing more frequently per day may be beneficial in some patients. Any questions?

Michael Johnson: There are no stakeholders or questions from the committee. With that we'll continue with oral glucocorticoids.

Stephanie Christofferson: Okay. The first slide kind of combines it all into one. We've got indications, dosage and availability. The glucocorticoids mediate a variety of inflammatory and immune responses. Therefore these agents are used for allergenic, dermatologic, gastrointestinal, and a lot of different indications. Specifically though budesonide is only indicated for Crohn's and budesonide ER is indicated for ulcerative colitis and then there is a new product that we can talk about a little bit more that's here. Deflazacort or Emflaza is indicated for Duchenne muscular dystrophy.

The next three slides list a variety of, again, the indications and dosages and availability of the products, but the frequency of administration, again, vary by disease state and it can be dosed up, in some products, up to four times per day. There's a lot of different formulations available as you can see in the last column. And there is generic products available. One I want to mention in particular is the new product out called Emflaza. This does have an indication… it's the only indication for the Duchenne muscular dystrophy. The medication is based on weight and indicated in patients 5 years of age and older. It comes in a tablet which can be crushed and administered or it comes in a solution, which can be taken immediately. Many of you probably already know, but Duchenne muscular dystrophy is a generic disorder which is characterized by progressive muscle degeneration and weakness.

It is primarily in males, but eventually it leads to wheelchair confinement. Safety and efficacy of the product has not been established in patients less than 5 years of age and also the medication does contain benzo alcohol which, of course, you need to be concerned for [inaudible] syndrome and [inaudible] in low birth weight infants.

I'll have you just skip to the last slide of this section. The rest of the slides here just talk about the rest of the products as far as dosages and availability, which we've already kind of touched base on.

So the American Academy of Neurology updated guidelines in 2016 to address Duchenne's disease. Their guidelines state that prednisone should be offered for improving strength and pulmonary function of these patients and prednisone may be offered for improving time to motor function, reducing the need for scoliosis surgery and delaying cardiomyopathy onset by 18 years of age. Emflaza they noted… may be offered for improving strength and time to motor function and delaying age of loss of ambulation by 1.4 to 2.5 years. They also note that it may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset and increasing survival at 5 to 15 years after follow-up. They also state that the Emflaza and prednisone may be equivalent in improving the motor function of patients. However, that prednisone may be associated with greater weight gain in the first years of treatment compared to Emflaza. However, they also note that Emflaza may be associated with a greater risk of cataracts than prednisone. Any questions on this class?

Michael Johnson: Any questions from the committee? I don't see any questions from the committee. We'll continue on with smoking cessation.

Stephanie Christofferson: Okay. Sounds good. The first slide looks at the indications. As you know cigarette smoking causes serious health problems within the United States and of course we don't need to go into that. I think we're all familiar with that. But cessation

medications have demonstrated the efficacy in treating tobacco dependence. There are both OTC and prescription nicotine replacement therapies which are available in various formulations and then we also have the prescription non-nicotine medications such as bupropion or Zyban, which is an antidepressant or Chantix, which is a nicotine receptor agonist. Guidelines do suggest that the combination of medication and behavioral therapy is more effective for cessation than either of those therapies alone. Of course all of these medications are indicated for smoking cession and there are generic options available in the class. Next slide.

In the nicotine replacement therapy you've got gums, buccals, lozenges and transdermal products. The dose of the products depend on the number of cigarettes or the level of nicotine addiction that the patient has and then as the therapy continues the amount of nicotine replacement therapy is tapered off over several weeks until hopefully smoking cessation occurs and the medications can be stopped. I do want to note that the Nicotrol products are available by prescription only. Just like the other nicotine replacement products they are gradually tapered off, as well. Next slide.

This slide here has the non-nicotine replacement therapies. These medications are generally started prior to the quit date and then therapy is typically 7 to 12 weeks for Zyban. For Chantix therapy is typically 12 weeks and then an additional 12 weeks for quitters to increase the long-term abstinence. Also for Chantix, which is kind of a newer approach there's a… what you call like a gradual taper approach where smoking is decreased by 50% the first four weeks and then another 50% the next four weeks following and then the goal is by 12 weeks that the patient has stopped smoking. There are warnings for serious neuropsychiatric events. Actually, there used to be boxed warnings. However, with some new trials that came out they removed the boxed warnings, but the warning just in general is still attached to those medications. These medications have also been removed from the REMS Program, but again in general there's just a warning about the

psychiatric side effects potentially with these products. Next slide.

There are no new guidelines for the products. However, for 2008 there were some guidelines that came out and basically they stated that all seven of the FDA approved medications for treating tobacco use are recommended as first line therapies. They also state that clinicians should consider Chantix 2 mg daily or the combination of a nicotine patch plus another form of a nicotine replacement therapy to be more effective than just a nicotine patch alone. Evidence does exist that combining the nicotine patch long-term with either the nicotine gum or a nicotine nasal spray increases the long-term abstinence of smoking cessation. It also states that combining Chantix with the nicotine replacement agents has actually been associated with a higher rate of adverse events such as nausea and headaches. They admit that there is really no well accepted algorithms to guide optimal selection of therapy along first line medications, but the nicotine replacement combinations especially helpful for highly dependent smokers or those who have a history of severe withdrawal. Any questions with that?

Michael Johnson: Any questions from the committee? I see no questions. We'll go ahead and continue on.

Stephanie Christofferson: The next we have is the anti-Parkinson's agents. The first slide reviews the indications. Despite the advances and treatments over the years there is of course no cure for Parkinson's. Symptomatic therapy can provide benefit for quite some time, but the disease state usually continues and the progression of Parkinson's eventually results in significant disability. Patients may not require treatment in early stages of the disease state; especially if they're not causing any functional impairment. But as the disease progresses therapy becomes more complex and usually there is a need for multiple medications and the use of rescue medications. As you can see in the first two slides there are nine different classes of medications that are used for Parkinson's, which include the anticholinergics, the DOPA

decarboxylase inhibitors, the dopamine precursor, DOPA decarboxylase inhibitor combinations, the MAO-B indicators. All these work a little bit differently and a lot of them are combined with levodopa to help boost levodopa concentrations and effectiveness of our patient or combat some of the issues that patients sometimes have with the levodopa prescription. Next slide.

The medications that we have here are the dopamine agonists, the COMT inhibitors, the dopamine precursor/DOPA decarboxylase inhibitor/COMT inhibitor combination and then we've got some other products which is the gabapentin prodrug and then the amantadine. I won't go into all the mechanisms of actions in all of these just due to the fact I'm sure you guys are all familiar with them and of course this would make the presentation a little long. If you have any questions on them I'll be happy to answer those. Next slide.

The dosing of the medications vary anywhere from once daily up to every three to five hours. The medications are available in a wide variety of formulations. I did want to mention that Duopa, this medication is used in patients with significant on/off phenomenon with the levodopa/carbidopa and it is actually… it's actually an enteral form of formulation. It requires the insertion of a PEG-J device and it is actually infused straight into the GI system over 16 hours, which of course is going to limit its use. But again it is reserved for patients that, you know, they are no longer able to use the more traditional products. Next slide.

This looks at the rest of the dosages and formulations of the products. Next slide.

The only thing I wanted to mention here is that for Horizant this is a medication that is indicated for restless leg syndrome, which dosing for this medication is usually taken shortly before bedtime or around 5:00 during the day, prior to bed. Next slide.

Again, there's no new guidelines for this class. In 2015 the Movement Disorder Society ranked the efficacy of the various treatments, which were based on placebo-controlled trials in patients with Parkinson's. They recommend oral levodopa/ carbidopa, the MAO-B inhibitors and dopamine agonists and they rate them all as efficacious monotherapy in patients with Parkinson's disease, but they did note that bromocriptine and ropinirole ER are considered likely to be efficacious. The anticholinergics, as well as amantadine they rated those as likely efficacious. They stated that there is really insufficient evidence to rate the [inaudible] administer of levodopa/carbidopa at this time. Any questions on that?

Michael Johnson: Any questions from the committee? I see no questions. Go ahead and continue on.

Stephanie Christofferson: Okay. Next we have the sedative hypnotics. The first slide looks at the indications and in this particular review there were five classes that were considered – the benzodiazepines, the Z drugs like Lunesta, Sonata, the Ambien products, the MT1 and MT2 melatonin receptor agonists, the sedative tricyclic antidepressant, which is Silenor and then a product called Belsomra which is a recson receptor antagonist. I did want to mention that Hetlioz, this medication is the only medication indicated for non-24 sleep wake disorder, which is a chronic [inaudible] rhythm disorder which usually happens in patients who suffer from blindness. There are many generic options available in this class. Next slide.

These drugs with the exception of Intermezzo should be administered immediately for bedtime or after the patient has gone to bed and who has had difficulty falling asleep. Intermezzo works a little bit differently and this is a medication that is used for middle-of-the-night awakening when patients have at least four more hours to sleep. Since many of the adverse effects appear to be dose-related with these products it's recommended that therapy start… be started low and then maintain at the lowest effective dose possible, which is especially important in the elderly. They do not guidelines that continuous you should be

avoided and patients should be encouraged to use the medications only when absolutely necessary. Next slide.

The only thing I wanted to mention here is with the Ambien products, which I'm sure everyone is aware of. A few years ago there was an indication change for these products in the fact that they recommended a lower dose in women due to next day drowsiness and side effects which was found to be due to a lower rate of clearance in women compared to men. Also to note is with all these different specialized formulations of zolpidem they really don't offer any significant clinical advantages over the tablets. Next slide.

In 2017 the American Academy of Sleep Medicine updated guidelines. They stated that of course, when possible, non-pharmacological measures should be sued to treat insomnia. If that doesn't work then they recommend the use of pharmacological agents. They still recommend that cognitive behavioral therapy be used, stimulus control and then sleep restriction. Those are all the options to be used prior to pharmacotherapy. They recommend that Sonata, triazolam or Rozerem versus no treatment at all be used for sleep onset insomnia. They recommend that Belsomra and Silenor compared to no treatment at all be used for sleep maintenance insomnia. And finally they recommend Lunesta, Ambien and Triazolam for both sleep onset and sleep maintenance insomnia. They do not recommend the use of trazadone or Gabatrol for sleep onset or sleep maintenance insomnia in adults and likewise they don't recommend over-the-counter medications or different supplements to help induce sleep. The American College of Physicians in 2016 updated their guidelines for the management of chronic insomnia. Similar to the previous guidelines they recommend cognitive behavioral therapy and then if that doesn't work they recommend then pharmacological therapy. They did not specify any one product over another. Their only statement is that they recommend the medications to be used short-term and they do not recommend them being used for extended periods of time. Any questions with that one?

Michael Johnson: I see no questions. We will go ahead and continue.

Stephanie Christofferson: Okay. The next topic we have is the antihyperuricemics, which of course are used for the treatment of gout. There are three stages in the treatment of gout. You've got the acute stage, you've got prophylactic to prevent acute flairs and then lowering… medications to lower excess stores of urate in patients. So after initial gout attack the choice of urate-lowering medications include the uricosuric drugs which is colchicine or probenecid or the xanthine oxidase inhibitors, which is allopurinol or febuxostat. The uloric actually offers an alternative to allopurinol for patients who failed to achieve serum urate levels less than 6 mg/dL after three months or patients who are intolerant to allopurinol. However, it is noted that uloric may have a greater risk of cardiovascular events compared to allopurinol. Zurampic is a uric acid transport inhibitor and it is actually approved as an add-on therapy for patients who have not achieved a target serum acid level with a xanthine oxidase inhibitor. Most patients' dose titration of an oral [inaudible] therapy agent can adequately achieve target uric acid levels, but it has been noted that approximately 3% of patients do not demonstrate… or do not respond to oral urate-lowering medications for various reasons. In those certain instances Krystexxa might provide an effective alternative to conventional therapy and be a treatment option for patients who are refactory to those other medications. In addition to prevention and treatment of gout flares, I did want to mention that Colcrys is also FDA approved for familial Mediterranean fever. Next slide.

There's only a couple things I want to mention here. It is the pegloticase. It should be administered in a healthcare setting intravenously over at least 120 minutes by gravity seed, a syringe type pump or an infusion pump and then also monitoring is important up to one hour after administration due to anaphylactic type of reactions. Also colchicine I just want to mention that [inaudible] post monitoring or prescribing with this medication, since it does interact with a lot of other medications and there is

different dosing things to keep in mind with that. All these medications are available in tablet formulation except of course with Krystexxa and then allopurinol has renal impairment, dosing considerations, and then again colchicine has both renal and hepatic dosing considerations. Next slide.

This just rounds out the rest of the dosage and formulation information on colchicine. Next slide.

And then lastly guideline updates. In 2017 the American College of Physicians released clinical guidelines for the management of acute and recurrent gout. They recommend corticosteroids, NSAIDs or colchicine for the treatment of acute gout as they are effective for the reduction of pain. Corticosteroids should be considered as a first-line therapy since they are generally safer, they are low in cost and have been shown to be as effective as NSAIDs with fewer side effects when you're treating gout. However, the guidelines also stated that there was no evidence that one NSAID is more efficacious than other when treating gout. The guidelines do recommend against starting long-term urate-lowering therapy in most patients. And initial gout… when they have initial gout attack or patients that have infrequent attacks, and their definition of that was less than two attacks per year. With patients that are having two or more attacks per year or… and those with problematic gout the guidelines state that prescribers and patients should consider the benefits and the risk of the medications before starting therapy. Allopurinol and uloric are, according to the guidelines, are equally efficacious at decreasing serum urate levels when dosed appropriately. The evidence shows that therapy reduces the risk for acute gout attacks after one year, but prior to that it does not reduce the risk. They also state that prophylactic low-dose colchicine or NSAID therapy reduces the risk for acute attacks when starting urate lowering therapy and that continuous therapy for greater than eight weeks was more efficacious than shorter durations. And finally the guidelines did not address Krystexxa claiming that the medication would likely… unlikely be prescribed by primary care providers. However, American College of Rheumatology, just

as a side note, only advocates Krystexxa as appropriate pharmacological therapy in patients with severe gout who, for whatever reason, they are refractory or they have intolerance to appropriate dose oral urate-lowering therapy. It's really like a third line agent for… in the treatment algorithm for this disease state. Any questions?

Michael Johnson: I see no questions from the committee. With that we'll continue on to the last topic.

Stephanie Christofferson: Okay. The last one we have are bile salts. The medications are primarily indicated to treat three different disease states – one before gallstones, the next being primary biliary cholangitis, which is a rare chronic autoimmune disease and also peroxisomal disorders and bile acid synthesis disorders due to single enzyme defects. There are generic options available in the ursodiol products and I did want to mention that Cholbam is one of the newer products indicated for the treatment of bio acid synthesis disorders due to the single enzyme defects. It's adjunctive treatment… also adjunctive treatment of the paroxysmal disorders including Zellweger spectrum disorders and the medication however should be initiated and monitored by experienced hepatologists or pediatric gastroenterologists. Another new product that is in this class is Ocaliva, which is for the indication of primary billary cholangitis in combination with ursodeoxycholic acid in adults with an inadequate response to UDCA, which is defined as a trial of at least one year or as a single therapy in patients who are unable to tolerate UDCA. I did want to mention that the cholic acid and Ocaliva is only available through select specialty pharmacies. There is a limited distribution with those products. Let's go to the last slide.

I'll just address some updates. The American Association for the Study of Liver Diseases updated guidelines in 2009. For gallstones basically pharmacological treatment is usually unnecessary and I guess the treatment of choice, if you will, for gallstones of course is gallbladder removal. However, in patients that, for whatever reason, they are at risk and they cannot have the gallbladder

removal there are some pharmacological options available; namely the ursodiol products, which is the drug of choice for dissolving cholesterol gallstones, but they have to be small gallstones in order for that to occur. And then if we moved into the primary biliary cholangitis ursodiol also plays a key role in the treatment and it is actually the drug of choice for this condition. However, the role of Ocaliva was not addressed in these guidelines since it wasn't available. However, up to 50% of these patients they do fail to adequately respond to ursodiol which of course could be detrimental. So the Ocaliva offers an additional option of treatment in patients with this disease state who cannot tolerate or who have had inadequate response to ursodiol. Again, the medication can either be used as monotherapy or in combination with ursodiol. Any questions?

Michael Johnson: I see no questions from the committee. There are no stakeholders for these topics. Thank you, Stephanie. I think this brings us to a motion as a committee so you're free to enjoy the rest of your day.

Stephanie Christofferson: Okay. Thank you so much. Have a great day. Bye, bye.

April Phillips: So the first slide is just a reminder of all the classes that we just went through. Our recommendation is that all products within each class are considered safe and efficacious within that class and are eligible for preferred status at the discretion of HCA and all non-preferred products require a trial of two preferred products with the same indication and different active ingredients before a non-preferred will be authorized unless contraindicated or clinically inappropriate.

Amber Figueroa: Especially looking at the sedative hypnotics, I'm wondering about grandfathering. Or are there going to be limitations, you know, the recommendations in here are not to be using it long-term and I think clinically a lot of people do use them long-term. So are limits going to be set on that?

April Phillips: Previously at HCA we had set a limit of one unit or one tablet per day because there were a lot of people that use them long-term and we were finding that there are certain occasions where they do need to be using them long-term. So that was our previous DUR approval that we had gotten.

Donna Sullivan: And before that we had limited them to 10 units in a 30-day supply, but we have removed that. Most of them were getting approved when they were wanting more than that. So that was why we just went to a daily dose limit and not trying to stop the chronic use or the… it was a lot of… more burden on the providers just to get an approval.

Amber Figueroa: And so for someone who has been on a medication for a year or two years and it is working for them, but it's not preferred, is there a way to grandfather them in but just for that class with this motion? I don't know that that would apply to any of the other ones. Maybe antihistamines.

Donna Sullivan: What you could do is you could… if you thought any of the drug classes that were needing to be grandfathered you could just name them, which ones you would want grandfathered.

Susan Flatebo: I think the anti-Parkinson's agents should be grandfathered.

Catherine Brown: I think the antihistamines ought to be grandfathered.

Michael Johnson: Looking at some of the other classes there are more limited products or the indications are different so I wouldn't think we would need to grandfather any of the other classes. Any other thoughts or discussion? No?

Diane Schwilke: I move that the Apple Health Medicaid Program implement the limitations listed on slide #115 for each drug class listed on slide #114 as recommended.

Lisa Chew: I second.

Michael Johnson: All in favor say aye.

Group: Aye.

Michael Johnson: All opposed same sign. All right. Thank you. Any other discussion or announcements? All right. I think with that the… this meeting is adjourned. Thank you.