

Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
P&T Meeting Notes
April 17, 2019

Lisa Chew: Good morning. This is Lisa Chew. Welcome. We're going to convene the Washington State Drug Utilization Review Board. I want to remind everybody that this is a recorded meeting. So, please speak into the microphone and state your name before making your comments. So, let's start off with introductions, please. We'll start at this end of the table.

Catherine Vu: I'm Catherine Vu, clinical pharmacist at Community Health Plan of Washington.

Petra Eichelsdoerfer: Petra Eichelsdoerfer for United Healthcare.

Thai Dang: Thai Dang, pharmacy student at Molina.

Dave Johnson: Dave Johnson, Molina.

Catherine Brown: Catherine Brown, committee member.

Susan Flatebo: Susan Flatebo, committee member.

Diane Schwilke: Diane Schwilke, committee member.

Lisa Chew: Lisa Chew, committee member.

Amber Figueroa: Amber Figueroa, committee member.

Constance Huynh: Constance Huynh, committee member.

Virginia Buccola: Virginia Buccola, committee member.

Nancy Lee: Nancy Lee, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Umang Patel: Umang Patel, Magellan.

Ryan Pistoressi: Ryan Pistoressi, Health Care Authority.

Emily Transue: Emily Transue, Health Care Authority.

Amy Irwin: Amy Irwin, Health Care Authority.

Jose Zarate: Jose Zarate, Health Care Authority.

Lisa Chew: Thank you. So, there are no announcements. So, we can go ahead and move onto our first, uh, drug, Onpattro.

Umang Patel: Okay. Just a little bit of a recap. Normally, how we... how the presentation will go, there will be an overview of disease state, indications, dosage, and formulations, and guideline updates. For some of these medications that we will be going over, there are not set total class reviews, because some of them are very niche specific disease states. So, there are new drug updates or NDU's posted in the link in front of you, as well. And so, if you notice that some of these are kind of a different format than historically done, that's essentially why.

So, for the first medication, Onpattro, on the next slide here, so this medication is for hereditary ATTR amyloidosis. Moving forward, it will be abbreviated as hATTR. So, the polyneuropathy of hATTR amyloidosis, previously referred to as transthyretin familial amyloid polyneuropathy, is a rare, progressive, and fatal disease. About 50,000 people worldwide have this. It is an inherited disease passed down through families that often affects the liver, nerves, heart, and kidneys, an inherited... excuse me, it is characterized by the deposit of abnormal proteins called amyloid in multiple organs of the body where it should not be causing disruption of the organ tissue structure and function. The deposit, most often, occurs in tissues of the nervous system, heart, and digestive tract. And the first symptoms of hATTR amyloidosis typically appear between the mid-20's to mid-60's, involving multiple tissues and organs and may often

seem unrelatable. For example, ocular symptoms can be visual changes. Nephropathy can be the damages to the kidney. Spinal stenosis can be caused by pain, tingling, or numbness along the spine caused by pressure of the nerves in the spine due to narrowing of the spinal cavity, due to amyloid deposits. Bilateral carpal tunnel syndrome, which is numbness and tingling in the hands and arms caused by a pinched nerve in the wrist. While there are other approved disease modifying agents in Europe and Japan, none are available in the U.S. Prior to the approval of Onpattro and Tegsedi treatment options for hATTR amyloidosis were limited and included mainly symptomatic management. And for immediate resolution of neuropathic pain, analgesics, such as diflunisal were recommended. Now, this overview is for both Onpattro, the first medication we'll be discussing and Tegsedi, which is after this one, as well. Moving forward, here you'll see the indication. So, in August, about August of 2018, FDA approved the first, it was an RNA interference therapeutic agent to treat the indication of polyneuropathy caused by hATTR amyloidosis in adults. Liver surgery may be considered in select cases.

And as you can see, the dosing is very... is weight dependent. For patients weighing less than 100 kilograms, the dose is .03 mg/kg once every three weeks. And if they are 100 or more kilograms, it is 30 mg once every three weeks. A healthcare professional should administer the IV infusion of Onpattro. If it is administered three or... less than three days of the missed dose, the original schedule should be continued, but if it has been longer, you should begin... restart the treatment regimen at that time. In terms of premedication, it is recommended at least 60 minutes prior to the start of the infusion to reduce the risk of infusion rate reaction, abbreviated as IRR. The premedications that should be administered include IV corticosteroid, oral acetaminophen, an IV H1 blocker, IV H2 blocker. And if certain premedications are not available, or if the patient cannot tolerate them intravenously, medications that are equivalent may be given orally. And if patients are tolerating the infusions but are experiencing adverse reactions to the corticosteroid premedication, it can be reduced to a minimum dose of 5 mg IV dexamethasone. Additional or higher doses of premedications may be required in patients to reduce their risk.

Just to give you kind of a clinical... take a step back, in terms of the mechanism of action for this, it is a double stranded RNA, si-RNA, which is an RNA interference therapeutic agent that causes the degradation of the mutation and [inaudible] type TTR, mRNA through RNA interference. This causes a reduction in serum TTR protein and protein deposits in the tissue. And if it wasn't clear already, please note that this medication is given IV.

On the next slide here, just some additional information in terms of pediatrics. The safety and efficacy of Onpattro has not been established in pediatric patients. And there is not currently data for patients who are pregnant. Key warnings and contraindications, infusion site reactions have occurred in patients. Again, alluding to the premedications that need to be given, such as corticosteroids, acetaminophen, and antihistamines that we just reviewed. This does occur. Occurrence of IRRs lead to an infusion interruption in about 5% of patients, and further led to permanent discontinuation in about less than 1% of patients. Most common symptoms are flushing, back pain, nausea, abdominal pain, dyspnea, and headache. This can also lead to a decrease in serum Vitamin A levels. It is advised for patients receiving Onpattro to take daily Vitamin A supplements at the recommended allowance. The doses of Vitamin A higher than the recommended allowance should not be given in order to achieve a normal serum Vitamin A level, as serum Vitamin A level does not accurately depict the body's total Vitamin A. If ocular symptoms occur, that suggests Vitamin A deficiency, such as night blindness. The patient should be referred to an ophthalmologist. And the most commonly observed adverse reaction in clinical trials were upper respiratory tract infections and infusion-related reactions. Moving onto hepatic and renal impairment, there is no dose adjustment that is necessary. And in geriatric patients, defined as greater than or equal to 65 years of age or older, there is no required dose adjustment. In the placebo-controlled study, a total of 62 patients that were greater than or equal to 65 years old, including seven patients that were over 75 years of age, received Onpattro, and there was no overall difference in safety and efficacy, but some older patients did have greater sensitivity. Again, this wasn't statistically significant, just noteworthy.

On the last page, so place in therapy. So, the major study for this is the Apollo Study. It was a multi-centered, international, randomized, double-blind, placebo-controlled, phase-3 trial for patients with polyneuropathy caused by hATTR amyloidosis. Patients were randomly assigned in a 2:1 ratio to receive IV Onpattro or a placebo every three weeks for 18 months. The patients ranged from 18 to 85 years of age and received premedications an hour before the infusion to reduce their risk of IRR. The primary endpoint was the change from baseline in the modified neuropathy impairment score, which is abbreviated as mNIS+7, which ranges from 0 to 304 with a higher score meaning more impairment at 18 months. Secondary endpoints included quality of life, motor strength, disability, gait speed, nutritional status, and patient reported autonomic symptoms. At baseline, nine months, and 18 months, all the efficacy endpoints were assessed. So, the results show that the mNIS+7 at baseline was 80.9 in Onpattro, and 74.6 in placebo. At 18 months, essentially, the mNIS+7 was -6 in Onpattro and 28 in the placebo with a statistically significant P-value of less than 0.001. So, a positive effect of Onpattro on mNIS+7 was observed as early as nine months. And secondary endpoints including quality of life, gait speed, etc., showed a statistical significance favoring the Onpattro treatment. A total of 40 patients discontinued the trial, of which 29 discontinued the placebo, and 11 discontinued the treatment arm. And it is important to note that a phase-3 multicenter open label extension study that evaluates the long-term safety and efficacy of this medication is currently enrolling and in process. And the estimated completion date is July of 2019.

Any questions?

Ryan Pistorosi:

Good morning. I'll be presenting the Onpattro Apple Health policy. On the next slide, we have the indication and products for this section. So, for this one, there is only one product, and only one indication. Then, as Umang previously mentioned, the hereditary amyloidosis was previously known as transthyretin familial amyloid polyneuropathy. Next slide.

So, we'll kind of see that terminology throughout, but for this one, the criteria does list either the diagnosis of either the hereditary amyloidosis or the familial, so either the newer or the older diagnosis, but it must be documented with an amyloid disposition on tissue biopsy, and the

identification of pathologic transthyretin variant using molecular genetic testing. So, this is really to confirm that this specific condition is the genetic one that this medication is indicated for, and by having this variant test, we are able to confirm it.

The next criteria is documentation of baseline disease severity using either the NIS or a different scale than what was used in clinical trials of polyneuropathy disability scale. And I believe that was used in the Tegsedi policy that will be rev..., or the Tegsedi trials that we'll be reviewing next. The reason for this is that these were the primary endpoints of the clinical trial. So, these are the scales in which the disease efficacy was measured against, and to which we have information and knowledge that this does improve this measure of an outcome. Patisiran is prescribed in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis. So, being prescribed by or in consultation with so that does help with some of the patients in rural Eastern Washington where they may not have access to these, but if there is at least a consultation, and that there is some expert oversight in the use of this medication for this very rare disease that it is able to have that kind of consultation to make sure that it is being managed properly.

So, the patient is not currently taking these listed products. The reason is that these are some of the other treatment options available to treat the hereditary amyloidosis. A few of these products you may not recognize their names, and that's, like, Umang said, they're not available in the U.S. They are available in Europe or in Japan, but because these medications have not been studied together it's not sure if they have a synergistic effect or potentially a detrimental effect. So, part of our policy that we're proposing today is to make sure that it is monotherapy, like it was studied in those clinical trials. The next criteria is that the patient has had no history of liver transplant, or the patient has a planned liver transplant in the future, as previously mentioned, there are very limited treatment options in the U.S. And a lot of patients had to go to liver transplant, but because it hasn't been studied in that population, or if someone is progressing to the point where they need a liver transplant, that would be the preferred therapy, because there may be other issues going on with their hepatic impairment. And the last criteria is that the patient

does not have severe renal impairment, end-stage renal disease, or moderate-severe hepatic impairment. And that is from the label. So, it has not been studied in those patient populations. And we're not sure how this drug may metabolize differently in some of those patients.

So, if all those criteria are met, then the request would be approved for six months. And then after those six months, it would come back for re-authorization criteria, and that is on the next slide. So, the next slide is a positive clinical response, as demonstrated by clinically-meaningful improvement in either of the scales, whichever one the physician is using to monitor that patient. So, if the patient does have a positive response to their neuropathy, in that they are demonstrating some effect, then it would be approved for twelve months.

Lisa Chew: Do we have stakeholders? Yeah? We have one stakeholder, Dr. Jennifer Luth. If you could come up to the podium, state your name, who you represent, and you will have three minutes for comments.

Jennifer Luth: Good morning. My name is Jennifer Luth. And I work with Alnylam Pharmaceuticals as a medical science liaison. In the time that I have allotted, I wanted to take a couple minutes to address the biopsy requirement. Currently, as our phase-3 criteria is for enrollment into the clinical trial, patients were not required to have a biopsy to be part of the patisiran [inaudible] trials. They needed to have a genetic diagnosis by genetic testing. Also, they needed to have documented polyneuropathy via the mNIS+7, which was our primary endpoint, by FAP staging, or by PND. Further, as a result of the approval of Onpattro, two of the three largest states have instituted Medicaid policies. Of note, patients are required to have a diagnosis by genetic testing of TTR and evidence of polyneuropathy, sensorimotor, or autonomic dysfunction. There is no biopsy requirement for these two Medicaid policies that are currently in place. That is the end of my comments. If you have any questions, I will be happy to entertain them.

Lisa Chew: Thank you. So, committee members, any comments or questions for Ryan or Umang?

Nancy Lee: I have a question about the reauthorization criteria and some of the clinical trials that, the one that was presented looked at, or found, reevaluated at baseline, nine months, and 18 months. And I wasn't sure, in terms of the documentation of possible clinical response at, like, six months. And whether or not we would see some of that based on baseline nine and 18. So, I'm wondering if you can comment on kind of the six months timeframe and what kind of clinical response demonstrated by clinically meaningful improvement, how you would assess that?

Ryan Pistorosi: So, typically, when we do drug authorizations, we look at a twelve month time period. So, that way, we get the chance to look at it. I think we are open to adjusting it to be nine months to mirror what was shown in the clinical trials, because that was one of the earlier endpoints. In terms of clinically meaningful response, different scales will have different ways of measuring what is a clinically meaningful improvement. So, a score of +1, a score of +2, a score of +10. So, whatever that cutoff is, then we would determine whether it is, and if the medication is working, that clinically meaningful improvement means that there are some tangible real-world outcomes. So, that way, it is improving their lives and improving the polyneuropathy. So, that is what we meant by clinically meaningful improvement in the reauthorization criteria.

Amber Figueroa: I had that concern, as well, because in the presentation, it says that at the 18, it doesn't even give scores that they, it says they assessed it but doesn't give scores at 9 months. So, at 18 months, the baseline improvement was decreased by only six points. So, I would think at six or even nine months, potentially you wouldn't see any decrease in points, but it may not increase the 28 points that the placebo found at 18 months. So, I would be in favor of increasing the evaluation time at a minimum to nine months and maybe closer to 12 months, just looking at the small changes on the scale when they evaluate it at 18 months. And I don't, yeah. I also had that question, as to what exactly we're looking for, as far as a number for improvement, or if the number stayed the same or even got two points worse, but would it have gotten 50 points worse if they weren't on the medication. Are they saying that their quality of life is better? Could they still get approved for the medication for another year, if on physical examination, we find something that

shows improvement or that they're saying that their quality of life is better, specifically. I mean, they're not just saying that. They can specifically say, I couldn't do this before, and now I'm able to do this and that. So, just some thoughts.

Ryan Pistoresi: So, kind of hearing what you were saying and trying to think about how we can maybe rephrase some of the reauthorization criteria. So, instead of maybe documentation of a positive clinical response, as demonstrated by a clinically meaningful improvement, and, and I ask, or PND, should we just, you know, request an updated score of the PND, and I ask to see is this medication maintaining function? So, are they potentially lowering their score or about the same rather than seeing a significant increase, like what we saw with the placebo, which would then signify disease progression and maybe that there are some other issues going on with either the patient or the medication. Would that be similar to kind of what your idea was?

Amber Figueroa: Yeah. I think that's fine. And I also think that it should be approved for 12 months instead of 6.

Ryan Pistoresi: For the initial authorization? Okay.

Nancy Lee: This is Nancy. I would concur with that and maybe also, as you mentioned, not just looking at NIS and the PND score in isolation, but also maybe including some of the secondary functional, because you mentioned functional, but more functional, concrete, specific to the patient. Like, what kind of functional improvement did they have from before?

Ryan Pistoresi: So, this is Ryan. So, should we also add that to the initial criteria? So, the... either of those scales, so the NIS or the PND, and also measures that the clinician wants to measure to show efficacy of the polyneuropathy.

Nancy Lee: This is Nancy. Yes. I would.

Ryan Pistoresi: Okay.

Nancy Lee: Yeah.

Ryan Pistoresi: So, let's see, oh, that's okay.

Amber Figueroa: I think maybe just using the secondary endpoints from the study, maybe just listing those out as examples of quality of life, motor strength, disability, gait speed, nutritional status, autonomic symptoms.

Ryan Pistoresi: Okay. So...

Amber Figueroa: That would be helpful.

Ryan Pistoresi: So, when it's back up, we'll try updating the third criteria of the initial criteria. And then the first criteria of the reauthorization. So, I propose that... keep it the same. So it says NIS or the polyneuropathy.

Female: We're on the third bullet?

Ryan Pistoresi: Yeah. I'm kinda thinking maybe it's, like, one is either the neuropathy or the polyneuropathy. And then two is other secondary measures, e.g., quality of life, motor strength, disability. So, kind of breaking that out into the two separate.

Female: So, sorry. You want two bullets?

Ryan Pistoresi: Yeah. Maybe just make a new bullet underneath that.

Amber Figueroa: You can do it on the next page, because it continues onto the next page, if you want.

Lisa Chew: Slide 12 I think.

Amber Figueroa: Oh, well, he's trying to put it with the...

Lisa Chew: Oh, I see.

Ryan Pistoresi: Yeah, just mainly because they're similar. So, they're both the documentation.

Amber Figueroa: ...yeah.

Ryan Pistoresi: I mean...

Female: Instead of or, you want this to be a new bullet? Is that correct?

Ryan Pistoresi: No. I was thinking a new bullet underneath the...

Female: [inaudible]

Ryan Pistoresi: ...yeah.

Female: Gotcha.

Ryan Pistoresi: And so, documentation of baseline disease severity from, sorry.

Female: He's thinking.

Ryan Pistoresi: Yeah.

Amber Figueroa: As evidenced by.

Ryan Pistoresi: As evidenced by. Okay. As evidenced by other measurable outcomes. Factors or outcomes. Okay. Factors. And then, we can put parentheses e.g., quality of life, motor strength, disability, gait speed, etc. Yeah, gait is G-A-I-T. Sorry. And then, yeah, just the typos.

Amber Figueroa: Typo on the quality. And it would be evidenced, not evidence.

Ryan Pistoresi: Evidenced. Yeah. Good. Great. Alright. So, let's just look at that real quick before we move to the reauthorization criteria. So, does that sound good?

Virginia Buccola: That sounds good to me. My question is, uh, I'm just curious, I don't know if either Ryan or Umang could talk a little bit about the need for both the biopsy and molecular genetic testing, and what the benefit would be to the duplication there.

Ryan Pistorosi: So, I guess the idea is that the biopsy would be demonstrating that there is polyneuropathy secondary to the amyloidosis. That it is not polyneuropathy maybe relative to other conditions, and that the genetic test does show that the cause is. That was our thought when looking at biopsy and the genetic test to help really determine that they have the genetic condition, for which this drug can treat. And that the polyneuropathy is secondary to amyloidosis that would be shown by biopsy.

Constance Huynh: So, when, it's a vague tissue biopsy. And so, I'm just wondering what would be the basis of, in terms of evidence, if previous studies have been showing that it wasn't required to do a biopsy. If we're doing a genetic test, it's just kind of this over-arching positive or negative for this, whatever the test is for. Whereas, the biopsy could be very singular. And there could be other organs that may be effected that may not be on that biopsy. So, if you're requiring both of them to be part of the criteria, as opposed to or, so the tissue biopsy or the genetic testing, that may be able to cover some of the organs that may not be on the biopsy. So, that's my question. Is it required... actually can we just change it to tissue biopsy or the genetic test?

Ryan Pistorosi: So, I would favor keeping at least the genetic test. I don't think a tissue biopsy, on its own, would be sufficient, especially since there are other conditions that could cause amyloidosis. There are several other ones in which there are other drug treatment options. And we wouldn't necessarily want to have that be potentially a gap. I mean, these are experts in the field that would be treating this condition, but if we were to look at changing this criteria, I would favor keeping the genetic test and then potentially looking at removing the biopsy but at least having some measure of polyneuropathy as the criteria. So, if you're thinking about options for that, that is kind of what I would recommend.

Constance Huynh: So, then, I would recommend that we change the and in between tissue biopsy and identification to or. No?

Amber Figueroa: Take out the biopsy.

Constance Huynh: Or take out the biopsy. Just remove the biopsy.

Ryan Pistorosi: I would favor...

Constance Huynh: That's fine.

Ryan Pistorosi: ...taking out the biopsy but putting in a measure of polyneuropathy, like, maybe diagnosis of.

Amber Figueroa: I think the time that that would be potentially helpful is if they have polyneuropathy, and they have the genetic proof that they have the amyloidosis but we're... the causative relationship isn't there. So, I would hope the clinician, if there's other things that could potentially be causing the polyneuropathy, would strike to biopsy if there's a question, before they put them on a gazillion dollar medication to just see if it'll help.

Leta Evaskus: This isn't my [inaudible]. I think the proposal might be, as documented by evidence of polymyopathy and identification of... I don't think you want... you need to take out amyloid deposition. And tissue biopsy, take that out. So, we can either have it this way, or we could say by evidence of polyneuropathy and whatever the committee prefers.

Lisa Chew: It looks like people are shaking their head. They want polyneuropathy and identification? Yes? Okay.

Susan Flatebo: But isn't that covered in the third bullet when it talks about documentation of baseline disease severity, such as using the neuropathic impairment score, polyneuropathy disability. Do we need to add it into the second bullet, as well?

Ryan Pistorosi: So, the reason that we had that, one is to show that there is positive clinical response, because that was the primary endpoint in the clinical trials. If we did not have evidence of polyneuropathy, there could be a patient with a genetic variant that doesn't have polyneuropathy that is requesting this. Since this is approved for the treatment of polyneuropathy, I would recommend having some criteria in there that matches the diagnosis on the FDA label. So, I think that is why we have it in two separate bullets for this criteria.

Amber Figueroa: I think it's okay like that, because you're saying, the first bullet is saying they have to have the presence of polyneuropathy. The third bullet is saying, now assess that with a numerical value. I think it's okay to have it both ways.

Lisa Chew: I have a question about the Vitamin A supplementation and how strongly that is required to be taken with this medication. It sounds like it's called out as a criteria on the Magellan documents, not as a mandatory criteria, but just wondering if that needs to be called out on the policy or in the criteria, to make sure patients get that.

Ryan Pistorosi: So, we're just looking it up real quick to see if we can provide a little bit more background on that, but we'll get an answer before we go through with the rest of this. I think while we're looking that up, we can move over to the reauthorization criteria and update that. And then, hopefully, we'll have an answer by that time. So, I recommend that we update this to say documentation of positive clinical response, as maybe supplied or provided by NIS or PND, or other measures from baseline. Let me see. We can remove, yeah. Just remove the clinically meaningful improvement. So, NIS or PND, or what else did we say on the other... other baseline measures.

Nancy Lee: I'd like to add to that other baseline measures of function.

Ryan Pistorosi: Function. Okay. Oh, baseline measures of function. Sorry, not and function. And then, on the previous slide, one other... change the six months to 12 months. I believe that was all the discussion, exception for the Vitamin A, which we're just getting a little bit more background information on, before we make that recommendation on how we may want to require it as a supplement for this condition.

Donna Sullivan: It really just says that they recommend supplementation for Vitamin A. There is an association with reduced serum levels of Vitamin A, whether it's symptomatic or not, symptomatic, the package insert just recommends supplementation.

Lisa Chew: I'm fine with leaving it out. So, the committee members want to review the motion and review the criteria and see if we want to make a motion?

Amber Figueroa: I move that the Apple Health/Medicaid program implement the clinical criteria listed on slides 10 through 12, as recommended.

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries.

Ryan Pistorosi: Okay. Perfect. So, moving forward to the next medication, Tegsedi. Again, the background was previously covered. So, we'll dive right into the indication, dosing, and availability. Now, for this medication, again, very similar. It is indicated for treatment of polyneuropathy of hereditary transthyretin mediated amyloidosis in adults. This is the second RNA interference therapeutic agent that was approved by the FDA in 2018, as well. The mechanism of action is very similar to the previous medication, where it is a double stranded RNA, siRNA, that causes degradation of the mutant Y-type GTR, MRNA through RNA interference, which causes a decrease in serum TTR protein and deposits. In terms of medication, or excuse me dosing, the recommended dose is 284 mg via subcutaneous injection once weekly. So, this is different from the previous medication where this is subQ, and the previous one was IV, possible injection sites include clean intact skin of abdomen, upper thigh, or outer area of the upper arm. And the injection site should be rotated. Tegsedi should be administered, as soon as possible, in the event of a missed dose. If it is administered within four days of the missed dose, the patient's original dosing schedule should be continued. If it has been more than four days, then the day that you restart the regimen will be the new dosing regimen. Patients and their caregivers can administer subsequent doses after being taught proper subcutaneous injection technique. And each dose of Tegsedi should be administered on the same day of each week. A healthcare professional should administer the first dose, and while Tegsedi does require refrigeration, prefilled syringes should be removed

at least 30 minutes prior to the use to allow the injection to come to room temperature. The available here, as you can see, are single dose vials of 284 mg per 1.5 mL.

On the next slide here, going into just same additional information. So, for pediatrics, the safety and efficacy has not been established. There is not a lot of data for patients who are pregnant; however, since Tegsedi, similar to Onpattro, does cause a decrease in serum Vitamin A levels, which is essential for normal embryo-fetal development, it is advised for patients to take Vitamin A supplements again, if they are pregnant. Renal hepatic impairment, a dose adjustment is not required in patients who have mild to moderate renal or mild hepatic impairment. The use of Tegsedi has not been studied in patients with severe renal impairment, endstage renal disease, or severe hepatic impairment. There is no dose adjustment required in patients greater than or equal to 65 years of age. In terms of drug interactions, it should be administered cautiously in patients who take medications that affect platelets, including both prescription, such as antiplatelet medication, such as adenosine, clopidogrel, prasugrel, and OTC such as aspirin, NSAIDs, etc., due to the risk of thrombocytopenia. And in addition, patients who take nephrotoxic medication, or medications which may impair renal function, should use Tegsedi cautiously, due to risk of glomerulonephritis.

In the next slide here, you'll see in terms of warning and contraindications, there is a lot here. I did try to kind of underline the main points. The most commonly observed adverse reaction in clinical trials were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. These ADRs occurred in at least 20% of patients treated and more frequently than in patients who received placebo. It is contraindicated in patients who have a platelet count less than 100×10^9 per liter, and patients who have a history of acute Tegsedi related glomerulonephritis, and in patients who have a known hypersensitivity. It may cause stroke, liver problems, and/or serious allergic reactions. Immediate medical attention should be sought for any signs or symptoms of stroke or hypersensitivity reaction. Prescribers should perform laboratory tests to assess hepatic function prior to initiation of Tegsedi and during treatment. And patients should inform their prescribers of any symptoms of hepatic injury or impairment.

Again, it does cause decrease in serum Vitamin A levels. So, it is advised for patients receiving Tegsedi to take daily Vitamin A supplements at the recommended allowance. Larger than recommended doses of Vitamin A should not be given in order to achieve the normal serum Vitamin A level, as it is not accurately depicted in the body's total Vitamin A level. And if ocular symptoms occur, that suggest Vitamin A deficiency, such as night blindness, you should be referred to an ophthalmologist. This medication does carry a black box warning, risk of thrombocytopenia and glomerulonephritis, and therefore must be dispensed through the REMS program. The thrombocytopenia caused by Tegsedi can be sudden, unpredictable, and potentially fatal. And treatment requires laboratory monitoring, to which patients must adhere. If patients present with signs or symptoms of thrombocytopenia, platelet count should be obtained as soon as possible. And the dose of Tegsedi should be held until results are available. In the event of uninterpretable results, which may be caused, remeasure, as soon as possible, and only restart Tegsedi once a confirmed normal platelet count is available. The second black box warning for glomerulonephritis can be cause to the point of renal failure, which could require dialysis. Some of these cases were also accompanied by nephrotic syndrome and suspected cases of glomerulonephritis must be quickly diagnosed and treated with immunosuppressants.

So, the placement therapy, according to their neuro TTR study, this was an international randomized double-blind placebo-controlled phase-3 trial of patients with hATTR amyloidosis and symptoms of polyneuropathy with an N of 172. Patients range from 18 to 82 years and were randomly assigned a 2:1 ratio to receive Tegsedi subcutaneous or placebo for 65 weeks. The endpoints were very similar to the previous medication where they looked at baseline mNIS+7 scores and also the Norfolk quality of life diabetic neuropathy scores at 66 weeks. The results showed at 66 weeks, changes from baseline, and the mNIS+7 was significantly less in the Tegsedi group. Again, the mean scores are there below. And at 66 weeks, the mean change in the mNIS+7 from baseline was 5.8 in Tegsedi, as opposed to 25.5 in placebo, which shows statistical significance. In the quality of life measure, change from baseline was significantly less in the Tegsedi group compared to the placebo group at 66 weeks. Treated patients experienced similar benefit regardless of subgroups, such as age, sex, region, NIS score, mutation status, and

disease state. And please note that a phase-3 open label extensive study is being conducted to evaluate the long-term efficacy and safety of this medication. And the results are expected after the study completion in September, 2022. Any questions?

Amber Figueroa: So, your end was 172. How many of these people ended up on dialysis or having fatal thrombocytopenia? Like, I don't know. I'm just wondering the frequency of these severe side effects?

Ryan Pistorosi: Let me look in to see how many specific patients did have to undergo dialysis; 3% of the patients that were in the Tegsedi treatment group.

Amber Figueroa: What's the percent of clinically significant thrombocytopenia?

Ryan Pistorosi: 3%.

Lisa Chew: There are no stakeholders for this drug.

Ryan Pistorosi: So, next up is the Tegsedi Apple Health Policy. For this one, again, one indication one product. As you may see on the next slides, the clinical criteria was the same as what we had originally proposed for the Onpattro. And given the robust discussion that we had previously, I think you would prefer that we have the same policy consistent for both medications and that you would use kind of the same one that you approved for Onpattro, as the baseline for this. Now, if there are other questions or discussion that you would like to have, it sounds like there was some interest in the thrombocytopenia and glomerulonephritis. We may be able to do that, but I think at least to start, we may just copy and paste the previous policy from Onpattro and use that to kind of... as a starting point.

Donna Sullivan: So, from this initial criteria?

Ryan Pistorosi: Yes. The next one, you don't need to copy and paste, since we only changed one number. That was the six to twelve. Then, the last page, oh yeah. We made a bigger change. Maybe we could go back and copy/paste. Yeah. That one. Thank you. Great. Thank you, Leta. So, we've updated it so that it reflects the original criteria, or the approved criteria that was for the Onpattro policy so we can start and go from

there and see if there's any further discussion, comments, edits, or recommendations that you have.

Amber Figueroa: It's fine with me. It's just when I'm 82, I don't want to be injected with this drug. I'm just saying. I'll have my old problems.

Lisa Chew: Any other comments from committee members regarding the motion edits/

Ryan Pistorosi: Really quick, just clarification for the thrombocytopenia question, in that specific study, it is 3%, but as I'm looking into more and more studies, that number seems to be going up to about 23%. Just to clarify.

Nancy Lee: This is Nancy, just to comment. Medication must be dispensed through the REMS program, too, so.

Lisa Chew: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 21 to 23, as recommended.

Constance Huynh: I second that.

Lisa Chew: Just a reminder, folks, state your name before speaking. Okay. All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Motion carries. We can move on to the next drug when you're ready.

Umang Patel: Okay. Perfect. So, the next medication we'll be going over is Ocrevus, or ocrelizumab. So, here we will touch base on multiple sclerosis. Again, I know we've reviewed this in the past, but just a quick overview. MS is a complex human autoimmune type inflammatory disease of the central nervous system, in which more than 2.3 million worldwide are afflicted. Although the etiology is predominantly unknown, the pathology of MS is characterized by demyelination and subsequent axonal degeneration, the nerve degeneration associated with MS can result in a wide variety of symptoms, including sensory disturbances, such as numbness,

paresthesia, burning, and pain in the limbs, optic nerve dysfunction, ataxia, fatigue, bladder/bowel/sexual dysfunction, and ultimately partial and complete paralysis. At the onset of the disease, MS can be categorized as either relapsing/remitting MS, which is observed in 85 to 90% of patients; primary progressive MS, which is observed in 10 to 15%. Relapses or attacks typically present subacutely with symptoms developing over hours to several days persisting for several days or weeks and then gradually dissipating. The attacks are likely caused by a migration of activated myelin reactive T-cells in the central nervous system causing acute inflammation with associated edema. The use of high dose corticosteroids to quickly relieve MS symptoms suggest acute edema and its subsequent resolution underly the clinical relapse and remission respectively.

On the next slide here, we have the indication, dosing, and availability. So, Ocrevus is indicated for the treatment of adult patients with relapsing multiple sclerosis, or primary progressive MS. The dosing here... the initial dose is 300 mg, as an IV infusion followed two weeks later by a second 300 mg IV infusion. Maintenance dose thereafter is 600 mg, as an IV infusion every six months beginning six months after the first infusion. The first two doses here should be diluted in normal saline. The infusion should start at 30 mL/hr and may be increased by 30 mL/hr every 30 minutes to a maximum rate of 180 mL/hr for a total duration of about two and a half hours or longer. Subsequent doses should be diluted in normal saline. And the infusion should start at 40 mL/hr and may be increased by 40 mL/hr every 30 minutes to a higher max rate of 200 mL/hr for a total duration of three and a half hours or longer. Premedication is recommended with 100 mg of IV methylprednisolone or an equivalent corticosteroid 30 minutes prior to each infusion and an antihistamine, such as diphenhydramine 30 to 60 minutes prior to each infusion. Addition of an antipyretic may also be considered, as part of the regimen. All patients should be observed for at least one hour following the completion of every infusion. If a dose is missed, administer missed dose as soon as possible. Subsequent doses should be administered six months following the rescheduled dose. And the doses should be separated by at least five months. Immediately stop the infusion and permanently discontinue this medication, should a life-threatening or disabling infusion reaction occur. Again, the availability, it

is available in 300 mg/10 mL, or 30 mg/mL, single dose vials. To kind of touch on the mechanism of action of this, it is a monoclonal... it is a humanized... it is a recombinant humanized CD20 monoclonal antibody. So, the precise mechanism of this is unknown; however, it targets and binds to the CD20, which is a self-service antigen present on the pre-beta and mature beta lymphocytes. This results in antibody dependence cellular cytotoxicity and complement mediated lysis.

Here we have the additional information. So, for pediatrics, safety and efficacy has not been established in patients less than 18 years of age. In terms of geriatric patients, clinical trials did not include a sufficient population of patients greater than or equal to 65 years old to determine if older adults respond differently. Key clinical trials limited the population to adults less than or equal to 55 years. In terms of patients who are pregnant, no data has... there is not sufficient data to inform a drug-related risk. Lymphocytopenia and transient peripheral B-cell depletion have been reported in infants whose mothers were exposed to other CD20 antibodies during pregnancy, again not this specific medication, but a similar mechanism of action. Ocrevus is a humanized monoclonal antibody of an immunoglobulin and immunoglobulins are known to cross the placenta. Women of childbearing potential should use contraception while undergoing treatment and for six months following the last Ocrevus dose. In terms of warnings and contraindications, the first being hepatitis B, no cases of hepatitis B virus reactivation in patients in clinical trials, reactivation has been reported with other, again, anti-CD20 antibodies. Hepatitis B screening prior to initiation is required, and it is contraindicated in patients with active hepatitis B infections. For infusion reactions, it is contraindicated in patients with a history of life-threatening infusion reactions. These include things such as pruritus, rash, urticaria, erythema, and etc. Healthcare providers should administer premedication prior to the infusion and use an antipyretic may be considered. Observe the patient for at least one hour following the infusion completion, and inform patients that infusion reactions could occur up to 24 hours. And immediately and permanently stop the infusion if there is life-threatening infusion reaction occurring.

To continue the warning and contraindications for infections in clinical trials, a higher portion of patients treated with Ocrevus experienced infections compared to patients treated with placebo. Ocrevus increased the risk of upper and lower respiratory tract infection, skin infection, herpes related infections; however, no increased risk in serious infection was found. It is important to note progressive multifocal leukoencephalopathy. This is an opportunistic viral infection of the brain caused by the John Cunningham or JC virus that primarily occurs in patients who are immunocompromised and usually leads to death or severe disability. No cases have been reported with Ocrevus, that's important to note; however, cases of PML could occur, as these have been reported with other anti-CD20 antibodies and other MS therapies. A full evaluation and workup should occur in any patient presenting with signs or symptoms suggesting PML. In terms of live attenuated vaccines, the safety of immunization with live or live attenuated vaccines following Ocrevus has not been evaluated. Administer all immunizations six or more weeks prior to the initiation of Ocrevus, and vaccination with live attenuated or live vaccines is not recommended during treatment, and until B-cell repletion upon discontinuation of Ocrevus. For malignancies, a higher rate of malignancy, including breast cancer, have occurred in patients with Ocrevus in clinical trials compared to active comparator or placebo. And patients should adhere to standard breast cancer screening guidelines. In terms of additional MS therapy, Ocrevus has not been studied in combination with other MS therapies, and additive immunosuppressive effects should be considered when using with other immunosuppressive therapies. Lastly, I know there is a lot of information here. It is a summary of guidelines, prior to the approval of Ocrevus, there was no pharmacologic agent FDA approved for the treatment of primary progressive MS. Thus, current guidelines focus on the use of these agents for relapsing MS. The subcommittee of the American Academy of Neurology, and the MS Council for the Clinical Practice Guidelines reaffirmed in 2003 and 2008 state, interferon beta have been demonstrated to reduce their attack rate, whether measured clinically or by MRI in patients with MS or with clinically isolated syndromes who are at high risk of developing MS. It is appropriate to consider interferon beta for treatment in any patient who is at high risk for developing clinically definite MS, or already has MS, or secondary progressive MS and is still experiencing relapses, but the effectiveness of interferon beta

in patients with secondary progressive MS, but without relapses is uncertain. These guidelines also state that it glatiramer acetate has reduced the attack rate, whether it measured clinically or by MRI in patients with relapsing MS and is appropriate to be considered for treatment in any patient who has relapsing MS. Based on trial evidence, interferons and glatiramer acetate have similar clinical utility. Other agents were not available at the time of this statement, but have since demonstrated efficacy in relapsing MS through clinical trials. While these guidelines state no one agent has consistent data supporting its use for primary progressive MS, other agents recommended based on their potential for benefit include cladribine, cyclophosphamide, methotrexate, and cyclosporine. An update to this guideline is in progress. Newer agents not addressed in the clinical guidelines with the exception of dalfampridine have demonstrated improvement over placebo controlled trials in absolute risk reduction and other endpoints; however, comparative trials are limited with MS agents to make any definitive conclusion that one agent is superior to the other. Another oral agent improves walking speed, but it has no effect on the underlying disease. The role of Ocrevus in the treatment of RMS has yet to be fully determined. While it's demonstrated efficacy over interferon beta in the OPERA trials, its utility may be limited due to its competition in the class in tolerability, such as infusion related reactions, potential for PML that we discussed earlier. And as Ocrevus is the first drug FDA approved for primary progressive MS and has demonstrated a benefit in disease progression in the condition for which treatment is primarily symptomatic, it will likely play a significant role in the treatment of patients with this condition. Any questions?

Lisa Chew: Thank you, Umang. Any questions from the committee? So, we do have one stakeholder, Dr. Shirley Quach. Hi. Please come up to the podium, state your name and who you represent. And you will have three minutes.

Shirley Quach: Hi. My name is Shirley Quach. And I am a managed care liaison with Genentech. Thank you for your time and thoughtful effort in reviewing Ocrevus; however, please consider the removal of the two set [inaudible] requirement for RRMS and the ambulation requirement for PTMS and include Ocrevus as an initial treatment option. What we have heard from

neurologists is that time is [inaudible]. Current MS guideline bodies, they highlight the important of access to highly effective therapies early on in order to control disease activity, prevent accumulation of disability, and prolong people's ability to remain active and engaged, in order to protect their quality of life. Once MS progresses, patients don't get back what was lost. And treatment choice should be individualized and left to patients and providers. Ocrevus, as shown, was studied in OPERA 1 and 2, which are two phase-3 studies in patients with RMS and was compared against an active comparator, Rebif. And it demonstrated superior efficacy in multiple endpoints with similar rates of adverse events. Also, about 74% of our patients in the studies were considered treatment naive, previously untreated in the two years prior to study. And in our open label extension study, disability progression was lower in those patients who started Ocrevus earlier than those who started with Rebif and then switched over to Ocrevus. ISER also ranked Ocrevus among the most effective DMT for RMS for [inaudible] reduction and reduction of disability production and stated that Ocrevus had the lowest serious adverse events rate among all DMTs evaluated. In an up to date, they recently updated their guidelines. And they state that treatment should be individualized, that for those patients who value advocacy, Ocrevus is listed as an option for initial treatment. And Ocrevus is the only FDA approved agent for PPMS based on our oratorical pivotal trial. So, patient access to effective treatment should not be limited by their limited disability. All of these reasons have led Ocrevus to being the number one prescribed DMT for MS patients starting a new therapy. And these are also reasons why Ocrevus should be added as a preferred agent for initial therapy, because if you waste time using less effective products, patient disease may progress. And they do not get the neurons that were degenerated or loss. So, thank you for your time. And I welcome any questions you may have.

Lisa Chew: Any questions? Thank you, very much. Okay. Ryan, would you like to go through the?

Ryan Pistorosi: Sure. So, I'll be walking through the Ocrevus Apple Health policy. So, for this, we have two different indications for the one product. So, we have the relapsing remitting multiple sclerosis criteria that we'll walk through first. And then the primary progressive multiple sclerosis criteria that

we'll walk through second. So, we'll walk through both together. There is one motion at the end for both of these together. So, we can go through them. So, for the relapsing remitting multiple sclerosis policy, we have the diagnosis, patient's age 18 and older. For our criteria, the patient must have an inadequate response to two or more medications FDA approved for the same indication and/or medications that are considered a standard of care. So, as you may remember when we previously reviewed multiple sclerosis, we had six preferred products on our PDL. So, two orals and four self-injectables. The patient is not concurrently taking other disease-modifying therapies for multiple sclerosis. So, this medication has not been studied in combination with any other MS drugs. Test results for hepatitis B viral infection are negative. So, as Umang mentioned when he was going through the clinical criteria, there is a potential reactivation of hepatitis B with other anti-CD20 therapies. So, it is recommended to screen for that. And then, if there is infection or negative, it is contraindicated. Dose does not exceed FDA or compendia-supported limitations. So, as Umang mentioned, there is some different dosing for this. So, this is just requiring that it be specific for the relapsing remitting multiple sclerosis. Thank you.

On this slide, for patients previously treated with disease-modifying drugs with long-lasting treatment effects, so natalizumab and alemtuzumab, an appropriate washout period has elapsed prior to planned treatment with Ocrevus. That's because these are very longacting drugs. So, you don't necessarily want to start it in one week. You'll still have drug in your body. And this is similar to the previous criteria that we had mentioned of not using MS drugs concurrently. Then, for patients with an EDSS of 6.5 or greater, so this is people with very severe disability for their relapsing remitting multiple sclerosis, that they have imaging evident of active disease and documentation of at least one relapsing event in the last two years. And the documentation that the provider has discussed the benefits and risks of continuing disease modifying therapy. So, if patients meet all of that criteria, the request would be approved for 12 months.

On the next slide is the reauthorization criteria. So, after those 12 months, when a request comes back, we would just have documentation

of clinical benefit, as determined by the prescriber. So, as long as the prescriber who is monitoring and evaluating and treating this patient feels that this medication is continuing to work, as long as they're able to justify that, we'll continue to approve it for 12 months.

For the primary progressive criteria on the next slide, the patient has the diagnosis of primary progressive multiple sclerosis. And this is according to the revised Macdonald criteria, the patient is age 18 or older, that there is documentation of oligoclonal IGG bands in the cerebral spinal fluid, that there are T2 lesions on brain or spinal cord imaging, and that the ambulatory stage of the disease is an EDSS score of less than 7.

On this slide is the continuation of that criteria. So, the patient is not currently taking other disease modifying therapies for multiple sclerosis. That the test results for viral hepatitis B are negative, and that the dose does not exceed the FDA or compendia supported limitations. With this one, it's also approved for an initial 12 months. Same reauthorization criteria. So, if the provider can justify clinical benefit based off of whatever information that they have regarding the use of this treatment, that it then would be approved for another 12 months.

Lisa Chew: Any questions from the committee?

Catherine Brown: I just have a question. Is there any role for JCV testing? Or is this something that regardless of whether someone's positive or negative, you might still choose to use it?

Ryan Pistoresi: So, we don't have that in the criteria for this medication. There are other medications for multiple sclerosis that can activate the virus and, and lead to PML, but we don't actively have that as a criteria to check. We feel that the providers who are knowledgeable about this medication and that are going to be prescribing it will be checking it. We can even look for it in the chart notes, as we're doing the reviews for these medications, but we don't want to have that necessarily be a barrier, in case that the provider feels that the risks, I mean, that the benefits outweigh the risks for that specific patient, but if you would like, we could add that potentially to the hepatitis B line of this criteria to say

hepatitis B and JC virus if, if you would feel more comfortable with us and our, okay. I see a head shaking no. So, okay.

Catherine Brown: That sounds fair to me.

Susan Flatebo: My only question is on the, the relapsing/remitting policy, the third bullet, the patient must have an inadequate response to two or more medications, how about if you have a patient that is JCV positive, and maybe the neurologist doesn't want them to be on one of the other approved medications, because their risk for PML could be higher. So, they are looking to Ocrevus because there are no reported cases of PML. Could maybe you change that bullet to inadequate response to two or more, or unable or... I don't know what the wording would be, but maybe the Ocrevus would be a better choice for them, because they are JCV virus positive.

Ryan Pistorosi: So, we do have six preferred therapies, and of the six preferred, I don't believe any of them have any JVC. Really, the only ones that do are the infused therapies, and those are all non-preferred currently. Those were reviewed at the December meeting. When we made that decision, those were left, but we didn't have that as the PA criteria. If the provider is evaluating their patient, and that they have this justification, they can submit, in their prior authorization, and explain the rationale for why this criteria may not be appropriate for this patient. And if we do evaluate that, and that some of the other therapies, they're able to justify why Ocrevus is the appropriate therapy to the point that you explained, we can consider that.

Susan Flatebo: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 33-38, as recommended.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. This is Lisa Chew. So, we're a little bit ahead of schedule. Should we take a 15-minute break? Okay. So, 10:25? Am I adding that right? 10:25? Okay. Thanks.

Alright. We're gonna go ahead and reconvene and talk about the next drug class, thrombopoiesis stimulating proteins.

Umang Patel: Thank you. So, the next class here, uh, for thrombopoiesis stimulating proteins, just to give a little bit of a clinical step back. So, for platelets, these are small circulating cell particles that do not contain a nucleus and are released into the blood stream by megakaryocytes that reside in the bone marrow and function to maintain hemostasis by aggregating and forming platelet plugs at sites of injury to limit blood loss. Thrombocytopenia is generally defined as a platelet count of less than 100×10^9 per liter. It can result in bruising, bleeding, and fatal hemorrhaging, as well. Causes can include decreased bone marrow production by megakaryocytes, splenic sequestration of platelets and increased destruction of platelets. Immune thrombocytopenia, abbreviated as ITP, was previously known as immune thrombocytopenic purpura and idiopathic thrombocytopenic purpura. It is defined as a platelet count of 100×10^9 , and it is an immune mediated disorder, in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system.

On the next slide here, for immune thrombocytopenia, in children, ITP is usually an acute self-limiting disease that often occurs two to three weeks after a viral infection or immunization. Spontaneous remission in children typically occurs within two to eight weeks. In adults, ITP has an insidious onset with no preceding viral or other illness and typically has a chronic course. Many adult cases of ITP are diagnosed incidentally after a routine complete blood count, or a CBC. Signs and symptoms are highly variable and range from asymptomatic with mild bruising or mucosal bleeding to frank hemorrhage from any site. Severity in adults is dependent on the presence of active bleeding, platelet count, patient age, lifestyle related to risk of bleeding, and presence of additional risk factors for bleeding, such as uremia or chronic liver diseases. Primary ITP is defined as an autoimmune disorder with isolated thrombocytopenia in the absence of other causes or disorders that might cause

thrombocytopenia. The diagnosis remains one of exclusion. No robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. It is also defined by the length of time since diagnosis. Newly-diagnosed is less than three months. Persistent is between 3 to 12. Chronic is over a year. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present. Secondary causes may include drug-induced autoimmune disease, such as systemic lupus and viral infections, such as HIV or hepatitis C. Severe ITP occurring at any time indicates bleeding, which requires treatment or the occurrence of new bleeding symptoms, which requires additional treatment or increased dose to control bleeding.

On the next slide, to continue the overview, thrombocytopenia secondary to chronic liver disease occurs in 64 to 84% of CLD patients with cirrhosis or fibrosis, and 6% of CLD patients without cirrhosis. Liver disease related thrombocytopenia is thought to generally be caused by decreased production, splenic sequestration, and increased destruction of platelets. Patients with CLD often require invasive procedures and are at increased risk of bleed, related to the procedures. For treatment, interventional management had been used in an attempt to correct splenomegaly associated thrombocytopenia; however, the only invasive tool to increase platelet count is platelet transfusion, which has risks of allergic reaction, infection, and iron overload, if it's used chronically. While there are guidelines available for platelet transfusion in adults and thrombocytopenia treatment recommendations for patients with cancer or idiopathic ITP, there are no specific guidelines for the treatment of thrombocytopenia in CLD patients who are undergoing an invasive procedure. Doptelet and Mulpleta have been proven efficacious for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure.

So, on the next slide here, we have indications that will continue onto the next slide. No generics are available. As you can see, Doptelet is indicated for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure. Promacta is indicated for the treatment of thrombocytopenia in adult and pediatric patients greater than or equal to one year of age with chronic idiopathic ITP who have had

an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should only be used in patients with ITP whose degree of thrombocytopenia in clinical condition increase the risk of bleeding. It is also indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow initiation and maintenance of interferon based therapy. It should only be used in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of the interferon based therapy or limits the ability to maintain the interferon based therapy. Safety and efficacy for this have not been established in combination with direct-acting antivirals. It is also indicated for treatment of patients with severe aplastic anemia who have had insufficient response to immunosuppressive therapy, and it is not indicated for the treatment of myelodysplastic syndrome. Then, for the last medication, Tavalisse, is indicated for the treatment of thrombocytopenia in adult patients with chronic ITP who have had insufficient response to a previous treatment. To take a step back for the mechanism of action, for these... so Doptelet, Promacta, and Mulpleta, which will go on, on the other slide, in a second, are oral thrombopoietin receptor antagonists, excuse me, agonists, that induce proliferation and differentiation of the megakaryocytes that I spoke about earlier in the bone marrow progenitor cells. So, this, obviously, causes an increase in platelets.

On the next slide here, we have Mulpleta, and we have Nplate. So, Mulpleta is indicated for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure. Nplate treatment of thrombocytopenia in patients with chronic ITP who have failed to achieve an adequate response with corticosteroids, immunoglobulins, or splenectomy. It should only be used in patients with ITP whose degree of thrombocytopenia and clinical conditions increases their risk of bleeding. It is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome or any cause of thrombocytopenia other than chronic ITP, and it should not be used in an attempt to normalize platelet counts.

On the next slide here, we do have the dosing and availability. Again, this will go on to the next two slides. As I give you a chance to kind of look at the dosing and titration, I will give a little bit of overview information. As

you can see, all medications here are available as tablets, with the exception of Nplate, which is a subcutaneous medication. For pediatrics, safety and efficacy have not been established in patients for any product in this category with the exception, sorry, I just lost my place there, of Promacta for the treatment of ITP in patients less than one year of age. In terms of geriatric patients, clinical studies did not, for Mulpleta and Doptelet, did not include an adequate number of patients to establish a difference, and in clinical studies of Promacta and Tavalisse, no overall differences were observed. Nplate dose adjustment in the elderly may be needed due to an increased prevalence of hepatic, renal, and cardiac impairment. For patients who are pregnant, there is insufficient data on the use of Doptelet, Promacta, and Mulpleta in pregnant women to inform a drug associated risk to the fetus. Nplate is a category C, and while there is no available data for Tavalisse in pregnancy, based on findings in animal studies, use of this medication during pregnancy may cause harm to the fetus.

So, on the next slide, the last medication, Promacta, is here, as well, again, with the dosing, the titration schedule, and availability. To continue over, I guess, special populations, for hepatic and renal impairment in this class, the initial dose of Promacta should be reduced when treating patients with chronic ITP. No dose adjustments are needed for Doptelet, Tavalisse, in patients with hepatic impairment. No clinical studies have been conducted for Nplate in hepatic impairment. For renal impairment, no dosage adjustments are needed for Doptelet, Tavalisse, or Mulpleta, and no clinical studies have been conducted for Nplate. Lastly, there is an interesting side note to consider, a reduction in the initial Promacta dose may be needed for patients of Asian ancestry, specifically Chinese, Japanese, Taiwanese, and Korean, and for patients who have hepatic impairment, as well.

On the last slide here, so to kind of bring it all together, according to the guidelines of the American Society of Hematology in 2011, for adults, treatment for a newly diagnosed patient is considered a platelet count of less than 30×10^9 . Treatment decision should consider the presence and severity of bleeding, the rapidity of desired platelet count rise, and the possible adverse effects. In the management of adults with ITP, firstline treatments include longer courses of corticosteroids, which would be...

such as prednisone, and should be tapered off over short courses of corticosteroids or IVIG. IVIG may be used with corticosteroids when a more rapid increase in platelet is necessary. Either IVIG or anti-D may be used as a firstline therapy if corticosteroids are contraindicated. If IVIG is used, the dose should be initially 1 gm/kg, and it may be repeated, if necessary. The guidelines recommend splenectomy for patients who are unresponsive to, or relapse after, initial corticosteroid therapy. Thrombopoietin receptor agonists may be considered for patients at risk for bleeding who have failed at least one other therapy and who relapse after splenectomy or have contraindication to splenectomy. These receptor agonists may also be considered in patients at risk for bleeding who have not had a splenectomy and have failed one line of therapy, such as corticosteroids or IVIG. For adult patients after splenectomy, no treatment is recommended if the platelet count exceeds 30×10^9 , and keep in mind fostamatinib was not available at the time of the guideline development, and that is Tavalisse. Any questions?

Lisa Chew: Any questions from the committee members? No. So, we do have one stakeholder, Dr. Klein. Alright. Please state your name and who you represent, and you will have three minutes for your comments.

Sarica Klein: Good morning, I'm Sarica Klein. I'm with Dova Pharmaceuticals as an MSL, and I wanted to go into a little bit about Doptelet, which is our product. So, Doptelet, which is avatrombopag, was approved almost a year ago, May 21st, 2018, for the treatment of thrombocytopenia in adult patients with chronic liver disease scheduled to undergo a procedure. So, as was just mentioned, thrombocytopenia is common in patients with CLD and increases in severity with worsening liver disease. It presents a significant challenge in patients with CLD who require multiple invasive procedures that carry a bleeding risk. In fact, several medical societies do suggest a platelet count of above 50 to conduct these procedures. The safety and efficacy of avatrombopag were established in two identical randomized double-blind placebo-controlled trials. Adults with CLD and severe thrombocytopenia who were scheduled to undergo a procedure were divided into two cohorts according to baseline platelet count. The low baseline cohort, which were those patients that had less than 40,000, received avatrombopag 60 mg or placebo versus the high baseline cohort, which were those that had between 40 and 50 baseline platelet

count. Those patients received avatrombopag 40 mg or placebo. Treatments were administered on days one through five, and patients were scheduled to undergo the procedure five to eight days after the last dose. In both of these trials, avatrombopag significantly reduced the need for platelet transfusion or rescue procedures for bleeding, which was the primary endpoint compared to placebo. In the pooled analysis of both studies, 66.9% of patients treated with avatrombopag 60 mg met this primary endpoint compared with 28.6% of placebo treated patients. Similarly, 88% of patients treated with avatrombopag 40 mg had a response compared with 35.8% of placebo treated patients. Results of key secondary endpoints also support the efficacy of avatrombopag over placebo. A significantly greater portion of patients actually achieved greater than 50,000 platelet count on procedure day. Overall, the treatment emergent adverse events were similar between avatrombopag and placebo treated patients. The most common were pyrexia, abdominal pain, nausea, headache, fatigue, and peripheral edema. There was one portal vein thrombosis in an avatrombopag treated patient. As you know, the TPLRA's have been associated with thrombin and thromboembolic complications in patients with CLD. Portal vein thrombosis has been reported in patients with CLD treated with TPLRA's. In conclusion, avatrombopag is a viable alternative to platelet transfusions in patients with thrombocytopenia and CLD prior to a scheduled procedure. I'd love to entertain any questions, if there are any.

Lisa Chew: Any questions from the committee? Alright. Thank you, Dr. Klein. Ryan, would you like to go through the policies?

Ryan Pistorosi: This is Ryan Pistorosi, and we'll be walking through the TPO Apple Health Policy. On the next slide, you will see we finally have more indications and more products. So, the way that we've organized this is based off of their FDA labels. So, as you saw in Umang's presentation, there are a few different products that are approved with different indications. The way we structured this policy today is to walk through the different disease states, and these drugs could be used for any of these disease states, because they do have the FDA approval. So, we'll be going from ITP to aplastic anemia, then to the hepatitis C associated thrombocytopenia,

and then thrombocytopenia in patients with chronic liver disease who are undergoing procedure.

So, for the ITP, our criteria, as proposed, is patients with a diagnosis of chronic immune thrombocytopenia purpura, or ITP, documentation of platelet count less than 30,000/mL, that's the easier way to read that. The third one is, patients have history of failure contraindication, or intolerance to at least one of the following: Corticosteroids or immunoglobulin, or rituximab, or they have a previous history of splenectomy. Then, if they meet this criteria, then the request would be approved for 12 months. For the reauthorization criteria, documentation of a positive clinical response, so if their platelet count increases, they would be able to continue on the medication just showing that there is some efficacy that this drug is working for them and that it's helping resolve it, knowing that this is a chronic condition.

For the aplastic anemia criteria, the criteria are a diagnosis of aplastic anemia, and the only other initial criteria is history of failure, contraindication, or intolerance to at least one course of immunosuppressive therapy. The appropriate immunosuppressive therapy could include, but are not limited to, Atgam or Thmoglobulin, or cyclosporine. So, if they have tried those, and they do not work, or if there is contraindication or intolerance to those, then they would be approved for six months.

Similar to the ITP, criteria, and reauthorization criteria is documenting an increase in platelet count. So, if we see that the medication is working, we would then again approve it for the longer duration of 12 months. For the HCV-associated thrombocytopenia, the patient must have chronic hepatitis C associated thrombocytopenia. So, they must have hepatitis C and then from that hepatitis C, then develop thrombocytopenia that is not secondary to other causes. That it is attributable to hepatitis C, that the thrombocytopenia is preventing the initiation of interferon based therapy. We're limiting the ability to maintain interferon based therapy. So, it is a bit dated, but there are potentially patients out there who are still seeking to use it that may not be candidates for DAA therapy. They are very few and far between, but it is possible. The last criteria that the patient has one of the following: A reason why they cannot use a DAA for

hepatitis C, or they are planning to initiate and maintain interferon based therapy, or they are currently receiving interferon based therapy. So, we don't necessarily anticipate this to be a frequent request, but we want to make sure that we have criteria in place, in case we do get these requests for these very rare and unique patients. Then, if all this criteria is met, it would be approved for six months.

Then, there is a reauthorization criteria after six months. We would need to see positive clinical response, so like we've seen on all the others, an increase in platelet count. And that the patient is currently on the interferon based therapy for chronic hepatitis C. So, one of the reasons that this could occur is that there may be a delay in initiating the interferon based therapy. Usually interferon based therapy is six months to potentially up to a year. So, we would allow for the reauthorization criteria, had they started that therapy. Then, if that is approved, then it would be for the six months, and that should then include the end total of 12 months that they should be on the interferon based therapy for chronic hepatitis C. So, very rare, but we want to make sure that the criteria is in there, in case we do get a request for it.

Lastly is the chronic liver disease patients. So, for this, this is really based off of what's in the FDA label. So, age 18 and older, and it needs to be used for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure. So, this procedure should be within eight days after the last dose. So, no other criteria, as long as they have thrombocytopenia and chronic liver disease and that they are undergoing a procedure for which they need to correct it, we do have this policy in place for them. So, if the criteria are met, the medication would be approved. There is no reauthorization criteria for this, as this isn't really a chronic disease. You don't have chronic scheduled procedures typically, but in case that you do, we would have to approve it each time to make sure that the doses are being scheduled appropriately, relative to when the procedures are occurring. So, we went through four different criteria. So, if you do have questions, we can kind of bounce back and forth between that. Or if you maybe prefer, since we do have similar structures in the future for the ESA's and the colony stimulating factors, if you would like to just stop and do one at a time, we can look at that and then move on, but I'll leave that up to you.

Lisa Chew: Maybe we should go by condition by condition and then... people are okay with it?

Ryan Pistorosi: Okay. So, we'll start with the ITP. So, obviously, if you want to reference which drugs we're talking about, you can flip back to that page where we do have the approved medication. So, that way, you can see, okay. For this one, we're talking about three drugs, Promacta, Tavalisse, and Nplate.

Lisa Chew: Any comments or edits that folks want to make on this initial criteria for ITP? Let's move to the reauthorization criteria. Okay. Let's move on to the next condition, aplastic anemia. Let's move on to the reauthorization criteria. The next condition is HCV-associated thrombocytopenia. Then, the reauthorization criteria. Then, the final, the chronic liver disease policy.

Amber Figueroa: I move that the Apple Health Medicaid implement the clinical criteria listed on slide 51 through 57, as recommended.

Nancy Lee: I second that.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. So, we move on to granulocyte stimulating factors. Sorry. Erythropoiesis stimulating agents. Sorry.

Umang Patel: I had a little bit of a heart attack there. Okay. So, the next topic will be the erythropoiesis stimulating agents. A quick overview, so anemia is a frequent complication effecting approximately 3 million Americans. It's associated with the number of serious disease, such as chronic kidney disease, CKD, diabetes, heart disease, cancer, as wells as chronic inflammatory conditions, like, rheumatoid arthritis and irritable bowel disease. These conditions can cause anemia by interfering with the production of oxygen carrying red blood cells. Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment, itself.

Erythropoietin is a glycoprotein produced in the kidneys that stimulates red blood cell production from bone marrow. It acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the red blood cells. Endogenous production of this by the kidneys is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which, in turn, stimulates erythropoiesis. In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL, and may increase 100 to 1000 fold during hypoxia or anemia. In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia, and anemia in cancer patients may be related to the disease, itself, or the effect of concomitantly administered chemotherapy agents, essentially.

So, the next slide, here we have the first of a few slides to show the indications of the medications in this class. Here, we have Aranesp and Mircerca. None are available in generic. For Aranesp, the indications, there are two main indications, treatment of anemia associated with CKD, including patients on dialysis and patients not on dialysis, and treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, a minimum of two additional months chemotherapy is planned. Now, it is important to note, it is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure wherein whom anemia can be managed by transfusion, for use in patients receiving hormonal agents, therapeutic biologic agents, or radiotherapy, unless receiving concomitant myelosuppressive chemo, as a substitute for red blood cell transfusion in patients who require immediate correction of anemia. Aranesp has not been demonstrated in control trials to improve quality of life, fatigue, or patient well-being. The next medication here, we have Mircerca, which is treatment of anemia associated with chronic renal failure in three subset populations, the first being adult patients on dialysis and adult patients not on dialysis. Pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after a hemoglobin level was stabilized with an erythropoiesis stimulating agent. Keep in mind, Mircerca has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well being. It is not indicated

for the treatment of anemia in patients receiving cancer chemo, and it is not indicated as a substitute for red blood cell transfusion in patients who require immediate correction. To quickly go over the mechanism of action for this, these are glycoprotein manufactured by recombinant DNA that has the same biological effects as endogenous erythropoietin. So, essentially, it's an erythropoiesis stimulating agent similar to the other colleagues in this class, as well. They all, in some way, form either being synthetic, work in a way to essentially, like the title says, stimulate erythropoiesis.

The next slide here, we have Epogen and Procrit. The indications here, treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, to decrease the need for red blood cell transfusion, treatment of anemia related therapy with zidovudine in HIV infected patients with endogenous serum erythropoietin levels of less than or equal to 500 u/mL. Treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and upon initiation, hemoglobin is less than 10 gm/dL, and there is a minimum of two additional months of planned chemo indicated to reduce the need for allogenic red blood cell transfusion among patients with perioperative hemoglobin of greater than 10 to between 10 and 13 who are at high risk of perioperative blood loss from elective, noncardiac, nonvascular surgery. It is not indicated for use in patients receiving hormonal agents, just like its other colleagues in this class. Patients receiving myelosuppressive therapy when the anticipated outcome is a cure or in whom anemia may be managed by transfusion. As a substitute for red blood cell transfusion, patients undergoing cardiac or vascular surgery, or for patients who are willing to donate autologous blood preoperatively. It has not been demonstrated in the controlled clinical trials to improve quality of life, fatigue, or well-being, as well. Before we go on to the next slide, this class does carry a black box warning. And it is important to note that. Patients on ESA's are at an increased risk of death, myocardial infarction, stroke, a venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Patients with CKD experience greater risk for death, serious adverse CV reactions and stroke when administered. In cancer patients, ESA's shorten overall survival and/or increase the risk of tumor progression. Additionally, Epogen and

Procrit, and its biosimilar Retacrit increase the rate of DVTs in perisurgical patients not receiving prophylactic anticoagulation, deep vein thrombosis prophylaxis should be considered for these perisurgical patients. As a consequence, there is a REMS program. Previously, the FDA required darbepoetin to be prescribed and used under a REMS program when used for patients with cancer; however, the REMS requirements for these agents were discontinued in April of 2017.

Then, to continue on the last indication for Retacrit, here we have the treatment, as you can tell the indications are very similar treatment of anemia associated CKD in patients on dialysis and not on dialysis to decrease the need of red blood cell transfusion. Treatment of anemia due to zidovudine, treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and reduce the need of allogenic red blood cell transfusion among patients with perioperative hemoglobin ranging between 10 to 13.

On the next slide here, we have the dosing. I won't go over the specific dosing for each one, but as you can tell, it is stratified based on its indication. I will give you all a minute to review it for the next two slides.

And on the next slide here, we have the availabilities, either single dose, multidose vials, or prefilled syringes that can also be available in autoinjector form.

It is important to note that Epogen, Procrit, and Retacrit, the last two rows there, all contain... all formulations contain albumin, just as an FYI.

So, to go over the guidelines, there are multiple governing bodies, the first being the National Comprehensive Cancer Network, NCCN, guidelines in 2018, state that ESA's are associated, again, with an increased risk of thrombosis, decreased survival, and shortened time to tumor. Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin levels sufficient to avoid transfusions, to prescribe according to the FDA guidelines, and to obtain patient consent. This should be discontinued once the course of chemotherapy has been completed and anemia resolves. There is not enough evidence to

support the use of ESA's for the treatment of anemia related to myelosuppressive chemotherapy with curative intent in patients receiving non-myelosuppressive therapy or patients with cancer not receiving therapy. According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative in '07, each ESA is effective in achieving and maintaining target hemoglobin levels. They recommend a level of 11 to 12 for dialysis or nondialysis patients with CKD and to avoid hemoglobin levels exceeding 13 g/dL. The FDA published a safety communication regarding a more conservative dosing approach to ESA's in patients with CKD due to increased risk of CV events. They warned an increased risk, again, of death, CV events, strokes in patients when their hemoglobin levels were greater than 11; however, no clinical trials have been performed, which identified a hemoglobin target level or ESA dose that would not increase these risks. For PEG-Epogen, Mircera, it is approved for the treatment of anemia due to CKD in adult patients that are both receiving and not receiving dialysis. It is not indicated for the correction of anemia in cancer patients. For Retacrit, it is the first FDA approved biosimilar. It was approved for the treatment of anemia, again, due to CKD in patients on dialysis and not on dialysis, and for allogenic red blood cell transfusion. That is just the important note, it was the first biosimilar.

On the next slide here, according to the American Society of Clinical Oncology, and the ASH 2010 joint guidelines, before initiating therapy for anemia in a patient with cancer, consideration should be given to the risk of thromboembolism, the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent. While the FDA label now limits the indication for ESA use in patients receiving chemotherapy for palliative intent, no study has evaluated outcomes of the ESA therapy by subgroups. The optimal hemoglobin level at which to initiate ESA should be between 10 to 12, but it is not definitively determined. As a result, the decision to initiate ESA therapy in patients with anemia should be guided by clinical judgment, consideration of risk and benefits, and patient preference. When warranted by clinical conditions, red blood cell transfusion is an option. Evidence does not exist to support improved effectiveness or safety with alternative starting doses, dose schedules, or dose modifying schedules, starting and modifying dosage should follow the FDA dosing

guidelines, and the product information of each ESA. It should be discontinued when chemotherapy is concluded. Assuming an appropriate dose increase has been attempted in non-responders, as outlined in the FDA approved label, ESA therapy should be discontinued if there is less than a 1 to g/dL increase in hemoglobin or no decrease in transfusion requirements after six to eight weeks. Non-responders should be investigated for underlying tumor progression, iron deficiency or other etiologies. These guidelines recommend against the use of ESA's for the treatment of anemia associated with malignancies who are not receiving concurrent myelosuppressive chemo, except for patients with lower risk of myelodysplastic syndrome to avoid transfusions, and they maintain that all ESA's are equivalent with respect to safety and efficacy. Any questions?

Lisa Chew: Any questions from the committee members? There were no stakeholders for this class.

Ryan Pistorosi: Alright. I'll be walking through the ESA Apple Health policy. So, the way that we structured this is, we have three policies that we'll be reviewing, and these are the indications for these policies. So, the first two are specific to specific conditions. So, we have got the policy on anemia associated with chronic kidney disease. The next would be the anemia of prematurity for patients who are less than six months. And then, we have the general anemia policy, which is kind of the catch all policy that is listed for all these indications. And if you'll see, you now, within that, we've got a lot of the ones that were referenced by Umang and the NCCN guidelines. So, patients on chemotherapy where the intent of treatment is palliative, not curative, or for the myelodysplastic syndrome to reduce transfusion deficiency. So, that's kind of just a, a general catch all. So, you'll see kind of what that criteria is and why it's different from some of the other ones when we get to that slide.

On the next slide are the list of the products. So, rather than doing what we did on the previous slides and list the indications and products together, otherwise, it would be like trying to read a newspaper with the real fine print up there. So, we just split that all. The intent of this slide is just to say the conditions where the products are appropriate or for the approved indications.

So, let's start with the anemia associated with chronic kidney disease policy. So, for this one, diagnosis of chronic kidney disease, the most recent hemoglobin level is less than 10 g/dL, and the documentation of adequate iron stores as indicated by current, meaning within the last three months, serum ferritin level greater than or equal to 100 mcg/L, or serum transferrin saturation greater than or equal to 20%. So, if that criteria is met, it would be approved for six months. Then, for the reauthorization criteria, if they have continued hemoglobin level less than 11 g/dL, so if they start out below 10 and then get up but are not quite at the appropriate level, they still have anemia, as defined by now 11 or lower, they can continue to receive it. And if there is documentation of positive clinical response, such as increase in platelet count, as submitted by prescriber, then it would be approved for 12 months. So, we can stop here and look at just this policy before we move on to the next one. Since, I think it's easier to kind of go in stages rather than do all of them at once and then go back and have to re-review. So, unless there are other comments otherwise?

Susan Flatebo: The first bullet continued, hemoglobin level than 11. So, if they have... if they come to the clinic and they have 11.1, you're going to hold it, but does that mean that you have to start all over? You... does this... you're saying they have to discontinue it?

Ryan Pistorosi: So, that's a good question. If they came in at 11.1, would we discontinue it? So, in order to prevent that from happening, do you have an idea for how you may want to structure, like, 11.5 or 12? Is there some idea for, like, kind of to say, if they do get over and they're not anemic, maybe there are other things that they are doing relative to anemia that they're able to resolve.

Susan Flatebo: In my mind, I don't think you would necessarily want to stop, but you would, of course, want to hold that dose. I don't think you would want to have to reinitiate this person. Maybe the dose is too high, because I think it does have in the package insert about decreasing the dose by 25% if they do approach 11 or get above 11. I don't know if you would necessarily just want to decrease it, because maybe it's working for this patient. Maybe they were less than 8. Now, they're above 11. They just

need a dose adjust of the Aranesp or the Procrit or the ESA agent. I don't know if we could have, like, verbiage to say how often the CBC or the hemoglobin levels should be checked, but as long as they're within goal range, can continue.

Ryan Pistoresi: So, do you have an idea of what goal range is? I mean, so if you see someone in practice, and they are at 11.1, you would hold the dose, not necessarily at that authorization, but you would want to be aware of the need to continue it. I'm trying to think, if that were to happen then they could potentially be denied and then to have to go back to that and then just be checking the iron stores and they were at 10 or lower.

Susan Flatebo: I think your goal would be, of course, to be less than 11, but you may have, like, outliers where they could be above 11 at a certain point in time, but I don't think you would necessarily want to stop the ESA agent, because maybe, like I said, maybe it is working for this patient, but maybe you could just word it ongoing hemoglobin monitoring with dosing adjustments, as needed. I just don't think we should be saying that you would want to necessarily stop it just because they have one hemoglobin above 11.

Amber Figueroa: I'm wondering if we could just change, because correct me if I'm wrong. This is a medication that's used chronically with CKD patients. So, you may hold it one time, but the next time they come for dialysis, you're gonna give it to them, based on their results. So, I'm wondering if we could just pull out, for the reauthorization criteria, the continued hemoglobin level less than 11, and just do the documentation of positive clinical response, but the provider isn't going to continue to give it, if they don't need it. That's my thought. They're looking at those things all the time and holding, reducing.

Susan Flatebo: And I would say maybe if, like, they have continued hemoglobin level above 11 for six months, maybe then you would say, yeah. It should be discontinued and the patient would need to be exactly decided whether they want to reinitiate them, but again, they would have to start over and be less than 10 to actually start over.

Ryan Pistorosi: So, one of my thoughts is maybe changing from continued hemoglobin less than 11 to hemoglobin less than 11 on average in the last three months. That way, if there is one that is above 11 but then the rest of the time is underneath that, and if it is an average, then if there are multiple readings above 11, then the average would then be suggestive of above 11. That way, if they are above 11, they can hold it, and then bring that average within the last three months or six months to be in that range, which sounds like it's the goal range for therapy. So, maybe an average rather than a one time number may fit better?

Amber Figueroa: That's what I think, because of course, you're not going to want to, you're not gonna give it if they're above 11, because it's not safe, but then, at the same time, at least you're monitoring them and making sure that their hemoglobin is where you want it to be. Then, of course, you could have something adjust doses, as needed, to keep them below 11.

Ryan Pistorosi: Right. So, with this as an average, then that will also prompt the provider to have numerous kind of check-ins to see where they are. I mean, if they have a one-time point, if they're only checking it once, then if they are at 11, then this would kind of prompt them to maybe check it more often, potentially. I mean, I'm just trying to think about how this would... how requests may come in. Since I don't do the authorization requests, I don't know what they typically look like or how often these are being checked, but I think maybe an average may be a compromise to kind of what, what you were thinking, and let me know if that works, or if you want to set... I think you also said six months. If you think maybe an average over six months would be better, we can look at that, as well.

Amber Figueroa: I think an average is too complicated. I would say may... if you keep it the initial criteria for only six months, then I would say a level less than 11 in the previous... at one point in the previous three months, or if you change the initial criteria to approve for 12 months, then you can adjust that and one level of less than 11 in the last six months or three months. I think an average is too complicated. It requires too much mentation.

Ryan Pistorosi: So, let's update this to say hemoglobin level of less than 11 once... at least once, maybe not just say once, because if it's twice...

Amber Figueroa: Documented.

Ryan Pistorosi: ...documented in the previous three months. Okay.

Lisa Chew: This is a minor point, I think, but the increase in platelet count doesn't really apply to this, I think. It's an increase in...

Ryan Pistorosi? Yeah. I think that may have been an error. So, documentation of positive clinical response, as demonstrated by the prescriber. So, if it's not platelet count, like it was for the TPO's, then I think that would be fine.

Susan Flatebo: you could say documentation of positive clinical response, as evidenced by decrease in blood transfusions.

Ryan Pistorosi: As an example. Yeah.

Lisa Chew: Are committee members comfortable with this wording? Okay. So, we can move on to the next condition?

Ryan Pistorosi: So, the next condition is the anemia of prematurity policy. So, for this one, documentation of refusal of transfusion due to religious or cultural reasons, and the patient is less than six months of age, and the most recent hemoglobin level is less than 10 g/dL. So, if they meet this criteria, the request would be approved for three months.

For the reauthorization criteria, the patient continues to be less than three months of age, and the hemoglobin level is less than 11, since this is not a chronic one, I don't know if we need to have that same language that we just discussed. So, maybe just leave it as the 11. Then, document positive clinical response, we can remove that e.g. And I don't think we need to have the same one, as documented by fewer transfusions, because they're refusing transfusions for cultural or religious reasons. Then, if they are approved, then it would be approved for just three more months, because then they would be over six months of age.

Leta Evaskus: Do you want to use the same example in this one, as we did for the previous, for the third bullet? No? Okay.

Lisa Chew: Are committee members comfortable with the initial and reauthorization criteria for this? Okay.

Ryan Pistorosi: Alright, for the general anemia policy, so this one is the general one that includes a lot of indications. So, if they have any of the indications listed on this slide, they only need one. Then, the only other criteria with the general anemia policy is that they have to have a most recent hemoglobin of less than 10, so similar to what we saw in the other ones. We can remove the documentation of positive clinical response from this, since this is an initial criteria, not a reauthorization criteria. So, I think I added it to one too many slides. So, then, if that criteria is met, it would be approved for three months. Then, if they continue to have anemia, and they do the reauthorization request, that criteria is the level less than 11. So, we can change that criteria to match what we had for the chronic kidney disease where it says level less than 1 within the last three months... level less than 11 in the last three months, and documentation of positive clinical response where we can also include the decrease of blood transfusions. Thank you, Leta.

Lisa Chew: Is everyone comfortable with the general anemia policy, that it's?

Nancy Lee: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 71 through 77, as recommended.

Constance Huynh: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Now, we can get to G-CSF.

Umang Patel: Perfect. Thank you. So, the next topic here are granulocyte colony stimulating factors, or colony stimulating factors for Apple Health PDL. In terms of... so just an overview of the disease state. Febrile neutropenia is a myelosuppressive chemotherapy can induce neutropenia, defined as less than 500 neutrophils per mL, or less than 1000 neutrophils per mL,

and if predicted to climb to less than or equal to 500 during the 48 hours after the dose. Febrile neutropenia, which is accompanied by a temperature greater than 38.3 degrees Celsius orally or greater than 38 degrees Celsius over one hour, which is a dose limiting toxicity of chemotherapy. This can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad spectrum antibiotic use, which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes. The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported. CSF are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and improved relative chemotherapy dose intensity. So, in terms of biosimilars, in 2018, the FDA approved biosimilars Nivestym and Fulphila, the reference products are Neupogen and Neulasta, respectively. Biosimilars must demonstrate there are no clinically meaningful differences in safety and efficacy from the reference product; however, small differences in clinically inactive compounds are permissible. Currently, biosimilars are not considered interchangeable products. Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection. Neupogen, Nivestym, Zarxio, Neulasta, Fulphila, and Granix are granulocyte colony stimulating factors, and Leukine is a granulocyte macrophage colony stimulating factor. Colony stimulating factors act on the hematopoietic cells and stimulate proliferation, differentiation commitment, and some end cell functional activation.

On the next slide here, we have the various indications for the medications in this class. None are available in generic. The various indications are cancer patients receiving myelosuppressive chemotherapy to reduce the incidence of infection, acute myeloid leukemia patients receiving chemotherapy, bone marrow transplant, peripheral blood progenitor cell collection and therapy, severe chronic neutropenia, and hematopoietic syndrome of acute radiation syndrome. Now, I kind of went over the mechanism of action, but just to kind of break it down for all of these, Leukine is a recombinant human GM-CSF produced by recombinant DNA technology in yeast, which triggers proliferation and differentiation of hematopoietic progenitor cells. Neupogen, Nivestym, RCO, Neulasta, Fulphila, and Granix are G-CSF's

that are produced by recombinant technology that uses E.coli that acts on hematopoietic cells by binding to specific cell surface receptors, stimulating differentiation, commitment, proliferation, and it stimulates the cell growth and development of neutrophils. Nivestym and Zarxio, as mentioned earlier, are biosimilars for Neupogen and Fulphila.

On the next slide here, we have the dosing and availability. Again, I won't go over each specific dosing, as you can see they are weight based dosing, and it is stratified by indication, but I will give you a few minutes just to see, along with the availability on the right hand side.

Continued on the next two slides, we have Neulasta and Fulphila's dosing and availability, again, stratified by dosing by indication. Lastly, we have Leukine with its dosing and availability for its indications, as well.

So, to go over the guidelines, the NCCN guidelines in 2018 stated there was less evidence available to support the therapeutic use of CSF for febrile neutropenia, as an adjunct to antibiotics compared to prophylactic use. The guidelines recommend therapeutic treatment based on the patient's prophylactic therapy use. Safety data appears similar between Neupogen and Neulasta, and the subcutaneous route is preferred for all five agents. To date, there are insufficient head to head comparative studies of the clinical benefits of G-CSF and GM-CSF. Subcutaneous Neupogen, Zarxio, Granix, and Neulasta have a category 1, and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia. Neupogen, Zarxio, and Granix can be administered the day after chemotherapy up to three to four days after chemo, and through post-nadir recovery. In terms of Neulasta, based on data from clinical trials, it should be administered the day after chemotherapy; however, administration up to three to four days; however, administration up to three to four days after chemo is also reasonable, according to guidelines. There is evidence to support the use of chemotherapy regimens every three weeks with Neulasta. Efficacy data exists for Neulasta in chemo regimens given every two weeks. Insufficient data to support dose and schedule of weekly chemotherapy regimens. Therefore, the use of Neulasta should not be used. Since Neulasta is longacting, patients who receive prophylactic Neulasta should not receive additional CSF. For patients who have not received

prophylactic CSF, the guidelines recommend an evaluation of risk factors related to infection complications or poor clinical outcomes. If risk factors are present, then CSF should be considered. In terms of Leukine, no longer recommended for prophylactic use of CSF in patients taking chemotherapy and radiation currently, concurrently has not been studied. Therefore, NCCN guidelines do not recommend CSF in such patients.

Continuing the guidelines, Neupogen, Zarxio, and Leukine have a two-way recommendation for therapeutic use and can be used until post-nadir, absolute neutrophil count or the ANC recovery to normal or near normal levels. Granix and Neulasta have only been studied for prophylactic use. These guidelines stratify patients into three risk groups based on the chemotherapy regimen and patient related risk factors, the first being high risk, which is greater than 20% risk of developing febrile neutropenia. They recommend patients receive prophylactic CSF regardless of intent of treatment. Intermediate, which is 10 to 20% risk of developing febrile neutropenia, and they recommend individualized consideration of CSF based on the likelihood of developing febrile neutropenia, consequences of developing it, and implications of interfering with chemotherapy. Lastly, low risk, which is less than 10% risk. It does not recommend the routine use of CSF in patients with low risk of developing febrile neutropenia due to lack of cost effectiveness and availability of alternative treatments. However, choosing to administer CSF maybe considered if the treatment is curative or adjuvant, and the patient is at serious medical consequences of febrile neutropenia. Biosimilars, in general, NCCN recommends Zarxio in the same instances as Neupogen; however, they do not recommend switching between the biosimilar and the originator product. The guidelines recommend Neupogen, Zarxio, or Granix for allogenic hematopoietic cell mobilization and for granulocyte transfusion. The guidelines state there is insufficient data for consideration with regard to Nivestym and Fulphila. Therefore, no recommendations were made.

On the next slide here, according to the American Society of Clinical Oncology in 2015, they note the availability of these agents to reduce the duration and severity of neutropenia and febrile neutropenia. No recommendation regarding the equivalency of the two colony stimulating

agents, granulocytes CSF, and GM-CSF. Neulasta, Neupogen, Zarxio, and Granix can be used for the prevention of treatment related febrile neutropenia. The choice of agent should be based on the clinical situation, convenience, and cost. The recommendations for the use of CSF are primary prophylaxis, include the prevention of febrile neutropenia in patients who are at high risk based on age, medical history, disease characteristics, and myelotoxicity of a chemotherapy regimen. They recommend the use of CSF when the risk of febrile neutropenia is greater than or equal to 20% starting with the first cycle and continuing through subsequent cycles of chemo. They take factors into consideration, concerns such as optimal chemo regimen, individual patient risk factors, and the intention of treatment that is curative, prolongation of life, or symptom control and palliation. A recommended secondary prophylaxis with CSF for patients who experience a neutropenic complication for a prior cycle of chemo, for which primary prophylaxis was not received, in which a reduced dose may compromise disease free overall survival or treatment outcome. CSF should not be routinely use for patients with neutropenia who are afebrile or used as an adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. They go on to further state that CSF should be considered in patients with fever and neutropenia who are at high risk for infection related complications, or who have prognostic factors that are predictive of poor clinical outcomes. High risk features included expected prolonged greater than ten days and profound neutropenia ages greater than 65 years, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction, invasive fungal infection, or being hospitalized at the time of development of fever.

Lastly, they state CSF can be used during or after chemotherapy or with plerixafor to mobilize peripheral blood progenitor cells, depending on the type of cancer and transplantation. CSF should be administered after autologous stem cell transplantation and may be administered after allogenic stem cell transplantation. They recommend Zarxio, future biosimilars may be used for the prevention of neutropenia. They recommend that the choice of agent depends on, again, convenience, cost, and clinical situation. Dosing and administration for Zarxio are identical for Neupogen. Any questions?

Lisa Chew: Thank you, Umang. Any questions for Umang? We do have on stakeholder, Dr. Sylvia Churchill. So, please state your name, who you represent, and you'll have three minutes.

Sylvia Churchill: Good morning. My name is Sylvia Churchill. I am a pharmacist here in Washington State, and I currently work for Amgen as a health outcomes and pharmacoeconomic specialist. Thank you for the opportunity to comment on the G-CSF class. Currently, only the short-acting agents are on the preferred drug list. There are no longacting agents. The main purpose of my testimony today is to advocate for the inclusion of a longacting G-CSF option to preferred status on formulary. So, Amgen produces both a short-acting and a longacting form of G-CSF, Neupogen and Neulasta. Neupogen is the short-acting, and should be injected daily starting the day after chemotherapy until the absolute neutrophil count returns above 10,000, for up to two weeks of daily injections. Neulasta, or pegfilgrastim, is a longacting G-CSF. It's given as just one injection per chemotherapy cycle. It has a unique elimination rate due to its neutrophil mediated clearance. So, serum concentrations are sustained until that absolute neutrophil count recovers. Then, the pegfilgrastim concentration will decline, as the neutrophil counts go up. Two randomized clinical trials have shown that one dose of Neulasta was as effective as 10 to 11 daily injections of short-acting Neupogen. And please refer to their PI's for indications, dosing, and full safety and efficacy information. As Dr. Patel noted, the NCCN gives Neulasta a class 1 recommendation for use in the prophylaxis of febrile neutropenia, which is the same class 1 recommendation as Neupogen and the biosimilar Filgrastim products. A sad fact is that patients often receive less than the indicated duration of short-acting G-CSF. These once daily injections are administered by the healthcare, which necessitates the patient coming into the office on a daily basis, and this is at a time that they are likely suffering the worst side effects of their chemotherapy regimen. They may not have adequate caregiver support, or they may lack reliable transportation. In fact, two retrospective claims analyses showed that less than 10% of patients received the recommended duration of eight or more days of therapy, and this subtherapeutic use of a short-acting G-CSF was associated with a higher incidence of febrile neutropenia, and a higher risk of hospitalization. So, in line with current ASCO recommendations, please allow the oncologists the option to select from

a short-acting or a longacting G-CSF based on the provider's knowledge of that patient's individual situation. Please consider the inclusion of a longacting G-CSF action to preferred status on formulary. Thank you, very much, and I am happy to answer any questions.

Lisa Chew: Thank you, Dr. Churchill. Any questions? No? Okay. Thank you.

Ryan Pistorosi: We'll be walking through the G-CSF Apple Health Policy. So, on the first slide, we have broken it out between the indications that are approved for the short-acting products, which are listed here. So, you may see that these are relatively long. That's because this is how they are written on the FDA label. So, you'll see that within these long indications are some of the actual disease states. So, in that first one, you see the febrile neutropenia. In the second one, you'll see the AML. Further down, you'll see the bone marrow transplant. So, we just were able to copy the exact language from the FDA label, but when we go through the policies, they'll be a little bit more clear about which conditions they are specific for and hopefully, that'll be a little bit more clear once we actually go through those policies.

The second slide is the list of the indications that are approved for the longacting. So, we'll see that there are only two here relative to the five that were on the last one. And then on the next slide are the list of the products. So, you'll see from here that we've got the filgrastim and the short-acting and the pegfilgrastim in the longacting. There are a few biosimilars for each. Okay?

So, for the first policy, we have the acute myeloid leukemia policy, and that is the filgrastim may be approved for patients set to receive induction or consolidation chemotherapy for AML, and that's it. So, a short, easy policy to look at. Since this is for the induction, there really is no, like, reauthorization criteria, but if they need to continue be on it, then we would be able to review and allow it.

The first big one that we have is for the primary prevention of febrile neutropenia. So, we will be going over the secondary prevention next, but for primary prevention, on this slide, we have filgrastim. On the next slide will be the pegfilgrastim criteria. You will see that they are relatively

similar. So, for filgrastim, they need to have one of the following criteria. So, a chemotherapy regimen that has a 20% risk for febrile neutropenia, or if the risk is between 10 to 20%, they must have one of the other criteria that is listed in the criteria below. So, if they have the 10 to 20% risk and they've had recent surgery or open wounds, or they have liver dysfunction, or they are over 65, any of those would allow us to approve that medication. And lastly, if the patient has experienced treatment delay of curative chemotherapy due to a dose limiting neutropenic event with the same dose and scheduled plan for future cycles. So, this fits under both the primary prevention and the secondary prevention, but if that is the situation in which, let's say they are less than a 10% risk of febrile neutropenia, but they are experiencing a delay due to that based off of their current regimen, then we would allow approval for that, too.

For the longacting colony stimulating factors, the pegfilgrastim would be approved if there is treatment failure with a preferred short-acting granulocyte colony stimulating factor and one of the following criteria. As you'll see, one of those following criteria are what we just reviewed. So, if they do meet the criteria for the pegfilgrastim and have an inadequate response, they would be able to step into the longacting granulocyte colony stimulating factor.

Did we want to pause and talk about?

Lisa Chew: Why don't we pause here and if people have questions or edits to the policy?

Ryan Pistorosi: And also with the AML one in case you wanted to review that, since we skipped over that quickly.

Susan Flatebo: So, they say that one pegfilgrastim is equivalent to, like, seven to ten doses of the filgrastim. So, when you talk about documented treatment failure, could that also be if the patient is unable to get to the clinic for those number of doses that they would need to have to make up for the one dose of the pegfilgrastim?

Ryan Pistorosi: I mean, certainly they can provide that in the documentation. So, really, this is looking at what is dispensed through the pharmacy and being

taken home. So, if they are unable to self-administer or there is some other issues going on, and that there is justification for using the longacting, we can consider that for those individual patients.

Amber Figueroa: I had a question about poor performance status. What does that mean? I'm a poor performer sometimes, too.

Ryan Pistorosi: So, that is a good question. Let me see if I can do a little bit of research from the policy and see if I can provide better clarification for poor performance status. I believe the poor performance status is if there is a patient with significant disability and just having issues with ambulation, maybe they need care. I can see if there's maybe a more clear way of defining what performance status is.

Susan Flatebo: I know the oncologists, they usually grade the patients on their performance status when they do their documentation. So, performance status of zero means that they have really no limiting activities, whereas if their dose, or if they are performance status two, then they have marked disability. So, they're usually... most chemotherapy patients have that in their chart, what type of performance status they are.

Amber Figueroa: So, it's, like, a functional gradation?

Susan Flatebo: Yes.

Amber Figueroa: Okay.

Ryan Pistorosi: So, common measure is the ECOG performance status measure. So, if someone had poor performance status on that or another similar type of scale that would qualify for that. So, there is some objective measure. There is some validated instrument out there that does monitor that. And there is a threshold for determining good versus poor performance status.

Lisa Chew: I just want to go back to Susan's comment about just patients with difficulty accessing the short-acting. Do you feel comfortable with the way it's worded and Ryan's response is adequate?

Susan Flatebo: I think so. However, most patients, they're not able to afford a prescription. So, they would have to return to the clinic to actually get these injections, and we've had several patients not get their full course of their colony stimulating factor, because they do have transportation issues. Just being able to get the longacting pegfilgrastim makes it a lot easier for the patient to return to the clinic than facing getting to the clinic for five to seven days. So, I don't know if treatment failure if that, yeah. I'm just concerned that the... does that cover that.

Ryan Pistorosi: Okay. So, let me just respond to that. So, for our Medicaid population who we're talking about this policy for, there is no cost share. So, zero dollar cost share at the pharmacy. So, there shouldn't be issues with people not being able to afford the medication when they get to the pharmacy. In terms of your... and we also do have transportation coordination. So, if our Medicaid clients have difficulty accessing transportation and need to see the provider, we do allow for transportation access. So, we do have that both through our programs. In terms of the language for treatment failure, we can look at some of the similar language that we used in other policies. So, maybe instead of treatment failure... so, treatment failure or contraindication or other, yeah.

Constance Huynh: I agree. I think that maybe we could put in compliance on there or as it's looking at the rate of actually being able to get the full treatment regardless of whatever it is, cost or transportation, if they do have those resources accessible to them, because I think 90% of not getting the full treatment is pretty high. So, I would recommend we put treatment failure or compliance on there.

Ryan Pistorosi: So, we will go to the... one more slide, Leta. Okay. So, then, on the second line after treatment failure.

Nancy Lee: maybe a suggestion would be inability to complete course of therapy.

Ryan Pistorosi: Okay. So, treatment failure or inability, okay. With short-acting.

Amber Figueroa: yeah. I agree. And I am sure this one that's a one-time one is buckoo more expensive than the other, but when you look at the cost of repeat

hospitalizations, because they're not completing it, I would bet that it comes out either even or cost savings ultimately.

Lisa Chew: Any other comments regarding the primary prevention policy? We're moving to the secondary prevention.

Ryan Pistorosi: Alright. So, for the secondary prevention of febrile neutropenia, the short-acting products may be approved for only one of the following criteria. So, the member has experienced febrile neutropenia with a previous cycle of similar chemotherapy with the same dose and schedule planned for future cycles. Or, the member has experienced treatment delay of curative chemotherapy due to dose limiting neutropenic event with the same dose and schedule planned for future cycles. Or, the member has experienced treatment delay of palliative chemotherapy due to dose limiting neutropenic event and dose reduction or delay in frequency of subsequent chemotherapy cycles is not recommended. For the second one, also with a longacting granulocyte colony stimulating factors, we can update that so that says treatment failure or inability to complete course of treatment with a preferred short-acting granulocyte colony stimulating factor and one of the following criteria. And as you'll see, the criteria is the same as it was for the short-acting. Inability to complete course of treatment. There we are. Okay? So, we can pause here and see if there is any discussion.

Lisa Chew: I'm just throwing things around. Any other comments or edits to this secondary prevention policy? Are we comfortable moving to the next? Okay.

Ryan Pistorosi: So, on the next one is the treatment of febrile neutropenia. So, this is only approved for the short-acting colony stimulating factors. So, it may be approved for treatment of febrile neutropenia if both of the criteria are met. So, the member has the diagnosis of the febrile neutropenia and they have one of the following high risk factors. So, if they have any of those factors and have the diagnosis, then they would be approved. So, any pause – discussion on this one?

Lisa Chew: Any comments or edits to this policy? Okay. We can move forward to the next.

Ryan Pistorosi: Okay. This one is specific for bone marrow transplant. So, if both of the following criteria are met, the short-acting one will be approved. Again, this is only approved for short-acting. So, it's administered 24 hours after the cytotoxic chemotherapy or bone marrow transplant, and the CBC and platelet counts are monitored daily during the neutrophil recovery.

Lisa Chew: Any comments or edits to this policy? Okay. Next.

Ryan Pistorosi: The next one is the analogous peripheral blood progenitor cell collection and therapy. So, this is also only approved for short-acting. So, if they meet both of the criteria, it would be approved. So, it is administered at least four days before the first leukapheresis procedure, and it is continued until the last leukapheresis.

Lisa Chew: Any comments? Okay. Next.

Ryan Pistorosi: Okay. So, second to last one is the severe chronic neutropenia. So, for this one, it may be approved after confirmation of diagnosis of severe chronic neutropenia by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. So, this is really to confirm the specific diagnosis of severe chronic neutropenia in that it is not neutropenia relative or secondary due to other causes that may be related. So, it would be approved after the confirmation of the correct diagnosis. So, it would also require ruling out some of the other diagnosis saying this is not related to chemotherapy or another condition because of XYZ.

Lisa Chew: Any other comments? Okay.

Ryan Pistorosi: And so the last one that we have for this is on acute radiation exposure. So, the short-acting or the longacting may be approved for hematopoietic subsyndrome of acute radiation syndrome when patients are exposed to lethal doses of total-body radiation but not doses high enough to lead to certain death, as a result of injury to other organs. This is including accidental or intentional total-body radiation of doses between 3 to 10 Gy.

Lisa Chew: Any comments or edits? Okay.

Ryan Pistorosi: Okay. So, we're through with that. So, we're at the motion.

Susan Flatebo: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 93 to 102, as recommended.

Constance Huynh: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. And it is now lunch. Right? Okay. Should we take an hour and come back at, like, 12:50? An hour and 2 minutes?

Ryan Pistorosi: Thank you.

Lisa Chew: Thank you. I'll take the silence as a chance to get started again. So, we are reconvening the committee, and we'll talk about alpha-proteinase inhibitors.

Umang Patel: So, the next topic will be alpha-proteinase inhibitors. The TCR is listed under enzyme inhibitors, systemic. That's why there are two different names here. So, again, a quick overview of the disease state. Alpha-1 antitrypsin deficiency, moving forward will be acronymed as AATD, is one of the three most common fatal genetic diseases in Caucasian adults. Severe AATD affects approximately 70,000 to 100,000 individuals and an estimated 25 million have at least one deficient gene. In adults, it can lead to chronic liver disease in the fifth decade of their life. It may present in neonates as jaundice and hepatitis, in infants as cholestatic jaundice, and in children as hepatic cirrhosis or liver failure. It is the leading cause of pediatric liver transplantation. Approximately 1 to 5% of patients with the diagnosis of chronic obstructive pulmonary disease are predicted to have AATD. As a cause of emphysema, it is seen in nonsmokers in the fifth decade of their life and during the fourth decade in smokers. Onset is accelerated by approximately ten years of cigarette

smoking. Patients with AATD frequently develop dyspnea 20 to 30 years earlier, around age 30 to 45, compared to smokers, with emphysema with normal AAT levels. The primary manifestation is early onset panacinar emphysema, and it most often manifests as slowly progressive dyspnea, although many patients initially demonstrate symptoms of cough, sputum production, or wheezing. Patients with AATD can experience emphysema, hepatitis, liver fibrosis, and cirrhosis.

On the next slide here, so the pathophysiology for this, genetic mutation in the SERPINA1 gene modifies configuration of the AAT molecule and inhibits AAT release from the hepatocytes. This leads to low alveolar AAT concentrations where the molecule would typically protect against antiproteases. In AATD, protease excess in the alveoli damage alveolar walls, resulting in emphysema. The accumulation of the excess AAT in the liver can also lead to destruction of hepatocytes and ultimately clinical liver disease. Since the major biochemical activity of the AAT molecule is inhibition of several neutrophil-derived proteases, the protein has been termed Alpha-1-antiprotease. Approximately 24 variants of the Alpha-1-antiprotease molecule have been identified, all of which are codominant alleles. The common form of AATD is associated allele Z or homozygous ZZ. Individuals with the allele have a 16% likelihood of surviving to age 60 years compared to an 85% likelihood for the general U.S. population. Other genotypes associated with this include the P1S, P1Z/Null, and P1Null. The S gene is more commonly found in people of Spanish or Portuguese descent, while the Z gene is detected more often in individuals of northern or Western European descent.

Moving forward here, we have the medications in this class. None are generic. We have Aralast NP, Glassia, Prolastin-C, and Zemaira. All are FDA indicated for congenital Alpha-1-antitrypsin deficiency with emphysema. We went into the clinical portion, but the mechanism of these, the major biochemical activity, or the AAT molecule, is inhibition of several neutrophil derived proteases and the A1 protease inhibitor plasma derived products are somewhat heterogeneous in their protein composition and chemical structure, and they are indicated as therapy for patients with lung disease in whom severe A1-P1 deficiency has not been established yet. Excuse me, they are not indicated for that.

On the next slide here, we have dosing, availability, storage, and stability here. As you get a chance to just kind of look over this slide, I'll discuss special patient populations. For pediatrics, this class has not been approved for the use in pediatrics. For pregnancy, safety and efficacy have not been established. These agents should only be given to pregnant women if clearly needed. In terms of geriatrics, the studies have not included a sufficient number of patients greater than or equal to 65 years of age to determine if the safety and efficacy is different than the younger population. In terms of hepatic insufficiency, there is no information available for the hepatic insufficiency on this class. Cases of severe A1-P1 deficiency that result in hepatic damage, including cirrhosis, are due to an inability of hepatocytes to excrete a modified form, thus administration of these medications is not expected to have an effect on the course of hepatic involvement. Lastly, for renal dose adjustment, there is no sufficient evidence for renal dose adjustment.

On the next slide here, we have the guidelines from the American Thoracic Society and the European Respiratory Society, AAT Deficiency Task Force. They do not recommend fetal testing or population screening, unless the prevalence of AATD is high, greater than one case per 1500 in the population. Smoking is prevalent, and adequate counseling services are available. Phenotyping is required to confirm AATD and it is recommended that AAT replacement therapy not be initiated without testing. Patients and healthcare providers can obtain a free Alpha-1 test kit. It's a fingerstick test, from the Alpha-1 research registry. The test screens for the most common genotypes that I discussed earlier, and if more extensive testing is needed to determine, both the patient and physician are notified. Test kits capable of detecting S and Z alleles on samples from mouth swabs have made genetic testing easier. These tests will not, however, detect the rare Null alleles. The clinical efficacy of any medication in this class in influencing the frequency, duration, or severity of pulmonary exacerbation has not been demonstrated. Clinical trial data suggest that A1-P1 augmentation therapy may slow the progression of emphysema when lung density is measured by a CT scan. It does recommend therapy with A1-P1 for patients who are deficient in AAT with an obstructive lung disease where obstructive lung disease is defined as an FEV-1 of 30 to 65% of predicted,

or a rapid decline in lung function as a change in FEV-1 of greater than 120 mL/year. The guidelines further state that A1-P1 do not confer benefit in and are not recommended for patients who have A1-P1 deficiency associated liver disease. In addition, these medications are not indicated in patients with lung disease in whom congenital A1-P1 deficiency has not been established.

The final guidelines by the Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines in 2016 were intended to simplify the 2013 ATS and European Respiratory Society guidelines. They recommend the following: AATD testing in individuals with COPD regardless of age or ethnicity; testing in individuals with unexplained chronic liver disease; testing in individuals with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis; parents, siblings and children, as well as extended family members of persons with AATD or others with an abnormal Alpha-1 gene should receive genetic counseling and be offered testing for AATD; diagnostic testing in symptomatic patients, phenotyping is recommended for at least the S and Z alleles. Any advanced or confirmatory testing should include PI typing, AAT level testing, and/or expanded genotyping. Recommends augmentation therapy for all AAT deficient patients who have AAT related lung disease, and they score less than or equal to 65% of pulmonary function test, and anyone with necrotizing panniculitis. For those with an FEV-1 greater than 65% predicted, the recommendation is to discuss on an individual basis the potential benefits of reducing lung function decline while considering therapy costs and lack of evidence. Providers should stress efforts to prevent exposure to tobacco smoke and facilitate cessation in individuals who currently smoke. The group does not suggest IV augmentation therapy for individuals with the following: MZ genotype, lung disease due to AATD who continue to smoke, AATD with emphysema bronchiectasis who do not have airflow obstruction, status post liver transplant, and liver disease due to AATD. Lung volume reduction surgery is not recommended in individuals with COPD secondary to AATD. Any questions?

Lisa Chew:

Any questions from the committee? There are no stakeholders for this drug.

Ryan Pistorosi:

Alright. Before we begin on the alpha-proteinase inhibitor policy, I did want to make a correction from something that I said during the last discussion on the colony stimulating factor. So, when I was discussing about the acute radiation exposure, I mentioned radiotherapy. I meant radiation when I was talking about it, because if there is accidental exposure to an external source, we could cover that. It's not just for people who are undergoing radiation therapy for, like, chemotherapy, but any type of radiation exposure. So, I just wanted to make that clear.

So, now, we can move onto the alpha-proteinase inhibitor policy. Thank you, Leta. So, on this page, we have the indications and products. So, for this drug class, there is only one indication, which is AATD. For our initial policy criteria, it would be for an FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of Alpha-1-antitrypsin with clinical evidence of emphysema. The diagnosis for AATD needs to be confirmed by all of the following, so genetic tests, confirmation of the P1 with the homozygous for the Z allele, so PIZZ, PIZ[null], or PI[null, null]. So, those three phenotypes for AATD, or other alleles determined to be increase of risks for AATD. The test levels for AAT are less than 11 micromoles/L or if they use one of the other assays that have a different cutoff, we provided those here in the policy, as well. So, if there is the immunoturbidimetry, the nephelometry, or the radial immunodiffusion, those cutoffs are listed there, as well. Then, as previously mentioned, the clinical evidence of emphysema, so documentation of emphysema with airway obstruction.

The initial criteria does continue on this slide. So, the prescriber must document that the members FEV in one second, FEV-1, is less than or equal to 65% of predicted. So, as Umang mentioned, for people that over the 65 predicted, there's not really the treatment therapies for them with IV therapy. They have other options for trying to do that. So, if it is 65 or less, this would be approved. It is one of the criteria to be approved. The prescriber must verify that the patient is a nonsmoker. So, if they were previously a smoker that they are going through the cessation of tobacco use. The prescriber must verify the patient does not have antibodies to IgA. The diagnosis was estimated by or established by or in consultation with a specialist in pulmonology, and that the patient's current weight

must be provided in order to authorize the appropriate dose of the drug required, according to the package labeling. So, the dose limit is 60 mg/kg every week. So, if we have the weight, then we are able to authorize the specific amount for that client. Then, for the reauthorization criteria, which we'll get into, just to see if there are any changes in weight for it to be properly dosed. So, if they meet all of the initial criteria, it is approved for six months. For the reauthorization criteria, a documentation of positive clinical response from pretreatment baseline for the Alpha-1 proteinase inhibitor treatment. So, just showing that there is some benefit to the patient using this therapy. That the prescriber must continue to verify that they are a nonsmoker, so that they have not, like, relapsed on tobacco cessation or that they do not become a smoker while on treatment, and that the patient's weight is provided. So, that way we can authorize the appropriate dose. And if all that criteria is met, the request would then be approved for 12 months. Any questions? Okay.

Lisa Chew: Any questions from the committee members or edits to the motion?

Dave Johnson: When you say nonsmoker, what about vaping?

Ryan Pistorosi: That's a good point. So, when we say smoker, we didn't say specific to tobacco use, and smoking and vaping are similar but not the same. So, we would look at maybe potentially expanding it to all tobacco. Or maybe, I guess, you know, you could vape without tobacco. Right? Yeah. I see some heads shaking yes. So, I'm not sure if there's, like, some umbrella term that captures both, smoking, marijuana use, vaping. That could potentially lead to a decline in pulmonary function. Should we consider expanding it to say nonsmoker, nonvaper, non-marijuana use.

Female: I don't know that there is evidence that vaping in the absence of tobacco decreases pulmonary function. The impact of marijuana is equivocal. And looking at the presentation, it looks as if the cigarette piece would really encourage people to quit, not that there was an adverse interaction between the two, but the cessation efforts should be supported. So, it's sort of interesting to... should that be translated into, if someone is unable to quit, they can't get the drug?

Petra Eichelsdoerfer: There is also the element of marijuana can be used via multiple routes, as can tobacco. So, the question there is, do you want to limit to inhalational use, as opposed to edible.

Ryan Pistorosi: So, after this discussion, I have some thoughts about updating the language. So, the prescriber must verify that the patient is a nonsmoker or initiating smoking cessation. Then, we can note that smoking includes inhalation, not edibles.

Virginia Buccola: I just want to comment that I think that if you get into everything that can be smoked, that's a deep hole.

Ryan Pistorosi: That's true.

Constance Huynh: We can also actually say conventional smoking, as a way to narrow it to actually the cigarettes, if that's what we're trying to go after.

Diane Schwilke: I don't think that's what we're after. I think we're trying to make it bigger than just cigarettes.

Constance Huynh: Right, but I think also... so I think what the study was looking at was actually in reference to the conventional cigarettes, and I don't know if what we're trying to do is to then kind of continue to limit the ability to authorize this use of medication. So, my concern is that the programs that we have for cessation currently are for conventional cigarette smoke. Then, to then try to do the patient education for decrease of vaping and marijuana use, I feel is maybe outside the scope of what the study is looking at. So, I would say that I would prefer to use and recommend that we use conventional. So, the prescriber must verify the patient is a nonsmoker of conventional cigarettes or initiating smoking cessation programs.

Ryan Pistorosi: So, to counter that, pipe smoking? I mean, it's difficult... the idea is that there is the alveoli damage that is related. If there is emphysema, are there other issues that could potentially be caused by other types of inhalation of recreational or other drugs. I'm encouraged by this conversation, because I think we're going to eventually find the right language that we want for this policy, but I'm just trying to play the

devil's advocate and say, the idea is not necessarily because they looked at smoking, because that was what approved then. I mean, now we have marijuana in the state and now vaping has taken off and seen exponential use over the last few years. So, because it wasn't approved then, and it wasn't necessarily studied, I don't necessarily know... the safety factor for that is unknown. Really, it's related to the alveoli damage that is caused by conventional smoking.

Nancy Lee: I'm wondering about this as a suggestion, prescriber should stress efforts to prevent exposure to factors that would worsen the lung function. No. Something. Exacerbate alveolar health, function, something like that. I don't know if that's too broad.

Donna Sullivan: So, what about the prescriber must verify that the patient is not a current inhaled recreational substance user or something like that.

Susan Flatebo: I think we should just leave it as, that the patient is not a, a nonsmoker or initiating smoking cessation. It's up to the... I'd say the provider, ordering doctor, to maybe counsel the patient on whether or not they're using other products, as far as vaping. I know I worked in pulmonary rehab for many years. Some of our worst patients with COPD were actually marijuana smokers, and I think leaving that as a nonsmoker, it doesn't specify what they're smoking. It's kind of up to the provider. I don't know if we should get too detailed in that.

Ryan Pistorosi: So, going acknowledge to Dave's original point, vaping may not be the same umbrella as smoking. I think there's a grey area. I mean, I've always thought of vaping as, like, smoking, but I guess technically it isn't. So, would we also say not smoker, non-vaper?

Virginia Buccola: I would want to leave some room for vaping in terms of a harm reduction model. I would imagine that most providers would rather their patients move to vaping rather than a direct cigarette or a direct... so that would make me feel like that might be a little too limit to put vaping in there.

Ryan Pistorosi: So, are you okay with the language as it currently is written? Okay. Thanks.

Female: We just had to [inaudible].

Ryan Pistorosi: Well, we did add the or initiating smoking cessation to the points that were mentioned earlier, that if someone... if they're having trouble quitting and they're trying, that we don't necessarily want to delay a therapy for a genetic condition that is causing emphysema and is effecting their FEV-1. So, we did add that in. So, I think that, in addition to all the other things that we considered, this may be appropriate. Then, when we review cases that come in, and we do see some of this information, we can have that discussion between clinicians and make sure that this is the appropriate therapy for our clients.

Lisa Chew: Any other comments regarding the initial or the reauthorization criteria?

Virginia Buccola: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 113-115, as recommended.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: And any opposed? And the motion carries. Okay. Let's move on to Alinia.

Umang Patel: Right. So, moving forward, the remaining topics will be drug specific. So, they are no longer a therapeutic class review. So, the first one here we'll discuss is Alinia. Just to go over the disease states specific to Alinia are giardia and cryptosporidium. So, for giardiasis, the most frequently diagnosed intestinal parasitic disease in the U.S., and it's caused by giardia lamblia. Diagnosis is done by detection of cysts or trophozoites in the feces, trophozoites in the small intestine, or detection of giardia antigens in the feces. Patients with giardiasis may experience mild or severe diarrhea or, in some instances, no symptom at all. Fever is rarely present. Onset of symptoms is generally one to two weeks after inoculation. Occasionally, some will have chronic diarrhea over several weeks or months with significant weight loss. It can cause failure to

absorb fat, lactose, vitamin A, and vitamin B12. Giardia is passed from feces of an infected person or animal and may contaminate food or water. Giardia lamblia can also be transmitted through anogenital, oral-anal, or digital-anal contact. Person to person transmission may occur in day care centers or other settings where handwashing practices are poor. Effective treatments for giardia infection include metronidazole, tinidazole, and Alinia. In terms of cryptosporidiosis, it's caused by protozoa cryptosporidium parvum. Intestinal cryptosporidiosis is characterized by severe watery diarrhea but may also be asymptomatic and is self-limiting in most otherwise-healthy individuals. Some infected people are asymptomatic and others, symptoms may range from mild to profuse diarrhea with passage of three to six liters of watery stool per day. In some outbreaks involving daycare centers, diarrhea has lasted anywhere from one to four weeks. Dehydration is a major concern, particular for pregnant women and young children and immunocompromised people in whom the infection becomes chronic. Immune status has a strong influence on the severity and duration of symptoms and illness. In people with HIV or other immunocompromising conditions, C. Parvum, infections may be severe, lifelong, and may contribute to their death. The FDA approved Alinia for the treatment of cryptosporidiosis in immunocompetent people.

So, on the next slide here, we have the indication, the dosing, and availability. Before I go into that, just the mechanism of this. It is a synthetic thiazolide anti-protozoal agent for the treatment of cryptosporidiosis and giardiasis. It works by interfering the PFOR enzyme dependent electron transfer reaction, which is essential for anaerobic energy metabolism. So, in terms of indications, it is indicated for again giardia lamblia. Oral tablet is indicated for patients 12 years of age or older. Oral suspension is indicated for patients one year of age or older. It's also indicated for cryptosporidium parvum, which is an oral suspension indicated for patients 1 to 11 years of age. So, again, dosing is stratified by indication. Adult dosing here 500 mg tablet every 12 hours with food for three days, or 500 mg of oral suspension every 12 hours with food for three days. Pediatric dosing is listed for G.Lamblia or C.parvum, and again, it's broken down by if the patient is 1 to 3 years of age, 4 to 11, or greater than or equal to 12 years of age. The availability for this medication are tablets and suspension as mentioned above.

Now, please note the tablets and suspension are not bioequivalent. So, the relative bioavailability of the suspension compared to the tablet is about 70%.

On the next slide here, just to give you an idea of additional information for specific patient populations for pediatrics, as I've mentioned, tablets have not been studied in patients less than 12 years of age. A single Alinia tablet contains a greater amount than is recommended for a pediatric patient less than or equal to 11 years of age. And the oral suspension has not been studied in patients less than a year old. For pregnancy, product labeling for this was revised to comply with the pregnancy and lactation labeling rule and advises there are no data for Alinia in pregnant women to inform of a drug-associated risk. Previously, it was considered a category B, as in beta. For warnings and contraindications, it is contraindicated in patients with hypersensitivity to the specific products or any other product component. To note, tizoxanide is the active metabolite is highly bound to plasma proteins over 99.9%. Therefore, caution should be used when administering this medication with other highly plasma protein bound drugs with narrow therapeutic indices, such as Warfarin. In terms of hepatic and renal impairment, PK studies of this medication have not been performed in patients with renal or hepatic insufficiency, so, using caution with patients in this patient population. In terms of geriatric patients, studies with Alinia, rifaximin for traveler's diarrhea, and tinidazole did not include a sufficient number of patients greater than or equal to 65 years of age. Any questions?

Lisa Chew: Thank you, Umang. Any questions? There are no stakeholders for this.

Ryan Pistorosi: We'll be going through the Alinia Apple Health policy. So, for this medication, there are two indications, but we'll only be reviewing the individual specific products. We're not going to be looking at metronidazole or some of the other options that can be used for these conditions. So, we have giardiasis and cryptosporidiosis. So, the criteria is that they must have a diagnosis of infectious diarrhea caused by one of the following. So, for giardia, it's the patient must also have failed prior treatment with metronidazole for this episode. And an episode is defined as no improvement or resolution of symptoms five days after

completing the regimen. So, five days after they complete the appropriate metronidazole regimen for giardia, if they continue to have these symptoms, that would be considered a failed treatment with that. Or if the patient has contraindication or intolerance to, or culture sensitivity testing showing antibiotic resistance to metronidazole. So, really, kind of stepping through that metronidazole is the firstline treatment. And then, if that doesn't work for the giardia, then the Alinia may be approved. For the cryptosporidiosis, that one doesn't require a trial of metronidazole, but it does require that the patient not be immunodeficient or infected with HIV, and that is from the drug's label. So, if they meet either of those criteria, we may approve the authorization, and the maximum doses are listed there. So, those are the... kind of the equivalent of what Umang presented for the pediatric and adult dosing, just written out per the mg because there is the difference he mentioned in the bioavailability between the suspension. So, the ones for 1 year to 4 years and from the 4 years to 12 years, those are the suspension doses. As you may flip back in your binder to the pediatric dosing. Then, for the adult, so 12 and older, that's a 500 mg or one tablet. So, it would be one tablet twice a day, which is equal to 1000 mg/day. Then, the course of treatment is three days. So, if the patient meets the criteria, they would be approved for a three-day supply. There is no reauthorization criteria for this. So, if they do request it, we would be looking at this initial criteria again.

Lisa Chew: Any comments or edits?

Nancy Lee: I move that the Apple Health Medicaid program implement the clinical criteria listed on slide 123 as recommended.

Amber Figueroa: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. Now, we move on to rifaximin.

Umang Patel:

So, to continue the GI, we'll have Xifaxan here. Again, to review an overview of the disease state, this may sound somewhat similar to the previous medication. This can all be found under the TCR, but for traveler's diarrhea, characterized by more than 2 to 5 loose stools per day. Symptoms can range from mild cramps and urgent loose stools to severe abdominal pain, fever, vomiting, and bloody diarrhea. If left untreated, most bacterial illnesses will resolve spontaneously over three to seven days, and viral infections about two to three. This is most often caused by E. coli followed by C. jejuni, Shigella species, salmonella. Ingesting contaminated food or water is the most common mode of acquisition for these. Approximately 10% of traveler's diarrhea is caused by parasitic infections, which can persist for weeks to months with giardiasis being the most common. So, for the treatment of this, antibiotic chemoprophylaxis for traveler's diarrhea is discouraged for most travelers due to mounting bacterial resistance. Symptomatic self-treatment of traveler's diarrhea includes replacement of fluids, although traveler's diarrhea in adults is not usually dehydrating. Symptomatic treatment with bismuth subsalicylate reduces the number of stools by approximately 50%. Other self-treatment options include synthetic opiates, such as loperamide and diphenoxylate. Antibiotics include fluoroquinolones, however increasing microbial resistance may limit their use, azithromycin, and Xifaxan. Agents no longer recommended due to drug resistance include neomycin, sulfonamides, ampicillin, doxycycline, tetracycline, and trimethoprim.

To continue the overview for irritable bowel syndrome, it's a functional bowel disorder, which can be chronic, relapsing, and often lifelong. It occurs in up to 15% of the population and is up to 2.5 times more common in women than men. Patients present with a combination of symptoms that are typically constipation predominant IBSC, diarrhea predominant IBSD, and/or alternating IBSM. Characterized by symptoms of abdominal pain or discomfort associated with the abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or not be relieved by defecation at least three days per month in the past three months. IBS is a chronic condition without a cure. Therefore, treatment is based on management of patient's symptoms and may require combination modalities. The 2014 American Gastroenterological Association Guidelines on the

treatment recommend Xifaxan and loperamide over no drug treatment in patients with IBSD. Lastly, for hepatic encephalopathy, it occurs in patients with cirrhosis and is characterized by altered consciousness, behavior such as apathy, irritability, disinhibition and motor function, caused by accumulation of nitrogenous substance, primarily ammonia in the blood. In advanced stages, it is referred to as hepatic coma, which may be preceded by seizures. The treatment goal is to reduce the nitrogen load from the GI tract and to improve CNS status. Treatment options include lactulose administered orally or by nasogastric tube or enema, nonabsorbable antibiotics, such as Xifaxan, and protein restricted diets. Antibiotics are usually second-line therapy. Neomycin and paramomycin can suppress the normal bacterial flora in the intestines that produce urease, an enzyme which breaks down urea into CO₂ and ammonia. Xifaxan is minimally absorbed and affects the normal bacterial flora of the intestines, and in severe cases of hepatic encephalopathy, combination therapy can be considered. In clinical trials, 91% of patients also received concurrent lactulose therapy for the management of hepatic encephalopathy.

To go on the next slide, there are various indications for Xifaxan, first being treatment of traveler's diarrhea caused by noninvasive strains of E. coli. Patients greater than or equal to 12 years of age. Xifaxan should not be used in patients with diarrhea complicated by fever or blood in the stool, or diarrhea due to pathogens other than E. coli. It's also indicated for the reduction and the risk of overt hepatic encephalopathy recurrence in patients 18 years of age or older, and it is indicated for the treatment of IBS with diarrhea in adults. Now, as you can see, the dosing is stratified by the indication. So, for traveler's diarrhea, 200 mg three times daily for three days with or without food. For hepatic encephalopathy, it's 550 mg twice daily with or without food. Irritable bowel syndrome with diarrhea is 550 mg three times a day for two weeks. The availability are tablets, as well.

On the next slide here, for special populations, we have pediatrics. So, for traveler's diarrhea, safety and efficacy have only been established in 12 years of age or older. Hepatic encephalopathy it has not been established in less than 18 years of age. IBS with diarrhea has not been established in less than 18 years of age. For pregnancy, no available data

in pregnant women. Teratogenic effects have been observed in some animal reproduction studies. So, warnings and contraindications, it should not be used to treat patients with diarrhea complicated by fever, blood in the stool, or diarrhea secondary to pathogens other than E. Coli, as I mentioned earlier. It has not been shown to be effective in traveler's diarrhea due to, and should not be used if one of these organisms are suspected, C. Jejuni, Shigella, and salmonella. It should be discontinued if diarrhea symptoms worsen or persist more than 24 to 48 hours. It is poorly absorbed in the systemic circulation and should not be used to treat systemic infections. Caution should be used when administering Xifaxan along with a P glycoprotein inhibitor, due to possibility of an increase in the concentration of Xifaxan. Lastly, in terms of hepatic and renal impairment, since it acts locally in the GI tract, no dosage adjustment is necessary for patients with any hepatic impairment; however, there is potential for increased systemic exposure with Xifaxan with severe hepatic impairment. Therefore, caution should be used when prescribing to patients with severe hepatic impairment defined as a Child-Pugh score category C. PK studies for this have not been performed in patients with renal insufficiency. Any questions?

Amber Figueroa: Can you, I didn't hear you say the mechanism of action.

Umang Patel: So, the mechanism of action is a non-immunoglycoside, semi-synthetic antibacterial. It binds to the beta subunit of the bacterial DNA dependent RNA polymerase, causes an inhibition of RNA synthesis in the bacteria. Since it's minimally absorbed, it's concentrated in the GI tract, as I mentioned earlier. Because it's minimally absorbed, it has a low risk of inducing bacterial resistance and a lower incidence of serious adverse effects.

Lisa Chew: Thank you, Umang. Any other questions? There are no stakeholders for this drug.

Ryan Pistorosi: We'll be going through the Xifaxan Apple Health policy. So, for this one, there are the three indications that Umang just reviewed. So, I'll be starting with the hepatic encephalopathy moving to IBS and then to traveler's diarrhea. So, for the hepatic encephalopathy criteria, the patient has to have a history of either the hepatic encephalopathy or liver

cirrhosis. The patient needs to have one of the following. So, they are either currently stabilized on and will continue to use lactulose at a maximum tolerate dose. So, we want them to maximize and use up as much lactulose as they can, or at least that they're able to tolerate, prior to moving onto Xifaxan. Then, if they have history of failure of lactulose at a maximum tolerated dose for at least 30 days, or contraindication, or intolerance to lactulose, they can meet that criteria. So, if they're not able to use it, then they can step through. The patient is greater than or equal to 18 years of age. The dose is less than or equal to 1100 mg/day. There is baseline documentation of serum ammonia or other measures, for which the provider will evaluate the effectiveness of rifaximin for hepatic encephalopathy. So, if all those criteria are met, this would be approved for 12 months.

The reauthorization criteria is, as you've seen before with the other policies, clinical improvement, so documentation of improvement in mental health, a decrease in serum ammonia levels from baseline, decrease in hospitalizations or ED visits, or other predefined clinical criteria, as specified by the provider. So, we want to make sure that this medication is working and having a positive impact, that it is helping to address some of the neurologic effects of hepatic encephalopathy, and the provider is able to really demonstrate any of these criteria. So, it may be something measurable or meaningful, like a reduction in hospitalization or ED visits, or simply a reduction in ammonia levels from baseline, which may be a little bit easier to attribute to this medication. So, upon the rereview after 12 months, if they're able to provide that and show us that the medication is working appropriately, it would be continued for another 12 months. So, we can pause there and do that before we step into the irritable bowel syndrome.

Lisa Chew: Any edits or changes to the criteria?

Ryan Pistorosi: Okay. So, the next one is the IBS-D. So, for this, the initial criteria is history of failure, contraindication, or intolerance to two prior therapies for the treatment of IBS-D. So, those can be antidiarrheal, so like loperamide, antispasmodic, so like dicyclomine, or a tricyclic antidepressant, so, like, amitriptyline. So, if any of those... if they've had two of those previous therapies within those classes. So, it could be, like,

two antidiarrheals, or an antidiarrheal and a TCA. That would then be able to be authorized for this. The patient is greater than or equal to 18 years of age. The dose is less than or equal to 1650 mg per day for 14 days. So, per the FDA label, it's approved for 14 day treatment. The patient has not used more than three courses of this treatment for IBS-D in their lifetime. That's because in all the clinical trials, it has not been shown for more than three courses of therapy. So, three 14-day courses of therapy.

So, if all those criteria are met, it would be approved for one 14-day supply of therapy. If they plan on continuing it for more than that 14 days, it would come back as a reauthorization criteria. So, the reauthorization criteria is documentation of improvement in IBS-D related symptoms from previous courses of treatment. So, if they'd been on, like, an antidiarrheal or a TCA and they still had issues, and then they step into the rifaximin, just showing us that this specific treatment has been effective. Documentation for the rationale of continued use for the rifaximin, and then that the patient has not exhausted the more than three courses per lifetime for treatment of IBS-D. If all those criteria are met, the request would be approved for up to two more 14-day supply. So, up until they reach that third course of treatment. So, we can pause there and see if there are any questions or comments.

Amber Figueroa: So, an initial criteria, it says, has not used more than three courses of treatment. So, let's say someone is coming in from another state. They've already had two courses of treatment, they would still need to meet the initial criteria. So, I think it needs to say no more than two. 'Cuz it's a three max. Right?

Ryan Pistoresi: So, the reason that it says three there for the initial criteria is if someone comes in from out of state, and they've already used all three. So, if they've used two, they would not meet the criteria. They have not used more than three courses. They would have used two. So, they would be Okay. Three or more. That's the key. So, yes. We can say two or more courses. Thank you. Do you like more than two or three or more? Just up to you. You can delete the two or more and then say more. Sorry. And then remove the three and replace it with a two. So, patient has not used more than two courses of treatment. There we go.

Lisa Chew: Any other changes or suggestions?

Ryan Pistoresi: Alright. Hearing none, we can step into the traveler's diarrhea policy. So, for the traveler's diarrhea or noninvasive strains of E. coli, our criteria...

Amber Figueroa: The reauthorization one needs to be fixed, too.

Ryan Pistoresi: You are correct. So, yes, we will update that. Okay. Thank you, Leta. Good catch. Okay. So, for the traveler's diarrhea policy, the patient has failed prior antibiotic treatment for this episode. An episode is defined as no improvement or resolution of symptoms after five days of completing the regimen, or contraindication, or intolerance to two of the following, and those are the azithromycin, the ciprofloxacin, or the levofloxacin. There is culture or sensitivity testing showing antibiotic resistance to all three of the following. So, if there is resistance to the azithromycin or the ciprofloxacin or the levofloxacin. Let me just reread this real quick. I think I may have made a formatting error when converting this over to the PowerPoint. So, I think it's supposed to say that they've failed two of those or they have antibiotic sensitivity to all of those. So, for example, if someone had antibiotic resistance to azithromycin and ciprofloxacin but not to levofloxacin, we would require that they try the levofloxacin but not the other ones in which there is resistance, and I can confirm this by pulling up our Word format, which we used to create these policies and not the PowerPoint slides. So, give me a second and just confirm that.

Emily Transue: I think on the second bullet it would be and, three ands.

Ryan Pistoresi: Yes. Okay. So, while I'm pulling that up, I'll read through the other criteria. Thank you. So, the patient has not previously failed rifaximin for the current episode or has a culture sensitivity testing showing antibiotic resistance to rifaximin, that the patient is greater than or equal to 12 years of age, and that the dose is less than or equal to 600 mL per day for three days. So, these are the 200 mg tablet, not the 550s that we saw for the previous two indications. So, it is a lower dose than what you see for hepatic encephalopathy or the IBS-D.

Lisa Chew: I guess the first two bullets are kind of confusing to me, because you failed the antibiotic treatment, and you have to show antibiotic resistance... 'cuz if you had antibiotic resistance, you wouldn't try those other... am I missing? Maybe I'm missing something.

Emily Transue: I think that would be an or.

Lisa Chew: It would be, should be an 'or.' Yeah. So the patient failed prior antibiotic treatment, that bullet, and then culture sensitivity, those two, it should be 'or.' I mean, I think.

Emily Transue: So, after levofloxacin, I think it would be 'or'. There you go.

Ryan Pistorosi: And yes, I can confirm, that was just an error for, for me when I was doing it. So, yeah. So, these two, those first two are supposed to kind of be one criteria to show have prior therapies been tried or are prior therapies not appropriate. So...

Catherine Brown: I have a question. Do they... they also... it's implied that it has to be E. coli. Correct?

Ryan Pistorosi: I don't think, yeah. So, that's correct. So, we haven't implied in the actual authorization criteria that it is E. coli. And as Umang mentioned, you don't want to use it for, like, the Shigella, salmonella, or campylobacter. Yeah, but it's not, like, one of the criteria that we test for it. So, but when diagnosing someone with traveler's diarrhea, would you do a culture and sensitivity and [inaudible]? So, that should be... so, yeah. We can add that to the policy, as one of the criteria to make it clear.

Amber Figueroa: I think it's clear when it says E. coli policy. It doesn't say traveler's diarrhea policy. So, I think it's clear. And you're asking for culture and sensitivity results.

Ryan Pistorosi: Yeah, but the culture sensitivity results don't necessarily say it's necessarily that bacteria. I mean, when they're filling out a form, you know, or the office staff, they may say, yes. It has resistance, but it

doesn't actually say, you know, what the bacterium is. If you would feel more comfortable if we had documentation...

Amber Figueroa: I think so.

Ryan Pistoresi: ...yes. Okay. So, if we want to have documentation from the providers that says, yes. This is specifically E. coli and not maybe E. coli and campylobacter or E. coli and Shigella, we can add that in as a criteria. Maybe at the very top and just say confirm E. coli. I think just say E. coli, because it's for this specific episode of treatment. So, I think it fits in with that. We'll maybe polish it up when we actually create the final policy that gets published and posted online.

Lisa Chew: Are we comfortable with this slide? Okay. And the reauthorization.

Ryan Pistoresi: Alright. So, for the reauthorization, so requests for renewal or extension beyond the authorized amount will be denied, because that would qualify as a treatment failure. So, unless they are able to provide the following two criteria, we would not allow an extension beyond what the limit is for the course of treatment. So if all other treatment options have been ruled out, and there is culture sensitivity showing that there is no antibiotic resistance to rifaximin, then they could be approved for an extension for that treatment episode, but otherwise, if they're still continuing to have diarrhea related to E. Coli and they've met some of the other criteria, we would recommend that they pursue other treatment options unless those treatment options have run out, and that's why they're doing this request. That's why we have those two criteria built in, to allow exceptions in unique circumstances.

Lisa Chew: Any comments on this slide?

Susan Flatebo: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 132 to 137, as recommended.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. We are scheduled for a ten-minute break. People are shaking their, no, yes? Should we break for 10 minutes, stretch our legs? Or just move on? Okay. We'll just move on.

Umang Patel: Alright. So, the next medication we'll go over is Crysvida. It is a very unique therapeutic class here. So, to kind of give you an overview of the disease state, X-linked hypophosphatemia, which will be abbreviated as XLH moving forward, also known as phosphate regulating endopeptidase on the X-chromosome. It is a dominant genetic disorder and is due to mutations on the chromosome XP22.1. This gene is expressed predominantly in bone and teeth. The mutations in the PHEX indirectly alters the degradation and production of FGF23 by osteocytes and osteoblasts. Excess levels of this act as a counter regulatory hormone and decrease renal phosphate resorption and renal production of 1, 25-dihydroxy vitamin D. This results in an excess of phosphate excretion and a decrease in intestinal phosphate absorption leading to hypophosphatemia. These abnormally low phosphate levels lead to defective mineralization and delayed ossification, resulting in a multitude of symptoms, but most notably rickets and/or osteomalacia. In adults, adult XLH affects approximately 9,000 to 12,000 adults. They experience symptoms, such as arthritis, decreased mobility, bone, joint, muscle pain, ligament, tendon attachment abnormalities, fractures, and softening of the bone. In contrast, therapy in children, for adults with XLH, once a patient reaches adult height and they're epiphyses has fused, the goal of therapy is to manage generalized bone pain and enhanced limited mobility. Crysvida, the approval of this medication represented the first therapy that is directed at the underlying disease process of renal phosphate wasting. So, it acts as an FGF23 blocking antibody by binding to and inhibiting the actions of FGF23, therefore restoring renal phosphate resorption and increasing the serum concentration of 1, 25-dihydroxy vitamin D.

I mentioned adult XLH in terms of pediatric XLH is estimated that it effects about 1 in 20,000 newborns. Most cases are diagnosed in childhood and with clinical presentations in the first two years of life. Diagnosis can be made by a combination of familial history of the disease,

clinical presentation, as well as classic biochemical profile that consists of low serum phosphorous, elevated alkaline phosphatase, and low 1, 25-dihydroxy vitamin D levels. Testing for FGF23 and genetic testing for PHEX is also available; however, these tests are also very inconclusive and not widely used. In terms of clinical presentation, poor bone health, abnormal bone formation, bone pain, low bone density, fracture, short stature, tooth abscesses, tinnitus, bow or knock-knee leg deformities, muscle pain and weakness, and waddling gait. The aim of therapy in pediatric XLH patients is to correct or minimize rickets or osteomalacia and to achieve normal growth. Use of oral phosphate transiently increases the serum phosphate concentration, lowering the plasma ionized calcium concentration, which further reduces the plasma calcitriol concentration; however, this can lead to secondary hyperparathyroidism due to both hypocalcemia and removal of the inhibitory effect of calcitriol on PTH synthesis, thereby aggravating bone disease and increasing urinary phosphate excretion. Therefore, administration of calcitriol is necessary to increase intestinal absorption of calcium and phosphate and to suppress PTH release directly.

In terms of this medication, again, it's indicated for the treatment of X-linked hypophosphatemia in adults and pediatric patients one year of age or older. It is a subcutaneous injection that should be administered by a healthcare professional. The dosing is stratified by both pediatric and adult patients, and it is weight based dosing. I won't go into each specific thing, but the dosing is obviously written out, and the availability are single dose vials in 10, 20, or 30 mg/mL. I'll give you all a second just to take a look at the dosing for your leisure.

Okay. The last slide for Crysvida, just a special populations. For pediatrics, again, the safety and efficacy has been established in patients one year of age or older. For pregnancy, there is no available data for use in pregnancy. If pregnancy occurs, serum phosphorous levels should be monitored throughout the pregnancy. In terms of warnings and contraindications, it is contraindicated with concomitant use of oral phosphate and active vitamin D analogs. Therapy with these agents should be discontinued one week prior to initiation of Crysvida. Patients who have normal or elevated serum phosphorous levels, as well as those patients with severe renal impairment or end stage renal disease are

contraindicated for use, as these conditions are associated with abnormal mineral metabolism. Crysvida carries a warning for hypersensitivity reaction, as well as severe injection site reaction and should be discontinued if these severe events occur. Based on mechanism of action, it can also cause elevation of serum phosphorous to above upper limits of normal and increasing the risk of nephrocalcinosis. Therefore, dose interruptions and/or dose reductions may be required. In terms of adverse effects, the most common, which is indicated as greater than 10% were headache, injection site reaction, vomiting, pyrexia, extremity pain, decrease in vitamin D, rash, toothache, tooth abscesses, myalgia, and dizziness. The effects in terms of dose adjustment for hepatic and renal impairment are unknown. In terms of geriatric patients, due to the limited number of patients greater than 65, study results should be viewed with caution in this age group. Any questions?

Lisa Chew: Thank you, Umang. Any questions? We do have one stakeholder, Awni Swais. Oh, I got that right? So, please introduce yourself and who you represent, and you have three minutes.

Awni Swais: Good afternoon. My name is Awni Swais, health outcomes liaison with Ultragenyx Pharmaceutical Medical Affairs. Today, I want to provide a testimony on Crysvida, AFGF23 monoclonal antibody indicated for the treatment of XLH in adults and pediatric patients' ages one year and older. XLH is an X-linked hereditary lifelong progressive disorder resulting from chronic hypophosphatemia, and it is an estimate 12,000 have XLH in the U.S., approximately 3,000 pediatric patients, approximately 9,000 adult patients. Pediatric patients with XLH may have rickets and osteomalacia characterized by radiographic images, lower extremity deformity, and short stature. Adult patients with XLH may have osteomalacia resulting in increased bone pain, fracture, pseudofractures, decrease of physical function, and repeated orthopedic procedures to stabilize the bone. Patients with XLH can be diagnosed based on biochemical markers, such as low phosphorous or low TMPGFR and clinical findings in the presence or absence of a family history. Now, Crysvida was studied in four pivotal clinical trials, two phase-two trials were conducted in 65 pediatric patients with XLH, and then two phase-three trials were conducted in 148 adult patients with XLH. In a trial with the pediatric patients with XLH, ages 5 to 12, patients who received

Crysvita every two weeks demonstrated an increase of 40% from baseline to six weeks 64, and mean serum phosphorous levels. 69% of the patients achieved a radiographic global impression of change score of substantial healing of rickets or higher through 64 weeks of treatment. In a trial, pediatric patients with XLH ages 1 to 4, patients receiving Crysvita every two weeks demonstrated an increased mean serum phosphorous levels at week 40 and decreased rickets severity score and increased radiographic global impression of change score. In a trial of adult patients with XLH, ages 18 to 65, 94% of the patients treated with Crysvita for 24 weeks had a serum phosphorous level greater than the lower limit of normal, which was significantly greater than the patient's treated with placebo at 8%. The most common adverse reactions reported pediatric patients were headache, injection site reactions, vomiting, fever, pain in the extremities, vitamin D decreased, rash, toothache, myalgia, tooth abscess, and dizziness. The most common adverse reaction reported in adult patients were back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, and blood phosphorous increased. Crysvita is administered by subcutaneous injection by healthcare provider every two weeks for pediatric patients, every four weeks for adult patients. Crysvita is the only FDA approved product for XLH, and with that, I respectfully ask the committee to have Crysvita added to the Medicaid formulary.

Lisa Chew: Thank you. Any questions? Okay. Thank you. Alright, Ryan, would you like to review the policy?

Ryan Pistorosi: Sure. Thank you. This is Ryan, and we'll be walking through the Crysvita Apple Health policy. So, gain, this is another one-indication, one drug review. So, this is one is for X-linked hypophosphatemia. Our criteria for Crysvita is as proposed. The diagnosis of X-linked hypophosphatemia confirmed by genetic testing for the PHEX gene mutations or a serum FGF23 level of greater than 30 pg/mL, and that the patient is one year of age or older, and that the serum phosphorous is below normal range for the age of the patient, and that the patient has not received oral phosphate or active vitamin D analogs in the previous week, and that the patient must have had an inadequate response or intolerance to oral phosphate and vitamin D treatment for at least six months, and that the patient does not have severe renal impairment defined as GFR of less

than 30 mL/minute, and the documentation of clinical sign or symptoms of disease (such as rickets, growth retardation, musculoskeletal pain, bone fractures) for patients that are greater than or equal to 18 years of age, and that it is prescribed by or in consultation with a specialist experienced in treating metabolic bone disorders. So, if all that criteria is met, the request would be approved for six months.

Then, it would come back for the reauthorization criteria. So, the reauthorization criteria is that the current serum phosphorous level is below the upper limits of the lab normal range, so depending on which labs range it is, as long as it's below the upper limit, and that they have had a positive clinical response to the drug defined as either an increase in serum phosphorous levels or improvement in symptoms, (such as the skeletal pain, linear growth, improvement in skeletal deformities, or reduction of fractures), or reduction in serum alkaline phosphate activity, or an improvement in radiologic imaging of rickets or osteomalacia, and that it is prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders. So, upon reauthorization, if they meet those three criteria, then they would be approved for 12 months.

Amber Figueroa: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 146 and 147, as recommended.

Nancy Lee: I second that motion.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. I'm not even going to try this. Let's move to the next drug, and there are no stakeholders.

Umang Patel: This is why I go by brand name whenever I present these. Alright. So, the next one is going to be Palynziq. For an overview of the disease state. So, phenylketonuria or PKU moving forward is an inherited disorder that increases the body's level of phenylalanine and is typically caused by phenylalanine hydroxylase deficiency. Humans cannot phenylalanine,

but it is a natural byproduct of the foods consumed. People with PKU cannot properly break down the extra phenylalanine to convert it to tyrosine. This means it builds up in the person's blood, urine, and body, and if PKU is not treated, it can build up to harmful levels. It is an orphan condition. The incidence is 1 in 13,500 to 19,000 births in the U.S. PKU varies from mild to severe. Severe is known as classic PKU. Without treatment, children with classic PKU develop permanent intellectual disability, light skin and hair, seizures, developmental delays, behavioral problems, and psychiatric disorders are common. Mild PKU, also known as variant PKU and non-PKU hyperphenylalaninemia, have a smaller risk of brain damage. Mothers who have a PKU and no longer follow a phenylalanine restricted diet have an increased risk of having children with intellectual disability, because their children may be exposed to, again, very high levels. The treatment, dietary restriction of phenylalanine is the cornerstone, usually treated with a strict low protein diet and phenylalanine free medical foods. Oral sapropterin, or Kuvan, can be used in adults and pediatrics as an adjunct to diet in patients responsive to tetrahydrobiopterin. Before moving forward, high foods... it does state to avoid high protein foods, so things such as milk, eggs, cheese, nuts, soy beans, things like that are kind of what is recommended for clinicians to tell their patients. So, Palynziq is an enzyme therapy for adult PKU patients who have uncontrolled blood phenylalanine concentrations, with current therapy along with specialized diet that I mentioned. It's a self-administered subQ after the initial healthcare professional administration. It does have a box warning for anaphylaxis, which I will go into detail in a second, which requires the patient carry an epinephrine auto injector and has a long dose initiation/titration process. Widespread adoption of Palynziq may be limited by the high rates of anaphylaxis associated with this use.

So, the next slide here, we have the indication, dosing, and availability. Before going into that, the mechanism of action for this, it is a pegylated phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia. It substitutes for the deficient phenylalanine hydroxylase enzyme activity in the patient with PKU, and thus reduces the blood phenylalanine concentration. So, it's a substitute of sort. So, this medication, again, it is indicated to reduce blood phenylalanine concentration in adult patients with PKU who have uncontrolled blood

phenylalanine concentration greater than 600 micromol/L on existing management. The adult dosing is stratified here below. So, obtain baseline blood phenylalanine concentration before initiating treatment, recommended initial dose is 2.5 mg subcutaneously, once weekly for four weeks. There is a stepwise titration dosing schedule, which I won't go into, but it's for your leisure in front. It does recommend to discontinue Palynziq in patients who have not achieved at least a 20% reduction in blood phenylalanine concentration after 16 weeks of continuous treatment. Reduce the dosage or modify dietary protein and phenylalanine intake, as needed, to maintain blood/phenylalanine concentrations within a clinically-acceptable range and above 30 micromol/L. For blood phenylalanine monitoring and diet, obtain the concentrations every four weeks until a maintenance dosage is established. After the dosage is established, periodically monitor blood phenylalanine concentrations. Counsel the patients to monitor dietary protein that I mentioned earlier, and phenylalanine intake. Premedication may be considered for patients who have hypersensitivity reaction. Administration instructions similar to other subQ medications, rotate injection sites. If more than one injection is needed for a single dose, this site should be at least two inches away from each other. The availability in single prefilled dose syringes are 2.5 mg, 10 mg, a 20 mg/0.5 and 1 mL.

On the next slide here for special populations, pediatrics, safety and efficacy have not been established. Clinical trials did not include any patients over 65 years of age for the geriatric population. For pregnancy, insufficient limited data available for use in pregnant women to determine a drug-associated risk. Studies of pregnant animals without PKU who were given Palynziq showed that it may cause fetal harm. Therefore, phenylalanine concentration needs to be closely monitored in women with PKU during pregnancy. Pregnant women should be advised of the potential risk to the fetus in either scenario. For warnings and contraindications, I mentioned earlier, it does carry a boxed warning for the risk of anaphylaxis, which may occur at any time during treatment. Measures to reduce the potential for anaphylaxis should be based on the severity of the reaction, recurrence, and clinical judgment, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids. As a result of

the anaphylaxis risk, there is also a REMS program for Palynziq requiring provider, both prescriber and pharmacy, and patient enrollment. In addition, an epinephrine auto-injector must be prescribed for all patients treated with Palynziq, and as with all therapeutic protein medications, there is potential for development of immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Lastly, for adverse effects, the most commonly observed adverse effect that was reported in 20% were injection site reactions, arthralgia, hypersensitivity, headache, generalized skin reactions, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and lastly fatigue. Any questions?

Lisa Chew: Thank you, Umang. Any questions for Umang? Okay. There are no stakeholders. So, Ryan, if you want to.

Ryan Pistoresi: Okay. We'll be presenting the Palynziq Apple Health policy. So, for this one, just PKU, and only one drug. So, for the PKU policy, we would require that the patient has a confirmed diagnosis of PKU established by a metabolic specialist, and that the patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L over the last six months prior to starting Palynziq, and that the treatment with sapropterin, or Kuvan, has been ineffective, not tolerated, or is contraindicated. And the way that we would determine ineffective is that the decrease in blood phenylalanine is less than 30% from baseline after one month from treatment. So, that 30% is kind of the expected amount that you would see from those drugs for the treatment of PKU. So, really, they go through dietary restrictions if they are not able to satisfy their disease with that. Then, they go to sapropterin, and if they're not able to do that, then they can step into Palynziq. The only other criteria that we have is that the patient is greater than or equal to 18 years of age, and that the Palynziq is not being used in combination with Kuvan. So, if all the criteria is met, it would be approved for six months.

At six months, it would come back for the reauthorization criteria. Then, we would just check to see, the blood phenylalanine level should have decreased by at least 20% from baseline, or is less than or equal to 600 micromol/L at the maximum dose of 40 mg per day. So, the difference

between the 30% and the 20% is, this is kind of the last line therapy. So, they've already tried diet. They've already tried sapropterin. So, we would continue to allow authorization when it is at least that 20%. So, if all that criteria is met, we would then approve it for 12 months.

Lisa Chew: Thank you, Ryan. Any comments or questions or edits?

Constance Huynh: So, I wanted to know if we needed to also then add something about putting an EpiPen with the initial criteria, since it was at a high risk of hypersensitivity reactions?

Ryan Pistorosi: So, there is the REMS program that requires prescriber and pharmacy and patient enrollment, and an epinephrine auto-injector must be prescribe for all patients treated with Palynziq. So, we didn't think about putting it in, as the authorization criteria, but it is part of the REMS program.

Constance Huynh: So, then it would be... there would be a safeguard with the REMS? That they would...

Ryan Pistorosi: Yeah. So, the REMS requires patient, provider, and pharmacy enrollment. So, hopefully that education is out there. If you would feel more comfortable, we could look at adding that in, but we thought it didn't need to be added, as a criteria.

Constance Huynh: For the record, I trust our pharmacists.

Ryan Pistorosi: Great. Thank you.

Diane Schwilke: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 155-156, as recommended.

Virginia Buccola: I second the motion.

Lisa Chew: All those in favor say aye.

Group: Aye.

Lisa Chew: Any opposed. And the motion carries. Okay, last drug, Brineura.

Umang Patel: So, the last medication we'll discuss here is Brineura. Overview of the disease state, so CLN2 belongs to a group of disorders known as Batten disease. It occurs in approximately 1 in 200,000 births worldwide. It is a lysosomal storage disorder in which genetic mutations disrupt the cells ability to dispose of waste. The mutation occurs in the TPP1/CLN2 gene causing deficiency of the TPP1 enzyme. This results in abnormal storage of proteins and lipids in neurons and other cells and impair cellular function and moto function. Neurodegeneration occurs and is characterized by seizures, loss of motor function, cognitive decline, and speech and visual impairment. The first symptom usually appears between ages 2 and 4, typically starting with seizures followed by regression of developmental milestones. Visual impairment appears at age 4 to 6 and progresses rapidly. Most patients lose their ability to walk around 6 years of age, and life expectancy is 6 to 12 years. Some patients may have a milder form of CLN2 with the first symptom evident after age 4, and life expectancy goes on until adulthood. So, Brineura is a recombinant form of human TPP1. It is the only medication approved by the FDA to slow disease progression in patients with CLN2 disease. There are no other approved treatment options for this disease. Current care focuses on symptom management, prevention, treatment of complications, and quality of life. Administration requires an implanted device and must occur under sterile conditions by a healthcare provider knowledgeable in intraventricular administration. Approval is based on efficacy in a very small nonrandomized trial, and a long-term study is ongoing to evaluate the long-term safety and efficacy.

On the next slide here, we have the indication, adult dosing, and availability. How this medication works via its mechanism is, it's a proenzyme. It's taken up by target cells in the CNS and is translocated to the lysosomes through CAD-ion independent mannose 6-phosphate receptors. It's activated in the lysosome, and the activated proteolytic form cleaves tripeptides and basically helps get rid of the waste, essentially. It's substituting what is lacking. It SI indicated to slow the loss of ambulation in symptomatic pediatric patients aged 3 years of age or older with late infantile neuronal ceroid lipofuscinosis type 2, also known as TPP1 deficiency. The recommended dose is 300 mg every

other week as an intraventricular infusion followed by infusion of intraventricular electrolytes over about four and a half hours. Pretreatment with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of the infusion. Aseptic technique must be strictly observed. It should be administered by or under the direction of a physician knowledgeable in intraventricular administration. Administered to the cerebrospinal fluid by infusion via surgically implanted reservoir or catheter. For complete information of this medication, there is a lot more detail in its prescribing info. The availability comes in a kit. As you can see, the kit is pretty cumbersome. So, it's listed in front of you.

Lastly, on the last slide here, we'll look at special populations. For pediatrics, again, safety and efficacy have been established in 3 years of age and older. There is no data reported for hepatic or renal impairment. No available data for women who are pregnant or animal reproductive studies to inform a drug-associated risk. In terms of warning and contraindications, it's contraindicated in patients with ventricular peritoneal shunts, and in patients with acute intraventricular access device related complications, such as leakage, device failure, or device related infection. In terms of adverse effects, if an intraventricular access device complication occurs, discontinue and refer to the device labeling for appropriate action. Hypotension has been reported during for up to eight hours after the dose in 8% of the population; 46% of patients experienced hypersensitivity reaction, such as pyrexia, vomiting, and during, or within 24 hours of the infusion. Again, premedication with antihistamines with or without corticosteroids is recommended. Anaphylaxis may occur, as well. In clinical studies, the most commonly reported adverse reactions defined as greater than 10% included pyrexia, EKG abnormalities, decreased CSF, protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, and pleocytosis. Additional adverse events can be found in the NDU that is available on the site. In terms of monitoring parameter, CSF should be routinely tested to detect subclinical infection of the device. Blood pressure and heart rate should be monitored before, during, and after the infusion. Lastly, EKG should be performed every six months in patients with history of bradycardia or structural heart disease, and it

should be performed during the medication administration, as well. Any questions.

Nancy Lee: I just wanted to clarify the dosing and chart on slide 160. Should it say just instead of adult dosing?

Ryan Pistorosi: It should be dosing-period.

Lisa Chew: Thanks, Umang. Any other questions? So, there are no stakeholders.

Ryan Pistorosi: We'll be walking through our last policy today. So, this is the Brineura Apple Health policy. Again, just one indication, one product. So, for our initial criteria is that the patient is 3 years of age or older and that they have a documented diagnosis of CLN2 confirmed by TPP1 deficiency, and/or genetic test showing a mutation of TPP1 gene on the chromosome 11p15, and that there is documentation of baseline CLN2 clinical rating scale, because this is a drug in which the patient population doesn't live very long. So, there's not a lot of information on a lot of studies for which to determine the efficacy of this drug. Since this was the scale used in clinical trials, we want to have baseline scales, so which way we can see that the decline in function is either... they're maintaining at function, or the decline is slower than what it would have been. That the medication is prescribed by or consultation with a specialist with expertise in the treatment of CLN2. So, examples could be a pediatric neuro-oncologist, a pediatric epileptologist, or a geneticist. And the patient is ambulatory, and there is documentation of no acute intraventricular access device related complicated. For example, leakage, device failure, or device related infection, or a ventriculoperitoneal shunt. If all that criteria is met, then they would be approved for six months.

After those six months, it would come back as a reauthorization criteria. And that criteria would require that there be documentation of positive clinical improvement, such as no decline in the CLN2 clinical rating scale, or it may be minimal decline. The medication is prescribed by, or in consultation with, a specialist so that there still is that ongoing relationship and still that monitoring with someone who is an expert in treating this very rare disease. That the patient still continues to be ambulatory, and that there still continues to be no issues with the device

or shunt. If that criteria is all met, then the request would be approved for 12 months.

Lisa Chew: Any edits to the criteria or comments?

Constance Huynh: I move that the Apple Health Medicaid program implement the clinical criteria listed on slides 164 to 165, as recommended.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. And we are adjourned. Thank you, everyone.