Pharmacy and Therapeutics (P&T) Committee Meeting Record

Date: Friday, May 22, 2015

Time: 9:00 a.m. – 3:30 p.m. **Location:** Idaho Medicaid, 3232 Elder Street, Boise, Idaho, Conference Room D

Moderator: Perry Brown, M.D.

Committee Members Present: Perry Brown, MD-Chair; Tami Eide, PharmD; David Calley PharmD; Kevin Ellis, PharmD; Mark Turner, MD; Troy Geyman, MD; Jeffrey Johnson, PA-C, PharmD; Steven Carlson, PharmD; Christopher Streeter, MD; Brian K. Crownover, MD; Leigh Morse, MD

Committee Members Absent: Mark Johnston, RPh

Others Present: Sarah Martinez, PharmD, Magellan Health Services; Chris Johnson, PharmD, Division of Medicaid; Jane Gennrich, PharmD, Division of Medicaid; Tammy Haugland, Division of Medicaid; Teresa Martin, Division of Medicaid

AGENDA ITEMS	PRESENTER	OUTCOME/ACTIONS
CALL TO ORDER	*Perry Brown, MD*	*Dr. Brown called the meeting to order.*
Committee Business		
➢ *Roll Call*	*Perry Brown, MD*	Dr. Brown completed the roll call and welcomed the P&T Committee members.
➢ *Reading of Confidentiality and Mission Statements*	*Perry Brown, MD*	Dr. Brown read the Confidentiality and Mission Statements.
➢ *Approval of Minutes from April 24, 2015 Meeting*	*Perry Brown, MD*	The April 24, 2015 meeting minutes were reviewed. The minutes were accepted as proposed.

➢ *DERP-In Progress Long-Acting Opioids Update*	*Tami Eide, PharmD*	**DERP- In Progress Long-Acting Opioids Update** Dr. Eide provided information on the Drug Effectiveness Review Project's 7th Update for the Long-Acting Opioid drug class. Several drugs have been added since the previous report. The review will be looking at comparative effectiveness and safety in chronic non-cancer pain. Effectiveness outcomes are reduction of pain and improvement in functional outcomes comparing long-acting vs. long-acting opioids; long-acting vs. short-acting opioids and differences in subpopulations. Comparative harms outcomes are drug withdrawals, drug withdrawals due to adverse events and incidence of specific adverse events. Comparators are between different long-acting opioids, long-acting vs. short-acting, between drugs with and without abuse-deterrent mechanisms, between drugs with different abuse-deterrent mechanisms and differences in subpopulations.
➢ *Outcome Studies for Long-term Narcotic Use*	*Tami Eide, PharmD*	**Outcome Studies for Long-term Narcotic Use** Dr. Eide reported on a recent systematic review on the effectiveness and risks of long term opioid use. This AHRQ review was used to facilitate the National Institutes of Health Pathways to Prevention Workshop. The systematic review evaluated evidence on the effectiveness and harms of long term (> than 3 months) opioid therapy for chronic pain in adults. There was no quality study identified that evaluated opioid therapy versus no opioid therapy long term (greater than one year) that evaluated outcomes related to pain, function, quality of life, opioid abuse or addiction. Some observational studies for chronic pain were identified for harms which showed an increased risk of overdose; opioid abuse and dependence; myocardial infarction and increased use of medications to treat sexual dysfunction. For some harms higher doses are associated with increased risk. The bottom line is that the evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. They found that no evidence evaluated the usefulness of risk prediction instruments such as urine drug screening, prescription drug monitoring program data and abuse-deterrent formulations for predicting misuse, abuse or addiction. The evidence did find that the rates of opioid abuse and dependence did vary depending on the daily morphine equivalent dose, with higher morphine equivalent doses being associated with a higher percentage of abuse. Factors associated with an increased risk for misuse include history of substance use disorder, younger age, major depression and concurrent use of psychotropic medications.
➢ *Oxycodone IR vs ER Utilization*	*Chris Johnson, PharmD*	**Oxycodone IR vs ER Utilization** Dr. Johnson provided a review of Oxycodone IR (immediate release) vs. OxyContin (extended release) utilization which demonstrated changes related to the addition of abuse deterrent properties to OxyContin and impact of prior authorization. Oxycodone IR use increased from 400 claims/month to 1000 claims/month from March 2010 to

		August 2014. Prior authorization was initiated in mid-August 2014 and oxycodone IR decreased to 600 claims/month from September 2014 to April 2015. The oxycodone 5mg strength had the most claims for the reporting years (2010 thru 2014) at approximately 3000 claims/year. This is probably due to its use for post-operative procedures as the most common narcotic analgesic surgeons prescribe per P&T discussion. OxyContin claims have decreased from 300 claims/month to 150 claims/month from March 2010 to April 2015. Dr. Johnson presented data demonstrating that the subsequent rise in oxycodone IR claims correlated with an OxyContin formula change in April 2010. Dr. Eide noted that OxyContin was reformulated to an abuse deterrent product and subsequently the number of claims for oxycodone IR rapidly increased from 400 claims/month to 600 claims/month from April 2010 to August 2011, while OxyContin claims decreased. Overall, OxyContin claims have decreased across all strengths but a steady increase in oxycodone IR 30mg was noted in 2014.
➢ *Hydrocodone Combination Products - Rescheduling*	*Tami Eide, PharmD*	**<u>Hydrocodone Combination Products - Rescheduling</u>** Dr. Eide reported on changes in Medicaid utilization of hydrocodone combination products since October 6, 2014 when the DEA rescheduled them from Schedule III narcotics to Schedule II. The DUR Board looked at utilization to determine if there would be a shift to other agents and to see the possible impact on opioid initiatives that were scheduled to be implemented. Idaho Medicaid saw a decrease in claims, expenditures and unique recipients from baseline in October, November and December. The number of claims and recipients did increase during January, February, and March, but remained below baseline. Acetaminophen with codeine and tramadol as alternatives did not see any changes in utilization. Costs did increase from baseline for hydrocodone combinations, mostly due to inflation. There was an increase also in the average quantity per claim, but not in the average days supply per claim.
Public Comment Period	*Perry Brown, MD* *Tammy Haugland*	**<u>Public Comment Period</u>** One (1) person signed up to speak during the public comment period. Two manufacturer representatives were pre-approved to provide testimony. Public testimony was received from the following speaker's:

Speaker	Representing	Agent	Class
Phil Peterson , MD	Self		Narcotic Analgesics
Rosalynde Finch	Biogen Medical Information	Plegridy	Multiple Sclerosis Agents
Roy Palmer, PhD	Pfizer	Embeda	Long-acting Narcotics

Drug Class Reviews and Committee Recommendations	*Perry Brown, MD* *Tammy Haugland*	**Drug Class Reviews and Committee Recommendations** Committee members were asked to base their recommendations for each drug class on the answers to the following questions: 1. Is there evidence to support clinically significant differences in efficacy or effectiveness between agents? 2. Is there evidence to support clinically significant differences in safety between agents? 3. Are there any agents that the committee feels strongly must be preferred or non-preferred? 4. Are there any recommendations for changes to PA requirements?
➢ *Antivirals, Oral*	*Sarah Martinez, PharmD*	**<u>Antivirals, Oral</u>** Dr. Martinez reported that there is one new product on the market, Sitavig (acyclovir), indicated for the treatment of recurrent herpes labialis in immunocompetent adults. There are no significant contraindications, warnings or drug interactions. It is available as a 50 mg buccal tablet, applied as a single dose to the upper gum and allowed to adhere and dissolve throughout the day. Dr. Martinez reviewed the CDC 2014-2015 influenza season recommendations for the use of oral antivirals. The recommendations did not change significantly from the previous season. TOP$ has moved the anti-influenza drug, amantadine to the anti-Parkinson's drug class/market-basket. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. Specifically they saw no advantage to Sitavig to currently available agents and recommended it be non-preferred.
➢ *Antivirals, Topical*	*Sarah Martinez, PharmD*	**<u>Antivirals, Topical</u>** There was no recent clinically significant information in this class to report on. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. They recommended prior authorization criteria which required failure of oral anti-herpetic therapy prior to approval of topical anti-herpetic agents.

➢ *Antibiotics, Inhaled*	*Sarah Martinez, PharmD*	**Antibiotics, Inhaled** Dr. Martinez reported on one new product, Kitabis (tobramycin) co-packaged with a nebulizer. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the tobramycin products. They discussed the advantage of the powder formulation in treatment length and subsequent possible improved adherence. They asked that current patients on the Podhaler formulation be allowed to continue on that formulation. As some of these products are only available through specialty pharmacy networks, it was requested that the Department do some education on these limited availability sources.
➢ *Antibiotics, Topical*	*Sarah Martinez, PharmD*	**Antibiotics, Topical** There was no recent clinically significant information in this class to report on. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Antibiotics, Vaginal*	*Sarah Martinez, PharmD*	**Antibiotics, Vaginal** Dr. Martinez reported on one new product in this class. Nuvessa (metronidazole 1.3%) is indicated for the treatment of bacterial vaginosis in non-pregnant patients. It is a gel administered intravaginally at bedtime as a single dose. A study comparing Nuvessa to the 0.75% gel administered once daily for five days showed a higher cure rate (30% vs 20%) and there were no clinically significant differences observed in adverse effects. **Committee Recommendations** The Committee concluded that there was some difference in efficacy for Nuvessa and it should be preferred if cost effective. In general they concluded that there were no differences in efficacy, effectiveness or safety between the agents.
➢ *Cephalosporins and Related Agents*	*Sarah Martinez, PharmD*	**Cephalosporins and Related Agents** There is no new significant clinical information for this class.

		Committee Recommendations The committee concluded that the evidence did not support differences in efficacy or effectiveness for the agents for susceptible infections. They reiterated that for safety reasons (serum sickness) cefaclor be non-preferred. It was requested that if cost-effective, amoxicillin/clauvaulinic acid XR be preferred to decrease pill burden in larger children.
➢ *Fluroquinolones, Oral*	*Sarah Martinez, PharmD*	**Fluroquinolones** Dr. Martinez reported that ciprofloxacin solution (for Cipro) is now available generically. Ciprofloxacin is now indicated for prophylaxis and treatment of plague due to *Yersinia pestis* in adults and children. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Macrolides/Ketolides*	*Sarah Martinez, PharmD*	**Macrolides/Ketolides** There is no new significant clinical information for this drug class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Tetracyclines*	*Sarah Martinez, PharmD*	**Tetracyclines** There was no recent information of significance in this class to report on. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. With continued shortages and consequent price increases, the committee recommended minocycline as the tetracycline to be preferred in acne treatment.
➢ *Antibiotics, Gastrointestinal*	*Sarah Martinez, PharmD*	**Antibiotics, Gastrointenstinal** Dr. Martinez reported that there is no new significant clinic information in this drug class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness

		or safety between the agents. They asked that Alina or tinidazole be available as first line treatment of giardia.
➢ *Antifungals, Oral*	*Sarah Martinez, PharmD*	**<u>Antifungals, Oral</u>** Dr. Martinez reported on an update to the black box warning for Sporanox (itraconazole). It has been expanded to include instructions to not administer it to patients with congestive heart failure. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. There was a recommendation to have terbinafine as a preferred agent with no therapeutic criteria.
➢ *Antifungals, Topicals*	*Sarah Martinez, PharmD*	**<u>Antifungals, Topical</u>** There are several new products in this class. Jublia (efinaconazole) and Kerydin (tavaborole) are both indicated for the treatment of onycomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. She reviewed application, duration of therapy, contraindications, warning, drug interactions and the most common adverse effects. Alevazol (clotrimazole) is a newly available OTC ointment. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee recommended that all topical toenail treatments be non-preferred due to low cure rates.
➢ *Antiparasitics, Topical*	*Sarah Martinez, PharmD*	**<u>Antiparasitics, Topical</u>** Dr. Martinez reported that Natroba (spinosad) is now indicated to treat head lice in patients six months and older (previously indicated for four year and older). **Committee Recommendations** The committee concluded that the evidence in general did not support differences in efficacy, effectiveness or safety between the agents. There are safety issues with lindane and it was recommended to remain non-preferred. They felt that permethrin remained a reasonable and efficacious first choice.

➢ *Antimigraine Agents, Triptans*	*Sarah Martinez, PharmD*	**Antimigraine Agents, Triptans** Dr. Martinez reported that there is no recent information of clinical significance in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. It was suggested that Cambia be moved to a different drug class based on pharmacology.
➢ *Skeletal Muscle Relaxants*	*Sarah Martinez, PharmD*	**Skeletal Muscle Relaxants** Dr. Martinez reported there is no new significant clinical information in the class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee recommended that a DUR be done on patients receiving these drugs long-term. The study should look at the drug, diagnosis, duration and other drugs used in combination.
➢ *Antiemetics/Antivertigo*	*Sarah Martinez, PharmD*	**Antiemetics/Antivertigo** Dr. Martinez reported that there are two new products. Akynzeo (netupitant/palonosetron) is indicated for the prevention of acute and delayed nausea/vomiting associated with initial and repeat courses of cancer chemotherapy including, but not limited to highly emetogenic chemotherapy. She reviewed clinical trials in which it was compared to oral palonosetron. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. Several members of the committee felt that ondansetron should be openly available for use in general nausea and vomiting. Since this is off-label and non-compendia associated use, the Department will explore whether it can be available on a limited basis to prevent ER admissions.
➢ *Ulcerative Colitis Agents*	*Sarah Martinez, PharmD*	**Ulcerative Colitis Agents** Dr. Martinez reported on one new product – Uceris (budesonide) rectal foam, indicated for the induction of remission in patients with active, mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge. Delzicol is now indicated for the treatment of mild to moderately active ulcerative colitis for patients two years and older (previously indicated only in

		adults). **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Analgesics, Narcotic long-acting*	*Sarah Martinez, PharmD*	**<u>Analgesics, Narcotic long-acting</u>** Dr. Martinez reported on several new drugs in this class. Hysingla ER (hydrocodone) and Embeda (morphine ER/naltrexone) which has re-launched following several years off of the market. She also announced that fentanyl is now available as a 37.5, 62.5 and 87.5 mcg/hr patches and that there is a new abuse-resistant formulation of Zohydro ER. Zohydro ER without the abuse deterrent is still available. New generics include hydromorphone ER for Exalgo and oxycodone ER for OxyContin. Dr. Martinez announced that the FDA has expanded the boxed warning for the opioid-containing products to include information about prolonged use during pregnancy and potential for neonatal opioid withdrawal syndrome. She discussed the FDA guidance on developing opioid drug products with abuse-deterrent properties. **Committee Recommendations** The committee concluded that there were no differences in efficacy or effectiveness between the agents, but there were some safety concerns particularly with the use of methadone. It was communicated that previous DUR studies had shown appropriate use and knowledge from those providers prescribing methadone. There was extensive discussion around better control around the use of all narcotic analgesics in chronic, non-malignant pain based on the patterns of use observed by both the Pharmacy and Therapeutics Committee and the DUR Board. The committee recommended that the Department work toward a total daily morphine equivalent daily dose of 120 mg. Doses over this should require prior authorization. The Department will need to work with prescribers and give them adequate time to taper patients currently on doses higher than this. It was recommended that there be a standard morphine equivalency chart available and resources on how to taper a patient down from high dose narcotics. Other recommendations to implement in the future included:

		• For chronic pain patients requiring continued opioid use that a long-acting agent be the primary pain treatment and that short-acting be in a smaller proportion to total daily dose and be used for break-through pain. • Provide and limit duration on narcotics for chronic non-malignant pain since evidence does not support this practice and may indicate an opposite effect • To limit the use of benzodiazepines, particularly multiple benzodiazepines in combination with opioids. • That the Department work with Program Integrity and the Attorney General's office to explore actions to decrease diversion, other fraud and abuse. • That the Department pursue legislatively a mechanism that would prohibit participants from paying cash for quantities not covered by Medicaid and pharmacies from participating in this practice.
➢ *Analgesics, Narcotic short-acting*	*Sarah Martinez, PharmD*	**<u>Analgesics, Narcotic short-acting</u>** Dr. Martinez provided review of the current products and utilization. She reported on a new product, Xartemis XR (oxycodone/APAP) which is the first extended release product containing oxycodone and acetaminophen. She also reported on the new product, Lazanda (fentanyl nasal spray) which is indicated for breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. It is contraindicated in opioid-non-tolerant patients, the management of acute or postoperative pain including headache/migraine or dental pain. She also announced that tramadol is now a schedule IV drug and that hydrocodone combination products are now schedule II. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. In addition to above recommendations for a total morphine equivalent daily dose of 120 mg, the committee recommended to limit individuals to one short-acting agent without a prior authorization. A DUR to look at short-acting narcotic utilization was recommended prior to implementing this. For acute pain they recommended duration of therapy not exceed 90 days.

➢ *Opiate Dependence Treatments*	*Sarah Martinez, PharmD*	**Opiate Dependence Treatments** Dr. Martinez reported on two new products in this class. Evzio (naloxone) is an intramuscular injection indicated for the emergency treatment of known or suspected opioid overdoses. Bunavail (buprenorphine/naloxone) is a new buccal film similar to Suboxone. Bunavail 4.2/0.7 mg is bioequivalent to Suboxone 8/2 mg sublingual film. Suboxone film is now indicated for induction of buprenorphine treatment of opioid dependence (previously approved only for maintenance treatment) Dr. Jane Gennrich provided an update on the pharmacy unit's ongoing monitoring program on Suboxone/Subutex patients that pay cash for opioids while on opioid dependence treatment. The state prescription monitoring program (PMP) is used to identify patients and a call is made to their provider. Providers are now being more proactive in reviewing the PMP reports themselves and are generally appreciative when Dr. Gennrich informs them of patients who are paying cash for opioids. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee recommended limiting Subutex (buprenorphine) to pregnancy only through a hard stop edit.
➢ *Hereditary Angioedema Agents*	*Sarah Martinez, PharmD*	**Hereditary Angioedema Agents** Dr. Martinez announced one new product Ruconest (recombinant C1 esterase inhibitor) indicated for the treatment of acute attacks in adults and adolescent patients with HAE. Ruconest is contraindicated in patients with allergies to rabbits or rabbit-derived products. Dr. Gennrich reviewed the Department's therapeutic criteria and guidelines for treatment of acute attacks and prophylaxis. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee approved the therapeutic criteria with a request to add a statement that danazol was contraindicated in pregnancy.
➢ *Immunosuppressives, Oral*	*Sarah Martinez, PharmD*	**Immunosuppressives, Oral** Dr. Martinez reported on one new generic. CellCept (mycophenolate mofetil) suspension is now available generically.

		Committee Recommendations The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Multiple Sclerosis Agents*	*Sarah Martinez, PharmD*	**<u>Multiple Sclerosis Agents</u>** Dr. Martinez announced two new products in this class. Plegridy (peginterferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis. She reviewed dosing, administration, contraindications, warnings and adverse effects. Lemtrada (alemtuzumab) is indicated for the treatment of relapsing forms of multiple sclerosis, generally in patients who have had an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis. It is contraindicated in HIV patients and has a black box warning for serious autoimmune adverse effects, life threatening infusion reactions and increased risk of malignancies. Because of these safety concerns there is a certification requirement for prescribers, pharmacies and drug administration facilities. Patients must be enrolled in a program and comply with ongoing monitoring requirements. She reviewed the information around two clinical studies that evaluated Lemtrada (alemtuzumab). Dr. Martinez also provided a product safety update that included a report of progressive multifocal leukoencephalophy (PML) in a patient who had used Gilenya for over four years and a report of PML in a patient who had used Tecfidera for over four years. **<u>Committee Recommendations</u>** The committee concluded that the evidence did not support differences in efficacy or effectiveness between the agents. Lemtrada does have safety issues, shouldn't be a first line agent and Idaho Medicaid should stick with the labeling restrictions through a prior authorization process. Similarly there are safety concerns with Gilenya and the committee recommended it also be non-preferred. They concluded that Plegridy had no clinical advantage. They also stated that although Copaxone 40 mg may have some compliance/adherence advantages, its inclusion as a preferred agent should depend on cost considerations.
➢ *Other Committee Business*	*Tami Eide, PharmD*	**<u>Other Committee Business</u>** The committee decided to change the amount of time for public testimony from 1 hour to 45 minutes due to the usual low number of speakers providing testimony. It was announced that the next P&T Committee meeting is scheduled for October 16, 2015.

		The meeting adjourned at 3:15 p.m.

Pharmacy and Therapeutics Committee Meeting
Public Comment

Phil Peterson, MD
I'm doctor Phil Peterson, MD. I'm a family practitioner in Orofino, Idaho. I've been practicing there for more than 22 years. I am here on my own time and my own money. There is nobody that has been motivating me to do this, except myself. I'm here because this is a topic that I feel is important to the safety of our patients and to our state. How long do I have?

Committee
We usually say about three minutes. I'm sorry, five minutes. We don't have a ton of people lined up, so as close as you can to five minutes.

Phil Peterson, MD
In 1982, the drug Selacryn, an antihypertensive, was removed from the market, secondary to toxicity. Thirty-six people died as a result of taking this medication. In the year 2001, the drug Baycol, a statin, was removed from the market, secondary to toxicity. Thirty-one people in the United States died as a result of taking this medication. In contrast, according to the CDC in 2010, over 16,000 people died as a result of taking prescription narcotics. This number does not include those who died of other causes, but with narcotics as a contributing factor. This number only includes those who died as a direct result of taking these medications. These are losses that would not be tolerated in any other category of medications. In spite of these numbers, these medications remain on the market. These medications do not prolong life. I believe statistics show that they are associated with an increased all-cause mortality, but they are felt to be necessary for the treatment of painful conditions. Now, in spite of all those comments I have just made, I actually would not want to practice medicine without these. Evidence shows that these medications are effective for treatment of acute and short-term pain. Safety is

a different issue, especially at higher doses. The evidence that these medications are effective for treating chronic or long-term pain, however, is extremely weak, or I would say not existent. We have seen promotion of the concept of long-acting narcotics, long-term treatment for chronic pain with narcotics, and a plethora of newer, stronger, and longer-acting agents come on to the market. The studies that got these on the market were studies that lasted weeks to months. They are not long-term studies. I could not find any long-term studies; if they're out there, I am unaware of them. These studies do not show what happens to these patients who are on these medications for years or decades. So I'm going to tell you what I see. This is observational data, since we don't have any random, controlled studies. What I see is, the long term use of these medications, they become less effective, doses tend to be escalated, and pain tends to increase. At one point, I interpreted this as a manifestation of the patient's underlying condition worsening. Now, at this point in my career, it's clear that this escalation of pain in chronic pain syndromes is at least partially and maybe mostly the result of daily narcotic use, not the cause of the escalating doses. The higher the dose of pain medication, the worse the escalation of the chronic pain. The level of pain seems to correlate with the dose of medication far more than with the severity of objective findings. As I think about my panel of patients, the chronic pain patients who are doing the best are the ones who elected years ago to not take narcotics, either for philosophical reasons or because of intolerable side effects. I look at the chronic pain patients that I have tapered totally off of narcotics, and they seem to be in less pain than they were taking them. So basically, we are in a situation where we are treating large numbers of patients with medications that are demonstrated to not be safe, and that we have no evidence that they're effective for what we are using them for. The situation is supported by a triad of patients who feel that they needed medications, practitioners who are either willing or feel pressured to prescribe them, and third party payers who are willing to foot the bill. That's why I'm here. That's you guys. I'm here to ask the Committee to be brave and strong and do the right thing; put stricter limitations on the coverage of these medications. There should be limitations on dose, limitations on duration, limitations based on diagnosis, limitations based on age, and limitations based on additive toxicity from medications that the patients are taking. It's the right thing to do. You'll increase the safety and health of our state. I believe that if we do this, there will be people who will live who otherwise may not. Thank you. I'm eager to entertain questions or challenges.

Committee
I have a question. If you talk about having limitations on dose, like in morphine equivalents, what would you recommend as far as the ceiling dose?

Phil Peterson, MD
We don't have good data on duration, but we do have good data on that. If you look at the state of Washington, they cap it at 120, with the exception that if you go to a pain clinic, they can get more. If you look at the data that they used, I look at the data and say it should be 100. That's where the break was. There's very clearly an increase in death rate above 100 morphine equivalents and that's something you

guys can do today. You could make that decision later this afternoon to put the cap at 100 morphine equivalents. I've been to one lecture that suggests that at 60 was where we saw an increase in central sleep apnea, but I've actually not seen the data. I only went to a lecture on that one, but that's something you guys could do today. Put a cap. Washington put it at 120, and their outcome data says they saw a decrease in death rate with that intervention. For age, there's evidence, I think not just my observation. Younger people who get started on chronic pain medications do far worse than older people as far as escalation of dose or development of chronic pain syndromes. We see people started on chronic narcotics with painful syndromes without objective signs. They do worse. There are diagnoses that we have specific recommendations to not use these medications, such as fibromyalgia. There is clear evidence that there is increased toxicity in using these in conjunction with benzodiazepines in particular. They should not be covered in combination. That's something you guys could do today. The duration would be the harder thing. I think the data there is far weaker and I think there's a large clientele out there that the decision would have to be made whether you would try to taper them off or just hold the line, but I think, clearly, anybody above 100 morphine equivalents of morphine could be tapered down. They could be tapered down safely. We taper them down, and they do not have an escalation of their pain. They may have a little bump as you go down, but in the end they do better. They're healthier overall.

Committee
You quoted a 2010 number. What was that national number, and did you have any states that...

Phil Peterson, MD
That came off the CDC. That came directly off the CDC site and I used the 2010 number, because that's the one I could find.

Committee
And what was it again?

Phil Peterson, MD
16,000. Yes?

Committee
In your experience, what's been the most effective treatment other than narcotics to control long-term pain? If we look at these different options, we'd like to make sure. I mean, we're with you we'd like to kind of target a good way to help control this chronic pain.

Phil Peterson, MD
Actually, in my experience, it's more what the patient does than what we do. If we can get them moving, keep them mobile, they will do

better. On a personal note, I'm frequently accused of being uncaring because I don't understand pain. I would give you my personal experience, since I'm up here and have a microphone. About a year and a half ago, I had a herniated disk. I went from hiking twelve miles per day during bow season to not being able to walk thirty feet. My partner said "Phil, we ought to give you a little hydrocodone". I said "No way in hell". I went to the pain clinic. I got injections and I still have pain, so I was hurting this morning when I got up. I still have pain. I went to the pain clinic, had an injection that actually also hurt. The pain clinic Dr. Flinders asked me "So, what pain medications are you on?" I said "I refused", and he said "You're a bright boy".

Committee
Do you have any cognitive behavioral therapy that you use or, like, coping skills that you recommend for your patients?

Phil Peterson, MD
We have pretty weak support for that in our area. Mostly what I try to do is get them moving. I try to get them to physical therapy, and probably the biggest cognitive thing is for me to try to get them to understand that if they're taking these medications long term, they will actually get worse. I think of chronic narcotics as being like the credit card of pain. It makes you feel a little bit better, but the bill always comes due later.

Committee
Thank you very much.

Rosalynde Finch, PhD
I'm Rosalynde Finch, I'm with Biogen, I'm a PhD Medical Outcomes Scientist with Biogen, and I'm here today to talk about Plegridy. Plegridy was approved last August. It's the first pegolated interferon beta-1A for relapsing forms of MS, with a prolonged half-life. It currently has an overall exposure of 1,932 patients, with 4,125 patients treated for at least two years. I'm here today to talk to you about the two-year data from the advanced study, and I just wanted to clarify why that is. The drug is actually approved on the basis of the one-year data which was submitted to the FDA, but it was a two-year trial, and the two-year trial was for safety, as well as maintenance of efficacy. So I'm going to speak specifically to the every-two-week dosing. In the trial, we did study every-four-week dosing as well, but saw greater efficacy with every-two-week dosing, and that is the approved dosing now, so on the label it's every two weeks. So in year two patients who were originally on placebo were then randomized to every-two-week dosing or every-four-week dosing. The placebo period was only for the very first year of the trial. So in terms of the results compared with the first year, the annualized relapse rate was further reduced in year two with two-week dosing. It was maintained with four-week dosing. The patients who started Plegridy every two weeks from the first year demonstrated improved efficacy versus patients that were initially assigned placebo, with a reduction in

annualized relapse rate of 37%. The risk of relapse was reduced by 39% versus placebo. The 12-week disability progression was reduced by 33%, and the 24-week confirmed disability progression rate was reduced by 41%. So over the two years, greater reductions were observed with every-two-week dosing versus every-four-week dosing for all end points, and Plegridy was well tolerated. Basically, the adverse effects we see are what is commonly reported for subcutaneous interferon, and those are injection site erythema, influenza-like illness, pyrexia and headache, and the majority of these adverse events were mild to moderate in severity. Over two years, the incidence of patients developing neutralizing antibodies against interferon were similar between the two dosing groups at a rate of less than 1%. So just to summarize, our two-year results from our pivotal trial showed that the clinical and the MI benefits were maintained with subcutaneous pegolated interferon beyond the placebo-controlled first year period. Numerically better efficacy was observed for patients that received continued Plegridy versus those originally randomized to placebo in year one. As I mentioned, greater efficacy was seen with every-two-week dosing versus the every-four-week, but the safety results showed that administration every two weeks versus every four weeks were very similar and well tolerated. So just to conclude, Plegridy offers an effective and safe treatment option for patients with the benefit of less frequent administration and the lowest rate of neutralizing antibodies of any of the interferon products available on the market. Thank you, and if you have any questions, I would be happy to address them. Thank you.

Roy Palmer, PhD

Good morning everyone. My name is Dr. Roy Palmer, PhD. I am an employee of Pfizer, and I'm here to continue the opioid theme and to talk a little bit about Embeda. There are two specific things I wanted to emphasize. In the Magellan Review, the Magellan Review is a little outdated; we've actually had revised labeling since the review, and I submitted some specific comments in a letter which you have. I have also submitted those to Magellan, so our indication and a number of other things were out of date. The most significant change in the label was the inclusion of human abuse potential studies, which I'm going to talk about a little as well. So as has already been discussed, I'm just glad you're already talking about opioids. The issue with opioids is not efficacy and safety so much, that's a separate issue, but the major health problem we have with abuse, misuse and diversion. So in an effort to try and minimize this, the pharmaceutical industry is working on new abuse-deterring opioids. We've seen with OxyContin with the change to an abuse-deterrent formulation, and we worked on a number of other abuse-deterrent opioids. Embeda is the first abuse-deterrent version of morphine. The way it works is a little bit novel. It contains naltrexone, so Embeda consists of a series of tiny little pellets. Each one contains an outer coating of extended-release morphine, and inside is naltrexone. So the naltrexone is not released if you just take it normally, it goes straight through the GI, but if an abuser attempts to manipulate, to crush these pellets to get a more immediate euphoria and high, they're actually exposed to the naltrexone, and that acts as an antagonist of the opioid receptors, so it minimizes the feeling of euphoria. We do this to try and minimize the attractiveness to abusers. So this has developed a whole new science around this, so the FDA has released guidance on how you test these drugs to show that abusers like them less, and that's these human abuse potential studies. So we take recreational drug abusers, people who on their weekends like to abuse medications who are not addicted. We give them the drug whole and they rate on a scale of

how much they like it. Then we give it crushed, and they rate on a scale of how much they like that, and we compare it directly head-to-head with comparators, such as immediate-release morphine or other extended MS Contin for example. So we've done four different studies which were approved by the FDA, reviewed by the FDA, and included in our label. Two of them were oral studies, so people taking them orally. One was actually a snorting study, so people snort the drug, and one IV study. In all of those studies, we saw a significant decrease in how much the patients said they liked the drug, how high they felt, and whether they would take it again or not, and these are the kind of validated end points by the FDA. So I think this is important data I would like you to include in your consideration. It addresses some of the major issues we've seen with this drug class. I do also need to say that even though we have showed a reduction in liking, abuse with Embeda is still possible through the oral, intranasal and IV routes, so it's not a cure all, but we do believe that abusers like the drug less, and so I'd like to ask you that if a physician in Idaho feels the need to prescribe Embeda for whatever reason, whether it's a high risk patient or the fear of diversion, I think it would be great if they were able to do that without too many obstacles. So I need to say Embeda's a class II scheduled medication and we have a box warning, which you have the PI that has all the information in that, but I have to quickly read out. We have box warnings for addiction abuse, misuse, respiratory depression, accidental ingestion can be fatal, even a single dose, neonatal opioid withdrawal syndrome is another warning, and interaction with alcohol. So thank you for your time and attention. I would be very happy to answer any questions.

Committee
Could you remind me? Embeda was on the market and then it wasn't available for a while, and then it was. What was the issue there?

Roy Palmer, PhD
There was a manufacturing issue that was basically a shelf life issue, so the naltrexone was oxidizing faster than the specs, so it wasn't meeting its shelf life requirements, so we had to reinvent the manufacturing process, and that, unfortunately, took about three years to do that, and as of February it has been re-launched. Thank you.