Pharmacy and Therapeutics (P&T) Committee Meeting Record

Date: Friday, April 18, 2014
Time: 9:00 a.m. – 3:00 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; David Calley, PharmD; Tami Eide, PharmD; Troy Geyman, MD; Jeffrey Johnson, PA-C, PharmD; Leigh Morse, MD; Berk Fraser, RPh; Stephen Carlson, PharmD; Greg Thompson, MD

Others Present: Paula Townsend, PharmD, Magellan Health Services; Mark England PharmD, Magellan Medicaid Administration; Jane Gennrich, PharmD, Division of Medicaid; Chris Johnson, PharmD, Division of Medicaid; Teresa Martin, Division of Medicaid

AGENDA ITEMS	PRESENTER	OUTCOME/ACTIONS
CALL TO ORDER	*Perry Brown, M.D.*	*Dr. Brown called the meeting to order.*
Committee Business		
➢ *Roll Call*	*Perry Brown, M.D.*	Dr. Brown completed the roll call and welcomed the P&T Committee members.
➢ *Reading of Confidentiality and Mission Statements*	*Perry Brown, M.D.*	Dr. Brown read the Confidentiality and Mission Statements.
➢ *Approval of Minutes from November 15, 2013 Meeting*	*Perry Brown, M.D.*	The November 15, 2013 meeting minutes were reviewed. Dr. Geyman made a motion to accept the minutes, Dr. Calley seconded and the Motion passed. The minutes were accepted as proposed.
➢ *DERP Update*	*Tami Eide, PharmD.*	**DERP Update** Dr. Eide provided an update of activities from the Drug Evaluation Review Project (DERP). There are three reports in progress. A combined Asthma-COPD report, which is a streamlined updated evidence review report, will be finalized in June. Updated streamlined evidence reports for Diabetes Drugs and Targeted Immune Modulators will be finalized in July. Streamlined reports include head to head trials only, and do not include placebo controlled studies. At the

		next meeting DERP governance meeting scheduled April 30, the following topics will be discussed as possible future evidence reviews: Hepatitis C Drugs, Lipotropic therapy- PCSKO Inhibitors, Inhaled Antibiotics and a Long-acting Opioid update.
➢ *Overview of the Joint National Committee (JNC 8) Hypertension Guidelines*	*Paula Townsend, PharmD Magellan Health Services*	**Overview of the Joint National Committee (JNC 8) Hypertension Guidelines** Dr. Townsend provided an overview of the report: The 2014 Evidence-based Guideline for the Management of High Blood Pressure. This report was restricted to randomized control trial (RCT) evidence and indicated that similar treatment goals are defined for all hypertensive patients except when evidence reviews supported different goals for a subpopulation. The recommended drug choice was among four drug classes (angiotensin converting enzyme inhibitors (ACEI), aldosterone receptor blockers (ARB), calcium channel blockers (CCB) or thiazide diuretics but not beta blockers (BB), with dosages supported by RCT evidence. Evidence reviewed addressed a limited number of questions judged to the highest priority and was reviewed by experts including those affiliated with professional and public organizations. The guidelines recommend a target blood pressure goal in patients 18-59 years without major comorbidities of less than 140/90. In patients 60 and older who do not have diabetes or chronic kidney disease (CKD), the goal is now less than 150/90 rather than 140/90 and in patients less than 60 years with diabetes or CKD, the new goal is less than 140/90. The first line drugs being endorsed include thiazide diuretics, CCBs, ACEIs or ARBs. Thiazides are more effective than a CCB or ACEI and ACEI are more effective than a CCB in improving heat failure outcomes. Blood pressure control rather than the specific class used to achieve that control was the most relevant consideration. Classes not recommended are alpha and beta blocking agents, vasodilators, beta blockers, central alpha-2 adrenergic agonists, direct vasodilating agents, aldosterone receptor antagonists, adrenergic neuronal depleting agents and loop diuretics.
Public Comment Period	*Perry Brown, M.D.* *Chris Johnson*	**Public Comment Period** Dr. Perry Brown reviewed Health and Welfare's Guidelines for Scientific Information Provided by Pharmaceutical Manufacturer Representatives. Five (5) people signed up to speak during the public comment period. Public testimony was received from the following speakers:

Drug Class Reviews and Committee Recommendations		
➢ *Angiotensin Modulators/Angiotensin Modulator Combinations*	*Paula Townsend, PharmD*	

Speaker	Representing	Agent	Class
Tosha Johnson, NP	Self	Eliquis	Anticoagulants
Susan Heineman,PharmD	Pfizer	Eliquis	Anticoagulants
Steve Hall, RPh	Boehringer Ingelheim	Pradaxa	Anticoagulants
Mark Handley, PhD	Astra Zeneca	Farxiga	Hypoglycemics, Sodium-Glucose Cotransporter-2 Inhibitors (SLGT2)
Laura Litzenberger, PharmD, MBA	Janssen	Invokana	Hypoglycemics, Sodium-Glucose Cotransporter-2 Inhibitors (SLGT2)

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 of 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?

<u>Angiotensin Modulators/Angiotensin Modulator Combinations</u>
Dr. Townsend announced one new product, Epaned (enalapril maleate), which is a powder for oral solution, indicated for the treatment of hypertension in adults and children >1month of age. There are four new generics, telmisartan (for Micardis) , telmisartan/HCTZ (for Micardis HCT), telmisartan/amlodipine (for Twynsta) and amlodipine/valsartan/HCTZ (for Exforge HCT).

Committee Recommendations
The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety within each subclass. They recommended that Epaned be prior authorized on a case by case basis and Texturna not be a first line agent.

➢ *Beta Blockers*	*Paula Townsend, PharmD*	**Beta Blockers** Dr. Townsend announced that there were no new significant clinical trials. A new product Inderal XL (propranolol ER) capsules, originally approved in 2003 became commercially available March 2014. It is indicated for the treatment of hypertension and similar to InnoPran XL, it is designed for once daily dosing at bedtime. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Calcium Channel Blockers*	*Paula Townsend, PharmD*	**Calcium Channel Blockers** Dr. Townsend announced there were no new significant clinical trials for this drug class. There is one new product in this class, Nymalize (nimodipine), an oral solution indicated for the treatment for improvement in neurological outcome by reducing the incidence and severity of ischemic deficits in adults with subarachnoid hemorrhage from ruptured intracranial berry aneurysms. Nimodipine has been available as a liquid filled capsule since 1988. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *PAH Agents, Oral*	*Paula Townsend, PharmD*	**Pulmonary Arterial Hypertension (PAH) Agents, Oral** Dr. Townsend reviewed the 2013 WHO classification of Pulmonary Hypertension which groups PAH patients into 5 different clinical groups based on causality. Dr. Townsend reviewed clinical studies for two new drugs in this class. Opsumit (macitentan) is an endothelin receptor antagonist indicated for treatment of PAH to delay disease progression. This drug has an embryo-fetal toxicity warning and is only available to females through the Opsumit REMS program. The second new drug is Adempas (riociguat), indicated in WHO Group 1 PAH to improve exercise capacity, improve WHO functional class and delay clinical worsening. It is also indicated for persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) after surgical treatment of inoperable CTEPH to improve exercise capacity and WHO functional class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. For the new drugs, the committee recommended that Adempas be made available for its' specific indications. The Committee recommended continuing therapeutic criteria for this class of

		medications.
➢ *Anticoagulants*	*Paula Townsend, PharmD*	**Anticoagulants** Dr. Townsend reviewed clinical studies supporting Pradaxa's (dabigatran) new indication for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days. Eliquis (apixaban) is also now indicated for the prophylaxis of DVT in patients who have undergone hip or knee replacement surgery. Dr. Townsend reviewed the clinical studies supporting this indication. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. The clinical PA criteria will be updated to reflect the new indications.
➢ *Platelet Aggregation Inhibitors*	*Paula Townsend, PharmD*	**Platelet Aggregation Inhibitors** Dr. Townsend indicated that there is no new significant clinical information for drugs in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Coronary Vasodilators*	*Paula Townsend, PharmD*	**Coronary Vasodilators** Dr. Townsend announced no new significant clinical information in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Lipotropics, Other*	*Paula Townsend, PharmD*	**Lipotropics, Other** Dr. Townsend reviewed clinical studies of a new drug, Juxtapid (lomitapide) indicated for treatment in homozygous familial hypercholesterolemia. Lomitapide is contraindicated in patients with moderate or severe hepatic impairment or active liver disease or in pregnancy and only available through a restricted REMS program. She also reviewed clinical studies for another new drug Kynamro (mipomersen), which is also indicated in patients with homozygous familial

		hypercholesterolemia. **Committee Recommendations** The Committee concluded that there was no evidence for efficacy, effectiveness or safety to support preferring one agent over another. They recommended that Kynamro and Juxtapid be designated as non-preferred and require prior authorization. They recommended a DUR study on the combined therapy of simvastatin and gemfibrozil.
➢ *Lipotropics, Statins*	*Paula Townsend, PharmD*	**Lipotropics, Statins** Dr. Townsend reviewed clinical studies, indications, dosing and adverse reactions for a new combination drug, Liptruzet (atorvastatin/ezetimibe). **Committee Recommendations** The Committee concluded that there was no evidence for efficacy, effectiveness or safety to support preferring one agent over another. They recommended that the preferred agent list include a high potency agent and that access be available for an agent with minimal adverse drug to drug interactions. They recommended that Crestor only require trial and failure of atorvastatin.
➢ *Topical Androgenic Agents*	*Paula Townsend, PharmD*	**Topical Androgenic Agents** Dr. Townsend announced that the AndroGel 1% pump is to be discontinued due to a decrease in utilization. The 1% packets and all 1.62% formulations will remain available. She reported that an FDA safety alert was issued for these products in January of 2014. The FDA is investigating the risk of cardiovascular events including stroke, myocardial infarction and death in men taking approved testosterone products. **Committee Recommendations** The committee concluded that there were no evidence based differences to support preferring any agent over another in this class. The committee recommended maintaining the current therapeutic criteria for this class of drugs.
➢ *BPH Treatments*	*Paula Townsend, PharmD*	**BPH Treatments** Dr. Townsend announced that there was no new significant clinical information for drugs in this class. **Committee Recommendations**

		The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Bladder Relaxant Preparations*	*Paula Townsend, PharmD*	**Bladder Relaxant Preparations** Dr. Townsend announced one new product, Oxytrol (oxybutynin transdermal patch) for OTC sale for women18 years and older. The prescription product remains available for both men and woman. Detrol LA is now available generically as tolterodine ER. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. The committee recommended that if the OTC oxybutynin patch was more cost effective than the prescription drugs that the Director of Health and Welfare approve the Bladder Relaxant Preparations as a covered OTC class.
➢ *Bone Resorption Suppression and Related Agents*	*Paula Townsend, PharmD*	**Bone Resorption Suppression and Related Agents** Dr. Townsend announced a new indication for Prolia (denosumab) for the treatment of adults and skeletally mature adolescents with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity. Fosamax solution is now available generically as alendronate solution. **Committee Recommendations** The committee concluded that there were no evidence based differences to support preferring any agent over another in this class. The Committee discussed the use of calcitonin salmon and the risk of cancer. They recommended that it be designated a non-preferred agent. They recommended grandfathering current patients and having the Medicaid pharmacy unit reach out to current patients and providers concerning continued use.
➢ *Colony Stimulating Factors*	*Paula Townsend, PharmD*	**Colony Stimulating Factors** Dr. Townsend announced a new drug Granix (tbo-filgrastim), which is indicated for the reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness

		or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Erythropoiesis Stimulating Proteins*	*Paula Townsend, PharmD*	**Erythropoiesis Stimulating Proteins** Dr. Townsend announced that there was no new significant clinical data. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Phosphate Binders*	*Paula Townsend, PharmD*	**Phosphate Binders** Dr. Townsend announced one new drug to the market. Velphoro (sucroferric oxyhydroxide) is indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. She reviewed the available information from two randomized clinical trials. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. They recommended that at least one calcium based and one non-calcium based product be available and daily pill burden be taken into account.
➢ *Hypoglycemics, Insulin*	*Paula Townsend, PharmD*	**Hypoglycemics, Insulin** Dr. Townsend announced that there was no new significant clinical information for drugs in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Hypoglycemics, Incretin Mimetics/Enhancers*	*Paula Townsend, PharmD*	**Hypoglycemics, Incretin Mimetics/Enhancers** Dr. Townsend reviewed information from a study published last year in JAMA Internal Medicine concerning a possible increased risk of pancreatitis and pre-cancerous pancreatic cellular changes with sitagliptan and exenatide. She also reviewed the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) consensus statement around this. Dr. Townsend reviewed a study on saxagliptin and cardiovascular outcomes in patients with Type 2 Diabetes Mellitus. She announced that Juvisync has been voluntarily discontinued by the

		manufacturer for business reasons. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Hypoglycemics, Meglitinides*	*Paula Townsend, PharmD*	**Hypoglycemics, Meglitinides** Dr. Townsend announced that this is a returning drug class for Idaho PDL review. The AACE Guidelines designate glinides as last in the hierarchy of usage for mono, dual and triple therapy because of efficacy and safety issues. Like sulfonylureas they have the highest hypoglycemia risk of non-insulin therapy. **Committee Recommendations** The Committee recommended that all of these agents be designated as non-preferred. The Committee recommended that Medicaid do a therapeutic consultation with the 13 users of these drugs.
➢ *Hypoglycemics, TZD*	*Paula Townsend, PharmD*	**Hypoglycemics, TZD** Dr. Townsend announced no new significant clinical data for this drug class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Hypoglycemics, Sodium-Glucose Cotransporter – 2 Inhibitors (SLGT2)*	*Paula Townsend, PharmD*	**Hypoglycemics, Sodium-Glucose Cotransporter – 2 Inhibitors (SLGT2)** Dr. Townsend announced that this is a new drug class. These agents are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes. She reviewed the clinical trials, indications and side effect profiles for the two drugs currently approved in this class, Invokana (canagliflozin) and Farxiga (dapagliflozin). **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. The Committee recommended that they be prior authorized through an electronic edit at point of sale that would require trial and failure of another Type 2 agent.

➢ *Growth Hormone/Growth Factors – Criteria Review*	*Jane Gennrich, PharmD*	**<u>Growth Hormone/Growth Factors - Criteria Review</u>** Dr. Gennrich reviewed the prior authorization criteria guidelines for growth hormone and growth factors. The Department has had the same Growth Hormone criteria for several years. She discussed growth hormone criteria for Chronic Renal Impairment, Growth Hormone Deficiency, Prader-Willi Syndrome, Turner Syndrome, Idiopathic Short Stature, Small for Gestational Age and HIV Cachexia. She then reviewed the therapeutic criteria for Increlex. The criteria match the FDA approved indication. Medicaid has not had a request for Increlex in the past two years.
➢ *Growth Hormone/Growth Factors*	*Paula Townsend, PharmD*	**<u>Growth Hormone/Growth Factors</u>** Dr. Townsend announced that there was no new significant clinic information for drugs in this class. She did note that Tev-Tropin is on long-term back order without a resolution date. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. Dr. Turner, Dr. Eide and Dr. Gennrich will be meeting with an endocrinologist prior to the May P&T Committee Meeting to discuss the Department's clinical criteria. We will continue review of this drug class at the May P&T meeting.
➢ *Pancreatic Enzymes*	*Paula Townsend, PharmD*	**<u>Pancreatic Enzymes</u>** Dr. Townsend announced that there was no new significant clinical information for this drug class. **Committee Recommendations** The committee concluded that there were no evidence based differences to support preferring any agent over another in this class.
➢ *Proton Pump Inhibitors*	*Paula Townsend, PharmD*	**<u>Proton Pump Inhibitors</u>** Dr. Townsend announced that AcipHex (rabeprazole) has a label extension for use in patients one year and older for treatment of GERD. There is a new product, esomeprazole strontium indicated for treatment of GERD, risk reduction of NSAID-induced gastric ulcers, pathological hypersecretory conditions and H. pylori eradication in combination with amoxicillin and clarithromycin. There is no clinical comparative data with other available agents for this drug. Dr. Townsend also reviewed the 2013 American College of Gastroenterology Guidelines for the Diagnosis and Treatment of GERD.

		Committee Recommendations The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness. The Committee recommended a DUR study on this drug class looking at QT interval issues, duration of therapy and histamine blocker step down therapy. They recommended that the PA form indicate that prior authorization is needed for a quantity of more than once daily therapy.
➢ *H. Pylori Treatments*	*Paula Townsend, PharmD*	**H. Pylori Treatments** Dr. Townsend announced that tetracycline is still not available at this time. There is one new generic, lansoprazole/amoxicillin/clarithromycin for PrevPac. Helidac is currently unavailable due to the tetracycline shortage that has been occurring since October. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents and that preferred status should be based on cost-effectiveness.
➢ *Other Committee Business*	*Tami Eide, PharmD*	**Other Committee Business** Our next P&T Committee meeting is scheduled for May 23, 2014. There was no other committee business. The meeting adjourned at 3:00 p.m.

Pharmacy and Therapeutics Committee
Public Comment
April 18, 2014

Committee

Do we have any providers? We have none signed up for medical provider or private citizens. So it's just the approved industry. Okay, great. So first off, we have Susan Heineman from Pfizer please, speaking about Eliquis.

Susan Heineman, PharmD

Good morning, I'm Sue Heineman, I'm a pharmacist and Medical Outcomes Specialist with Pfizer. I am here to respectfully request that Eliquis, apixaban, remain a preferred agent for both non-valvular atrial fibrillation, and our new indication, for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip and knee replacement surgery. The new doses for this new indication is 2.5 mg twice daily. For hip, it is 35 days and for knee, it is 12 days. It is taken 12-24 hours after surgery. There were three registration trials, ADVANCE-1, -2 and -3, that contributed to our getting this indication. They had the same primary efficacy outcome and the same safety outcome. The comparison was done with apixaban 2.5 m orally twice daily versus enoxaparin. In ADVANCE-3 and ADVANCE-2, which were the most recent ones, the dosing was a little bit different. I'll skip to the key points and the differences between the trials, and then if there are any questions after that. So in ADVANCE-3 that was published in the New England Journal of Medicine, and I believe that the articles were submitted, as well as my summary, so I'm not sure if you have that in front of you, but it may make the reading of the numbers a little bit easier. So, again, this was apixaban 2.5 mg twice daily versus enoxaparin 40 mg for DVT prophylaxis in total hip. ADVANCE-3. Apixaban was superior. It was a non-inferiority trial, but there are ways to set the statistics so that you can show non-inferiority and show inferiority, and you can also show superiority. So we did achieve superiority with the event rates of 1.4% in the apixaban group and 3.9% in enoxaparin. Major bleeding, which is also a primary safety outcome was 0.8% in apixaban and 0.7% in the enoxaparin group. Major bleeding with clinical relevant non-major bleeding was 4.8% with apixaban and 5% enoxaparin, and then all bleeding was reported with apixaban at 11% and 12% in the enoxaparin group. The mean treatment days were 34 days, and the mean time to get the medication was 19 days post-op. ADVANCE-2 was published in 2010 in the Lancet. This was the difference between this one; it had the same enoxaparin dose of 40 mg subcutaneously once daily, but this is the total knee. Again, a non-inferiority trial, showing superiority. Apixaban had 15% events compared to enoxaparin, which was at 24%, and then in the safety and the bleeding events, 0.6% for apixaban for major bleeding and 0.9% enoxaparin. Major plus clinically relevant non-major bleeding was apixaban 3.5% and enoxaparin 4.8%, and then all bleeding was 6.9% in apixaban and enoxaparin was 8.4%. Again, this is the knee, so the mean treatment days were 12, and post-op was the mean time of administration was on day-19. ADVANCE-1 was published in 2009 in the New England Journal of Medicine. This was total knee. The difference between this one was we used enoxaparin 30 mg subcutaneously every 12 hours. This did not meet the primary efficacy end point for non-inferiority; it did not achieve inferiority, it did not achieve superiority, it just did not meet the end point for non-inferiority. Event rates were 9% for apixaban, 8.8% for enoxaparin, with a P-value of 0.06. Major bleeding was 0.7% apixaban and 1.4% enoxaparin. Major plus clinical relevant non-major bleeding was 2.9% apixaban and enoxaparin was 4.3%. All

bleeding was reported in 5.3% of apixaban and 6.8% of enoxaparin. There was another piece that I submitted, and Tami, forgive me, I don't recall if you wanted to hear about the end-stage renal disease data.

Committee

No, thank you, though.

Susan Heineman, PharmD

But there were two changes in the package insert for that one, so it can be used in patients who are end-stage renal disease, as long as they are on hemodialysis, and then the bridging information was updated in the package insert, so that there is no bridging needed, and there are some recommendations on when to stop the medication. So that's the updated information. Again, just requesting that Eliquis remain a preferred agent on the PDL for both indications.

Committee

Thank you. Anybody have questions for Susan? Thank you very much.

Tosha Johnson, NP

Can I make a quick statement? I'm actually a provider, I signed on the wrong list, and I have a symposium to get back to. I am so sorry, and I apologize to all. This is my first time doing this, so I didn't know there was a list. I signed on the different one.

Thank you for allowing me, I won't take much time, but my name is Tosha Johnson, and I am a nurse practitioner, practicing at St. Alphonsus Cardiology program. I am not getting any compensation for being here today. I am here on, basically on behalf, to help the population that I see a lot of. I do see a lot of Medicaid people in our practice. Just to be able to have the new, novel oral anticoagulants remain on formulary, hopefully without a prior authorization, to be able to give us that ability to have different tools in our armory to be able to treat non-valvular atrial fibrillation. Especially now, she went ahead and gave us a good presentation on, it doesn't have to be renally dosed now all the way down into hemodialysis, and that's huge in this population. I guess that's all I really wanted to say is that to hopefully to be able to remain on the formulary as it currently is.

Committee

Does anybody have any questions for her?

Question

Specifically, are you just talking about Eliquis, or are you talking about the other agents?

Tosha Johnson, NP
Well Eliquis definitely, because Eliquis is the only one that you don't have to renally dose as far as all the way down into hemodialysis, where the other ones, there is some concern. You know, it's something that has to be able to be watched a little bit more. But all of them, you know, having something else on board other than Warfarin is ideal. Okay, thank you so much.

Steve Hall, RPH
Good morning, my name is Steve Hall. I am also a pharmacist and the Associate Director of Health Economics and Outcomes Research for Boehringer-Ingelheim Pharmaceuticals, and I wish to provide testimony for Pradaxa or dabigatran, which is a new generation oral anticoagulant. I'd like to review our new indications and also answer any questions you may have. So Pradaxa is a direct thrombin inhibitor with two new indications, recently approved by the FDA. These were just announced on April 7th of this year. It is now indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days. It is also now indicated to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. In both the treatment and reduction in risk of recurrent DVT and PE, the recommended dose of Pradaxa is 150 mg taken orally twice a day after 5-10 days of parenteral anticoagulation for patients with creatinine clearances >30 ml/minute. The dosing recommendations for patients with creatinine clearances of <30 ml/minute or on dialysis cannot be provided. Also, the concomitant use of Pgp inhibitors in patients with creatinine clearance <50 ml/minute should be avoided, and the concomitant use of Pradaxa with Pgp inducers reduces exposure to Pradaxa and should also generally be avoided. The RECOVER and RECOVER-II trials, which included patients with DVT and PE, who were treated with parenteral anticoagulant therapy for 5-10 days, showed that Pradaxa was non-inferior to Warfarin in reducing DVT and PE after a median of 174 days of treatment. It was associated with lower rates of overall bleeding and a higher rate of GI bleeding; 3.1% versus 2.4%. The RE-MEDY trial included patients who had been previously treated for an acute DVT and PE, with anticoagulant therapy for 3-12 months, and it showed Pradaxa was non-inferior to Warfarin, reducing DVT and PE after a median of 534 days of treatment. It also was associated with lower rates of overall bleeding and a higher rate of any GI bleeding; 3.1% to 2.2%. The RE-SONATE trial included patients who had been previously treated for an acute DVT and PE with anticoagulant therapy for 6-18 months, and it showed that dabigatran reduced the risk of DVT and PE recurrence by 92% compared to placebo after a median of 182 days of treatment. As we would expect, Pradaxa was associated with higher rates of any bleeding; 10.5% versus 6.1%, clinically relevant non-major bleeding, 5% versus 2%, and GI bleeding 0.7% versus 0.3% versus placebo. I also, in the interest of fair and balanced representation, it is important for Boehringer, as well as for me, to share our black box warning, which is a class effect with these agents, which is that premature discontinuation of any oral anticoagulant, including Pradaxa, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if Pradaxa is discontinued for a reason, other than pathological bleeding or completion of a course of therapy. And then

the second piece with regard to black box is that epidural or spinal hematomas may incur in patients treated with Pradaxa or receiving neuraxial anesthesia or undergoing spinal puncture. These could result in long-term or permanent paralysis, so patients should be monitored frequently for signs and symptoms and, if observed, should be treated urgently. As always, benefits versus risks should be considered. So, in summary, Pradaxa, a direct thrombin inhibitor, has three indications; first to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, and that's what we were approved for back in October of 2010, and then also the new indications; the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days, as well as to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. I will be happy to answer any questions that you may have.

Committee
Thank you. Any questions from the Committee members?

Steve Hall, RPH
Thank you much.

Committee
Thank you. Next up, I have Mark Handley from AstraZeneca.

Mark Handley, PhD
Good morning everybody. I'm Mark Handley from AstraZeneca, MSL. Thank you very much for giving me the opportunity to talk today on Farxiga. Before I begin, I just want to apologize. I have a really bad cold and, today, this morning, it decided to just really kick in, so I'm struggling a little and I'm not running on all cylinders, but away we go. You should have gotten my testimony by email yesterday. I'm not going to read it. Instead, I'm going to focus specifically on what you asked for, which is the long-term data, the weight loss data, the lipid data, and the blood pressure data. Excuse me, see, I'm not running on all cylinders. So just to level set us with the clinical trials, we had a very robust clinical trial, a study looking at patients from early in diabetes to late diabetes with common antidiabetics, such as metformin, TZDs, TPP4s, and insulin. With our 24-week data, as far as A1c reduction, we had a range reduction of -0.4 to -0.7. Now looking at the longer-period trials, which is what you were asking for, and all of this is in that testimony, you can find the references if you'd like, looking at long-term trials, one of the studies with metformin add-on to Farxiga or the other way around versus Glipizide add-on to metformin, had a reduction of -0.5 A1c at week52, and then four years later, it was still below baseline at -0.3. Additional trials looking at Farxiga plus insulin versus placebo plus insulin, we had an A1c below baseline at -3.5 at two years, and that was just a little bit of an increase from its initial drop. An additional two-year study with

metformin add-on, the two-year data, the A1c drop was still below baseline at -0.3, and that was just a little bit of an increase. Weight reduction was robust in all of our trials. The 24-week trial data had a weight range reduction of -8 kg to -2.2 kg. Now looking at the data that you're looking for, the longer-term data, in all of these trials, the weight remained constant at basically at the same level, with the long-term data range being -3.4 kg to about -5 kg at those longer-term trials that I just mentioned. Moving now to blood pressure, we looked at reduction of systolic blood pressure in most of our trials, and the range for that was a -1.3 to a -5.3 mmHg for those patients in phase-3 trials. And then finally, looking at safety, the 5% or greater adverse events for safety were female genital infections, nasopharyngitis, and urinary tract infections. Those seemed to be transient and went away after standard care. Looking at lipids, we did see an increase in total cholesterol of 2.5% versus 0% with placebo. Interestingly, and this is a class effect, there was an increase in LDL of 2.9% versus 1% with placebo. So that is covering the information that you asked. There is additional safety that you can look at on the PI if you want, and I hope that you have all of the information now to make an informed decision.

Committee
Thank you. Are there any questions? Thank you very much. Last up, we have Laura Litzenberger from Janssen.

Laura Litzenberger, PharmD, MBA
Good morning, I'm Laura Litzenberger with the Health Outcomes Group at Janssen, and I'm here today to provide additional information on Invokana, which is also a sodium glucose transporter inhibitor for type-2 diabetes. This information was omitted from the therapeutic clinical review that you have and relates to several endpoints of clinical interest, including glucose control, weight, blood pressure, lipids, and infection risk. Invokana also has had a very broad development program, studying the drug as monotherapy, in combination with metformin alone, in combination with metformin with sulfonylureas, and metformin TZDs. The efficacy of Invokana has also been compared directly to PPD inhibitors; sitagliptin and the sulfonylurea glimepiride. Invokana 100 mg and 300 mg once daily resulted in a statistically significant improvement in A1c of 0.77% reduction, with the 100 mg, and a 1.03% reduction with the 300 mg. The reduction in A1c is specific to what baseline level of A1c the patients had, so these reductions were based on people that had a baseline A1c of around 8, so what you would see is a 0.77% reduction with the 100 mg and a 1% reduction with the 300 mg dose. These results were similar throughout the development program when Invokana was given with metformin or metformin with other glucose-lowering agents, so the range for 100 mg was 0.6% to 0.9% reduction and at 300 mg, was 0.7% to 1% reduction. Meaningful, but smaller, reductions in A1c were also seen in elderly patients and patients with moderate renal failure, and statistically superior improvements in A1c were seen, when comparing Invokana 300 mg to glimepiride or to sitagliptin. The sustained A1c lowering effect was demonstrated at both one-year and two-year and blinded studies, so in the 100 mg, the sustained reduction was at 0.81% for the 100 mg, and 1.1% for the 300 mg. In addition to the A1c lowering, Invokana has positive effects on other interesting endpoints for diabetes management, such as weight and blood pressure. So, Invokana 100 mg provided a

2%-3% reduction in body weight, and Invokana 300 mg provided a 2%-4% reduction in body weight, and those are both statistically significant. Regarding blood pressure, the decrease in blood pressure for 100 mg was 2.5-5.4 mmHg, and 3.5-6.6 mmHg for the 300 mg. There were dose-related increases in LDL cholesterol; 100 mg was 4.4 mg/dL and 300 mg was 8.2 mg/dL. There were also dose-related increases in HDL and decreases in triglyceride, and the LDL to HDL ratio was virtually unchanged. The most common adverse events with Invokana were genital mycotic infections and urinary tract infections. Female genital mycotic infections occurred in 10.5%-11.5% of patients and led to discontinuation in 1.2%. In males, genital mycotic infections occurred in 4.2% and 3.7% of patients taking Invokana, and discontinuation was at 0.9%. Urinary tract infections occurred in 4.5%-6% of patients taking Invokana, and discontinuations in 0.3% of patients. So what we have is once-daily Invokana, which presents a new mechanism of action for the treatment of type-2 diabetes. It provides lowering of A1c, greater reductions in blood pressure, and greater weight loss. We request that you consider Invokana and add it to your PDL. Any questions?

Committee
Thank you very much.