Janet T. Mills
Governor

Jeanne M. Lambrew, Ph.D.
Commissioner

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TO: Maine Drug Utilization Review Board
DATE: 06/12/21
RE: Maine DUR Board **Meeting** minutes from June 8, 2021

ATTENDANCE	PRESENT	ABSENT	EXCUSED
Linda Glass, MD	X		
Lisa Wendler, Pharm. D., Clinical Pharmacy Specialist, Maine Medical CTR	X		
Mike Antoniello, MD			X
Kathleen Polonchek, MD	X		
Kenneth McCall, PharmD	X		
Erin Ackley, PharmD.			X
Corinn Martineau, PharmD.	X		
Non –Voting			
Mike Ouellette, R.Ph., Change Healthcare	X		
Jacquelyn Hedlund, MD, Change Healthcare	X		
Jan Wright, MaineCare Pharmacy Operations Manager	X		
Anne-Marie Toderico, PharmD MaineCare Pharmacy Director	X		

Guests of the Board:

CALL TO ORDER: 6:30PM

Anne- Marie Toderico called the meeting to order at 6:30 PM.

PUBLIC COMMENTS

Tom Parmelee from Aurinia: Highlighted the attributes of Lupkynis.
Brian Denger from Parent Project Muscular Dystrophy: Highlighted the attributes of Amondys 45.
John Rivituso from Chiesi: Highlighted the attributes of Bronchitol.
Beth Zanrucha from Sarepta: Highlighted the attributes of Amondys 45.
Nicole Trask from Janssen: Highlighted the attributes of Ponvory.
Mark Staveski from Oncopeptdies: Highlighted the attributes of Pepaxto.

OLD BUSINESS

DUR MINUTES

The March DUR meeting minutes were accepted.

Board Decision: The Board unanimously approved the above recommendation.

MAINECARE UPDATE

Introduced Anne-Marie Toderico the new MaineCare Pharmacy Director.

REVISED CLINICAL CRITERIA/PREFERRED REVIEW

- None at this time

NEW BUSINESS

INTRO: USE OF HYDROXYCHOLOQUINE AND CLOROQUINE PRE- AND POST COVID

One of the challenges of treating people with schizophrenia is compliance with daily oral medication regimens. It is estimated that the adherence rate is less than 60%. Contributing to low adherence is the side effect profile with antipsychotics, both short and long term. Additionally, patients may still hallucinate or have delusions that convince them to stop taking medications, even when they were being taken appropriately. In patients who struggle with medication adherence, there is the option of every 2 week or once monthly injectable long-acting antipsychotics (LAIs), either given IM or SC. This strategy can be employed in those who have a history of adequate response to oral treatment, but relapse due to non-adherence. Using long-acting antipsychotics can prevent hospitalizations and are a way to deal with issues that complicate compliance, such as substance use, lack of stable housing or social structure, and unstable disease. Using LAIs can identify patients whose disease refractoriness is due to compliance alone, versus those who have a sub-optimal response to oral treatment. Additionally, some patients may have a better response to a consistent blood level of drug, rather than the peaks and troughs that come with oral formulations. Some may find side-effects less bothersome. However, there are still potential issues with compliance since patients need to stay on a schedule and appear at the provider's office to receive the injections. Concern is that there may be excessive waste in the system if patients miss appointments or refuse the injection. Most LAIs are provided through "white bagging" which means prescriptions are filled, typically by a specialty pharmacy, and shipped to the provider office or clinic. Because they are labeled for an individual patient, they are not reusable for another patient. Additionally, injectable antipsychotic medications are substantially more costly than oral formulations. We will use paid, non-reversed Medicaid pharmacy and medical claims from calendar year 2019 (pre-COVID), excluding members with Part D, MaineRX and TPL. We will look at all pharmacy claims for monthly LAIs in calendar year 2019. We will determine if the monthly prescriptions filled at the pharmacy level were administered by looking to see if the appropriate CPT code was billed within 7 days of pharmacy billing. We will look at 5 antipsychotics that are administered on every 4 week schedules: Invega Sustenna®, Aristada® (except 882mg), Abilify Maintena®, Perseris®, and Haloperidol Decanoate. Zyprexa® Relprevv™ can be included in the analysis, but we will need to consider that it may be given every 2 or 4 weeks. The goal of the analysis is to evaluate compliance, persistence, and waste.

Board Decision: Add in provider prescribing into the analysis to see members are going to one provider or multiple.

PRESENTATION: USE OF HYDROXYCHOLOQUINE AD CLOROQUINE PRE- AND POST COVID

Hydroxychloroquine and chloroquine early on were touted as possible treatments for SARS-CoV-2 infections, due to their anti-inflammatory, antiviral and antithrombotic properties. These drugs interfere with autophagy and lysosomal activity, interact with membrane stability and alter signaling pathways and transcriptional activity, which can result in inhibition of cytokine production and modulation of certain co-stimulatory molecules. Data has shown that in invitro it has the capability of inhibiting viral

replication of several types, including influenza, HIV and hepatitis viruses. To date, there is no in vitro data suggesting it suppresses SARS-CoV-2. Additionally, the underlying therapeutic effects and mechanisms of action of the drug remain uncertain. On March 28, 2020, the FDA issued an EUA to allow hydroxychloroquine sulfate and chloroquine sulfate donated to the Strategic National Stockpile to be distributed and used for hospitalized COVID-19 patients. On April 24, 2020, after widespread panic buying and prescribing of the drugs in the outpatient setting, along with some adverse events and deaths, the FDA cautioned against their use outside of hospital settings or clinical trials. In the past few months, trials in both the inpatient and outpatient settings have shown no proven benefits from the use of hydroxycholorquine or chloroquine in the treatment of COVID-19 infections and therefore, current recommendations do not support its use for treatment in the inpatient or outpatient settings. Inpatient trial of 479 patients did not show a benefit in either 14-day clinical status or 28-day mortality, resulting in early termination of the trial. Other open-label trials also showed no benefit early on and the chloroquine arms were terminated early. Outpatient trials have shown no benefit in reducing hospitalization rates or time to symptom resolution. On June 15th, 2020, the FDA revoked the EUA to use hydroxychloroquine and chloroquine to treat COVID in hospitalized patients. We used paid, non-reversed Medicaid pharmacy and medical claims date from March 2020 – December 2020 excluding members with Part D, MaineRX and TPL. We looked at all members who were prescribed first dose of hydroxychloroquine or chloroquine in either inpatient or outpatient setting, excluding those with a rheumatologic diagnosis of SLE or arthritis. Will look at the number of days prescribed and see if in the outpatient setting, refills were given. We will look for the diagnosis of COVID and see if the number of prescriptions significantly decreased after the June FDA revocation of the EUA, both in medical and pharmacy claims.

Recommendation: There probably were a few prescribers using hydroxychlorquine or chloroquine for prevention or treatment of COVID, but use seemed not to be widespread in the Maine Medicaid population. Given the data did not show utility of these drugs in preventing or treating COVID infections, and given the fall in incidence of COVID infections, no specific intervention is warranted at this time.

Board Decision: The Board unanimously approved the above recommendation.

NEW DRUG REVIEW

Bronchitol® (mannitol); **PDL category-** Antiasthmatic- CFTR Potentiator and Combinations

D-Mannitol (referred to throughout as mannitol), the active ingredient of Bronchitol®, is a hexahydric sugar alcohol. The exact mechanism of action for its approved indication is not known. It is indicated as an add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with cystic fibrosis (CF). Use Bronchitol® only for adults who have passed the Bronchitol® Tolerance Test (BTT). (see Recommended Dosage section for further information). The safety and efficacy of Bronchitol® for the treatment of CF were assessed in 3 randomized, double-blind, controlled studies that were 26 weeks in duration. Study one included only adults and treatment with Bronchitol® resulted in a statistically significant improvement in FEV1; the treatment difference between Bronchitol® and control for the adjusted mean change in FEV1 from baseline over 26 weeks was 51ml.

Recommendation: Bronchitol® to non-preferred.

Clinical Criteria:

- For the treatment of patients ≥18 years of age with CF.

- Bronchitol will be considered as add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with cystic fibrosis (CF). Use Bronchitol® only for adults who have passed the Bronchitol® Tolerance Test (BTT). (see Recommended Dosage section for further information)

Board Decision: The Board unanimously approved the above recommendation.

Cabenuva® (cabotegravir and rilpivirine kit); **PDL category-** Antiretrovirals

Cabenuva® contains 2 long-acting HIV-1 antiretroviral agents, including cabotegravir co-packaged with rilpivirine. Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Rilpivirine is a diaryl-pyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase. Rilpivirine does not inhibit the human cellular DNA polymerases α, β, and γ. It is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per ml) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. The efficacy of Cabenuva® was assessed in two phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials (Trail 1 FLAIR; Trial 2 ATLAS) in HIV-1 infected subjects who were virologically suppressed (HIV-1 RNA <50 copies/ml). Cabenuva® must be administered by a healthcare professional and there should be an oral lead-in for about 1 month prior to the initiation of Cabenuva® to assess the tolerability of cabotegravir and rilpivirine. In 2 open-label, active-controlled non-inferiority studies comparing a cabotegravir plus rilpivirine regimen with current antiretroviral regimen, the primary endpoint (the proportion of subjects with plasma HIV-1 RNA greater than or equal to 50 copies/ml at week 48) was 2% in both studies with the cabotegravir plus rilpivirine regimen as compared with 2% in one study (FLAIR) and 1% in the second study (ATLAS) for the current antiretroviral regimen used.

Recommendation: Cabenuva® to non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Gemtesa® (vibegron); **PDL category**- Antispasmodics- Long Acting

Vibegron, the active ingredient of Gemtesa®, is a selective beta-3 adrenergic receptor agonist. Activation of the beta-3 adrenergic receptor increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling. It is indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. he safety and efficacy of Gemtesa® were assessed in a 12-week double-blind, randomized, placebo-controlled and active-controlled study that included patients with OAB. Patients were randomized to receive either Gemtesa® 75mg, placebo, or active control PO once daily for 12 weeks. For study entry, patients had to have symptoms of OAB for at least 3 months with an average of 8 or more micturitions per day and at least 1 urge urinary incontinence (UUI) per day, or an average of 8 or more micturitions per day and an average of at least 3 urgency episodes per day. UUI was defined as a leakage of urine of any amount because the patient felt an urge or need to urinate immediately. In addition, while no formal comparators have been made, Gemtesa® does not have a warning regarding increased blood pressure as does Myrbetriq® (mirabegron), a previously FDA approved beta-3 adrenergic receptor agonist. While blood pressure increases were not observed with Gemtesa®,

unlike those seen with Myrbetriq® (another FDA approved beta-3 adrenergic receptor agonist), head-to-head studies between the two agents have not been performed. There is no evidence at this time to support that Gemtesa® is safer or more effective than the other currently preferred, more cost-effective medications.

Recommendation: Gemtesa® to non-preferred.

Clinical Criteria:

- Use a preferred long acting antispasmodic.

Board Decision: The Board unanimously approved the above recommendation.

Vesicare® LS (solifenacin) **PDL category-** Antispasmodics- Long Acting

Solifenacin, the active ingredient of Vesicare® LS, is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergic mediated functions, including contractions of urinary bladder smooth muscle. It is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older. The safety and efficacy of Vesicare® LS oral suspension were assessed in two 52-week, open-label, baseline-controlled, sequential dose titration studies that included pediatric patients 2 year of age and older with neurogenic detrusor overactivity. In 2 open-label, baseline-controlled studies, patients in both age groups (aged 2 to less than 5 years and aged 5 to 17 years) treatment resulted in a change from baseline (improvement) in the maximum cystometric (bladder) capacity (MCC) after 24 weeks of treatment. Oxybutynin and Myrbetriq® (newly indicated) are also available for NDO for pediatric patients, but only Vesicare® LS is approved for use in pediatric patients 2 years of age and older. Comparator studies between Vesicare® LS and other agents were not found. Results suggested that mean increase from baseline to the end of treatment in MCC was 134.2ml with solifenacin 10mg versus 5.4ml with placebo ($p<0.001$). MCC was also significantly improved with solifenacin 5mg and oxybutynin versus placebo, with increases of 77.8 and 165.4ml, respectively ($p=0.007$ and $p<0.001$ vs placebo). The authors concluded that solifenacin 10mg significantly improved urodynamic variables as compared with placebo in patients with NDO due to MS or spinal cord injury. There were no clear differences between solifenacin 10mg daily and oxybutynin 15mg daily regarding urodynamic variables, although the study was not powered to show a difference between active treatments.

Recommendation: Vesicare® LS to be non-preferred.

Clinical Criteria:

- For the treatment of patients ≥ 2 years of age

Board Decision: The Board unanimously approved the above recommendation.

Abecma® (idecabtagene vicleucel); **PDL category**- Cancer

Abecma® is a BCMA-directed genetically modified autologous T cell immunotherapy consisting of a patient's own T cells that are harvested and genetically modified ex vivo through transduction with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). Autologous T cells transduced with

the anti-BCMA02 CAR LVV express the anti-BCMA CAR on the T cell surface. The CAR is comprised of a murine extracellular single-change variable fragment (scFv) specific for recognizing B cell maturation antigen (BCMA) followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signaling domains of CD137 and CD3 zeta. Binding of Abecma to BCMA-expressing target cells leads to subsequent CAR-positive T cell activation. It is indicated for a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory multiple myeloma (MM) after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Efficacy of Abecma® was assessed in an open-label, single-arm, multicenter study (KarMMa) that included adults with relapsed and refractory MM who had received at least 3 prior lines of antimyeloma therapy including an immunomodulator agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Abecma® has a box warning regarding increased risk of cytokine release syndrome (CRS), neurologic toxicities, HLH/MAS and prolonged cytopenias. Due to the risks of CRS and neurologic toxicities, Abecma® is available only through a restricted program under a REMS called the Abecma® REMS. In a small (N=100) open-label study in an Abecma®-treated population, the overall response rate was 72%.

Recommendation: Abecma® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Breyanzi® (lisocabtagene); **PDL category**- Cancer

Lisocabtagene maraleucel, the active ingredient of Breyanzi®, is a CD19-directed genetically modified autologous T cell immunotherapy administered as a defined composition of chimeric antigen receptor (CAR)-positive viable T cells (consisting of CD8 and CD4 components), to reduce variability in CD8-positive and CD4-positive T cell dose. The CAR is comprised of an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion T cell and persistence of Breyanzi®. It is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Breyanzi® is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma. The safety and efficacy of Breyanzi® were assessed in an open-label, multicenter, single-arm study (TRANSCEND) that included adults with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 lines of therapy who received Breyanzi® 2 to 7 days following completion of lymphodepleting chemotherapy. Breyanzi® has a box warning regarding increased risk of cytokine release syndrome and neurologic toxicities. Due to the risk of CRS and neurologic toxicities, Breyanzi® is available only through a restricted program under a REMS called the Breyanzi® REMS. In an open-label, multicenter, single-arm study, the overall response rate with Breyanzi® was 73%.

Recommendation: Breyanzi® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Fotivda® (tivozanib); **PDL category**- Cancer

Tivozanib, the active ingredient of Fotivda®, is a tyrosine kinase inhibitor. In vitro cellular kinase assays demonstrated that tivozanib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 and inhibits other kinases. In animal models, tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma. It is indicated for the treatment of adults with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies. The safety and efficacy of Fotivda® were assessed in TIVO-3, a multicenter, randomized, open-label study that compared Fotivda® with sorafenib in patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments, including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib. Treatment was continued until disease progression or unacceptable toxicity. In an open-label study compared with sorafenib, Fotivda® was more effective than sorafenib for the primary endpoint of progression free survival (p=0.016); however, overall survival was not significantly different. In a 2020 network meta-analysis by Manz et al2, the safety and efficacy of approved first-line tyrosine kinase inhibitors were assessed for the treatment of metastatic renal cell carcinoma. The authors concluded that while cabozantinib, sunitinib, pazopanib, and tivozanib did not differ significantly in efficacy (sorafenib was associated with a significantly shorter PFS when indirectly compared with cabozantinib), tivozanib was associated with a more favorable safety profile regarding grade 3 or 4 toxicities.

Recommendation: Fotivda® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Margenza® (margetuximab-cmkb); **PDL category**- Cancer

Margetuximab-cmkb, the active ingredient of Margenza®, is a HER2/neu receptor antagonist, a chimeric Fc-engineered IgG1 kappa monoclonal antibody produced by recombinant DNA technology. Margetuximab-cmkb binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytotoxicity (ADCC). It is indicated in the combination with chemotherapy, for the treatment of adults with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. The safety and efficacy of Margenza® plus chemotherapy were assessed in a randomized, open-label, multicenter study (SOPHIA) that included patients (N=536) with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized to Margenza® plus chemotherapy or trastuzumab plus chemotherapy until disease progression or unacceptable toxicity. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤2, >2), and the number of metastatic sites (≤2, >2). Patients were required to have progressed on or after the most recent line of therapy. Margenza® has a box warning regarding left ventricular dysfunction and embryo-fetal toxicity. In a randomized, open-label study that compared Margenza® plus chemotherapy with trastuzumab plus chemotherapy, margetuximab-cmkb improved primary progression-free survival over trastuzumab (p=0.033).

Recommendation: Margenza® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Orgovyx® (relugolix); **PDL category**- Cancer

Relugolix, the active ingredient of Orgovyx®, is a nonpeptide small molecule gonadotropin-releasing hormone (GnRH) receptor antagonist that competitively binds to pituitary GnRH receptors. Thus, it reduces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone. It is indicated for the treatment of adult patients with advanced prostate cancer. The safety and efficacy of Orgovyx® were assessed in a randomized, open-label study (HERO study; N=934) that included men with advanced prostate cancer requiring at least 1 year of androgen deprivation therapy and defined as biochemical (PSA) or clinical relapse following local primary intervention, newly diagnosed castration-sensitive metastatic disease, or advanced localized disease. In a clinical study compared with leuprolide, Orgovyx® resulted in a significantly greater proportion of patients with sustained testosterone suppression below castration levels from day 29 through 48 weeks of treatment; this difference between treatments of 7.9% met the criteria for both non-inferiority and superiority of relugolix ($p<0.001$ for superiority).2 However, the rapidity of PSA decline has not yet been shown to have clinical benefit compared with current treatment.

Recommendation: Orgovyx® to be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Pepaxto® (melphalan flufenamide); **PDL category**- Cancer

Melphalan flufenamide, the active ingredient of Pepaxto®, is a peptide conjugated alkylating drug. Due to its lipophilicity, melphalan flufenamide is passively distributed into cells and thereafter enzymatically hydrolyzed to melphalan. Similar to other nitrogen mustard drugs, cross-linking of DNA is involved in the antitumor activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of hematopoietic and solid tumor cells. In addition, melphalan flufenamide demonstrated synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines. It is indicated in combination with dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Pepaxto® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

Recommendation: Pepaxto® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Tepmetko® (tepotinib); **PDL category**- Cancer

Tepotinib, the active ingredient of Tepmetko®, is a kinase inhibitor that targets mesenchymal-epithelial transition (MET), including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations. In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. It is indicated for treatment of adults with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET)

exon 14 skipping alterations. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). The safety and efficacy of Tepmetko® were assessed in a single-arm, open-label, multicenter, non-randomized multicohort study (VISION study) that included adults with advanced or metastatic NSCLC harboring MET exon 14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In a non-randomized, single-arm study that included adults with advanced or metastatic NSCLC harboring MET exon 14 skipping alterations, epidermal growth factor receptor wild-type and anaplastic lymphoma kinase negative status, the overall response rate in treatment-naïve patients was 43% and in previously treated patients was 43%.

Recommendation: Tepmetko® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Ukoniq® (umbralisib); **PDL category**- Cancer

Umbralisib, the active ingredient of Ukoniq®, is a kinase inhibitor and inhibits multiple kinases. Umbralisib inhibited cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration in lymphoma cell lines in studies conducted in vitro. It is indicated for the treatment of: Adults with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. And adults with relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy. These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Marginal Zone Lymphoma- The efficacy of Ukoniq® was assessed in a single-arm, open-label, multicenter, multicohort study. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial. In an open-label, single-arm, multicohort study, patients with MZL had an overall response rate of 49%, while in the cohort of patients with FL the overall response rate was 43%.

Recommendation: Ukoniq® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Nextstellis® (drospirenone and estetrol); **PDL category**- Contraceptives- Monophasic Combination O/Cs

Nextstellis® is an oral contraceptive that contains drospirenone (a spironolactone analogue with anti-mineralocorticoid and antiandrogenic activity) and estetrol (a synthetic analogue of a native estrogen present during pregnancy that is selective for nuclear estrogen receptor-α (ER-α) and ER-β. Combined hormonal contraceptives (CHCs) prevent pregnancy primarily by suppressing ovulation. It is indicated for use by females

of reproductive potential to prevent pregnancy. Nextstellis® may be less effective in females with a BMI ≥30kg/m2. In females with BMI ≥30kg/m2, decreasing effectiveness may be associated with increasing BMI. The efficacy of Nextstellis® was assessed in a prospective, multicenter, open-label, single-arm one-year study in North America that included 1,674 females between the ages of 16 to 35 years. In females with BMI ≥30kg/m2, decreasing effectiveness may be associated with increasing BMI. In an open-label, single-arm study, a total of 26 on-treatment pregnancies occurred in 1,524 females, contributing 12,763 at-risk cycles. The overall Pearl Index was 2.65 per 100 woman-years of use. A trend of decreasing effectiveness with increasing BMI was observed in this study. To provide some basis for comparison, another contraceptive method, the Annovera® vaginal ring that contains segesterone acetate and ethinyl estradiol, has an overall pooled unintended pregnancy rate (Pearl Index) of 2.98 per 100 woman-years2 and condoms are generally cited as having a Pearl Index of 3-123.

Recommendation: Nextstellis® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Evkeeza® (evinacumab-dgnb); **PDL category**- Familial Hypercholesterolemia

Evinacumab-dgnb, the active ingredient of Evkeeza®, is an angiopoietin-like protein 3 (ANGPTL3) inhibitor monoclonal antibody (IgG4 isotype) produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. It binds to and inhibits ANGPTL3. ANGPTL3 is a member of the angiopoietin-like protein family that is expressed mainly in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab-dgnb inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C, and triglycerides (TG). Evinacumab-dgnb reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Evinacumab-dgnb blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively. It is indicated as an adjunct to other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). The safety and efficacy of Evkeeza® have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). The effects of Evkeeza® on cardiovascular morbidity and mortality have not been determined. The safety and efficacy of Evkeeza® were assessed in a multicenter, randomized, double-blind, placebo-controlled trial (ELIPSE-HoFH) that compared Evkeeza® with placebo in patients with HoFH (N=65) for 24 weeks. he safety and effectiveness of Evkeeza® have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). The effects of Evkeeza® on cardiovascular morbidity and mortality have not been determined and clinical trial experience has been limited as evidenced by the small sample size in the registration study, ELIPSE-HoFH. In this small placebo-controlled study, the least squares mean treatment difference between Evkeeza® and placebo in mean percent change in LDL-C from baseline (the primary endpoint) was -49%, which was statistically significant ($p<0.0001$). Comparator trials with other agents were not found.

Recommendation: Evkeeza® be non-preferred.

Clinical Criteria:

- Clinical PA required for appropriate diagnosis
- For the treatment of patients ≥ 12 years of age

Board Decision: The Board unanimously approved the above recommendation.

Gimoti® (metoclopramide HCl); **PDL category**- GI Anti-flatulent/ GI Stimulants

Metoclopramide, the active ingredient of Gimoti®, is a dopamine-2 receptor antagonist. Metoclopramide stimulates motility of the upper GI tract without stimulating gastric, biliary, or pancreatic secretions. The exact mechanism of action of metoclopramide in the treatment of GERD and diabetic gastroparesis has not been fully established. It appears to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs. It is indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. Limitations of use include that Gimoti® is not recommended for use in pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. And moderate or severe hepatic impairment, moderate or severe renal impairment, and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions. The effectiveness of Gimoti® has been established based on studies of oral metoclopramide for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. The systemic absorption after nasal administration is lower than that after oral administration given the same dose. Gimoti® offers patients and physicians a treatment option as a new dosage form. However, note that Gimoti® is not recommended in geriatric patients as initial therapy.

Recommendation: Gimoti® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Zokinvy® (lonafarnib); **PDL category**- Hutchinson- Gilford Progeria Syndrome (HGPS)

Lonafarnib, the active ingredient of Zokinvy®, is a farnesyltransferase inhibitor. It inhibits farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane. It is indicated in patients 12 months of age and older with a body surface area (BSA) of 0.39m2 and above:

- To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)
- For the treatment of processing-deficient Progeroid Laminopathies with either:
    - Heterozygous LMNA mutation with progerin-like protein accumulation
    - Homozygous or compound heterozygous ZMPSTE24 mutations

The efficacy of Zokinvy® is based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two phase 2 studies in patients with HGPS to those from a natural history cohort. Zokinvy® is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based on its mechanism of action, Zokinvy® would not be expected to be effective in these populations. The efficacy of Zokinvy® is based on results from the Observational Cohort Survival study, comparing survival data from 2 phase 2 studies in patients with HGPS to those from a natural history cohort. There were fewer deaths in the Zokinvy® group than the untreated group, and the mean survival time increased 2.5 years through the last follow-up time (11 years) compared to untreated patients.

Recommendation: Zokinvy® be non-preferred.

Clinical Criteria:

- Add new category HUTCHINSON- GILFORD PROGERIA SYNDROME (HGPS)

- In patients 12 months of age and older with a body surface area (BSA) of 0.39m2 and above
- PA required to confirm FDA approved indication.
- ZOKINVY: To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS). For the treatment of processing-deficient Progeroid Laminopathies with either: Heterozygous LMNA mutation with progerin-like protein accumulation OR Homozygous or compound heterozygous ZMPSTE24 mutations

Board Decision: The Board unanimously approved the above recommendation.

Lupkynis® (voclosporin); **PDL category**- Lupus- SLE

Voclosporin, the active ingredient of Lupkynis®, is a calcineurin-inhibitor immunosuppressant. The mechanism of action has not been fully established. Activation of lymphocytes involves an increase in intracellular calcium concentrations that bind to the calcineurin regulatory site and activate calmodulin binding catalytic subunit and through dephosphorylation activates the transcription factor, Nuclear Factor of Activated T-Cell Cytoplasmic (NFATc). The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens. It is indicated in the combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). The safety and efficacy of Lupkynis® have not been established in combination with cyclophosphamide. Use of Lupkynis® is not recommended in this situation. The safety and efficacy of Lupkynis® were assessed in a 52-week, randomized, double-blind, placebo-controlled study that included adults (N=357) diagnosed with systemic lupus erythematosus and with International Society of Nephrology/Renal Pathology Society (ISN/RPS) biopsy-proven active Class III or IV lupus nephritis (LN) (alone or in combination with Class V LN) or Class V LN. Results suggested that a significantly higher proportion of patients in the Lupkynis® arm than in the placebo arm achieved complete renal response at week 52. In the randomized, double-blind clinical trial assessing the safety and efficacy of Lupkynis®, a significantly higher proportion of patients in the Lupkynis®/MMF/corticosteroid arm than the placebo/MMF/corticosteroid arm achieved complete renal response at week 52. Other comparator studies were not found. While in one phase 3 study the combination of Lupkynis® plus MMF/corticosteroids was significantly more effective than MMF/corticosteroids for the primary endpoint of achieving complete renal response, there is no evidence at this time to suggest that Lupkynis® is safer or more effective than the other currently more cost-effective medications.

Recommendation: Lupkynis® be non-preferred.

Clinical Criteria:

- DDI: The concomitant use of Lupkynis is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inhibitors increases voclosporin exposure, which may increase the risk of Lupkynis® adverse reactions. Co-administration of Lupkynis® with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) is contraindicated. Reduce Lupkynis® dosage when co-administered with moderate CYP3A4 inhibitors (e.g. verapamil, fluconazole, diltiazem)

Board Decision: The Board unanimously approved the above recommendation.

Ponvory® (ponesimod); **PDL category**- Multiple Sclerosis- Non Interferons

Ponesimod, the active ingredient of Ponvory®, is a sphingosine 1-phosphate (S1P) receptor 1 modulator that binds with high affinity to S1P receptor 1. Ponesimod blocks the capacity of lymphocytes to egress

from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis is not known but may involve reduction of lymphocyte migration into the CNS. It is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The safety and efficacy of Ponvory® were assessed in a randomized, double-blind, parallel group, active-controlled superiority study that included patients with relapsing forms of MS who were treated for 108 weeks. Due to a decrease in heart rate with Ponvory® initiation, a first-dose 4-hour monitoring is recommended for patients with sinus bradycardia, first-or second-degree AV block, or a history of MI or heart failure occurring more than 6 months prior to treatment initiation and in stable condition. Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy during treatment initiation if treatment is started in certain patients (e.g. with prolonged QTc interval or with some pre-existing heart and cerebrovascular conditions). A phase 3 double-blind, superiority study compared Ponvory® with teriflunomide 14mg and results suggested that the ARR was statistically significantly lower in those treated with Ponvory® as compared with teriflunomide 14mg. While no statistically significant differences were observed in confirmed disability progression, the number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in the Ponvory® group than in the teriflunomide group. There is some evidence to suggest that Ponvory® may be more effective than teriflunomide 14mg for reducing the primary endpoint of annualized relapsed rate in a phase 3 study, as well as for some secondary MRI endpoints; however, there is no evidence at this time to support that Ponvory® is safer than teriflunomide or safer and more effective than the other currently preferred, more cost-effective medications.

Recommendation: Ponvory® be non-preferred.

Clinical Criteria:

- Clinical PA is required to establish diagnosis and medical necessity.
- Ponvory: Before initiation of Ponvory® treatment, assess the following:
  - Complete Blood Count (CBC)- Obtain a recent (i.e. within the last 6 months) CBC, including lymphocyte count.
  - Cardiac Evaluation- oObtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought and first-dose monitoring is recommended.
  - Determine whether patients are taking drugs that could slow heart rate of atrioventricular (AV) conduction.
  - Liver Function Tests- Obtain recent (i.e. within the last 6 months) transaminase and bilirubin levels.
  - Ophthalmic Evaluation- Obtain an evaluation of the fundus, including the macula.
  - Current or prior medications with immune system effects- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before starting treatment with Ponvory®.
  - Vaccinations- Test for antibodies to varicella zoster virus (VZV) before starting Ponvory®; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Ponvory®. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of Ponvory®.

Board Decision: The Board unanimously approved the above recommendation.

Amondys® 45 (casimersen); **PDL category**- Muscular Dystrophy Agents

Casimersen, the active ingredient of Amondys® 45, is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the 5-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a 6-member morpholino ring. Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping. It is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys® 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. The safety and efficacy of Amondys® 45 on dystrophin production was assessed in one study that included male DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. Interim analysis of an ongoing double-blind, placebo-controlled trial demonstrated statistically significantly greater mean dystrophin levels at week 48 from baseline with Amondys® 45 compared with placebo.

Recommendation: Amondy® 45 be non-preferred.

Clinical Criteria:

- Clinical prior authorization to verify diagnosis and use of stable dose of corticosteroid for at least 6 months.

Board Decision: The Board unanimously approved the above recommendation.

Qdolo® (tramadol HCl solution); **PDL category**- Narcotics- Selected

Tramadol, the active ingredient of Qdolo®, is an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mechanism of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Analgesia in humans begins approximately within one hour after administration and reaches a peak in about 2 to 3 hours. It is indicated in the adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Because of the risk of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Qdolo® for use in patients for whom alternative treatment options (e.g. non-opioid analgesics):

- Have not been tolerated or are not expected to be tolerated
- Have not provided adequate analgesia or are not expected to provide adequate analgesia

Tramadol has been given in single oral doses of 50mg, 75mg, and 100mg to patients with pain following surgical procedures and pain following oral surgery. It has been studied in 3 long-term trials involving patients with a variety of chronic painful conditions. Tramadol tablets, under the brand name Ultram®, have been available for many years, have been found to be safe and effective, and have the same indication as Qdolo®. The studies included in the Qdolo® prescribing information were the same as found in the Ultram® prescribing information. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Qdolo® for use in patients for whom alternative treatment options (e.g. non-opioid analgesics) have not been tolerated (or are not expected to be tolerated) or have not

provided adequate analgesia (or are not expected to provide adequate analgesia). The efficacy of Qdolo® was based on that of immediate-release tramadol tablets, which have been available for numerous years and been found to be safe and effective.

Recommendation: Qdolo® be non-preferred.

Board Decision: The Board unanimously approved the above recommendation.

Qelbree® (viloxazine hydrochloride); **PDL category**- Stimulant- Stimulants Like

Viloxazine, the active ingredient of Qelbree®, is a selective norepinephrine reuptake inhibitor. The mechanism of action for its approved use is not clear; however, it is thought to be mediated by inhibiting the reuptake of norepinephrine. It is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age. The safety and efficacy of Qelbree® were assessed in three short-term, randomized, placebo-controlled, monotherapy studies that included pediatric patients 6 to 17 years of age with ADHD. It does have a box warning regarding suicidal thoughts and behaviors, thus all Qelbree®-treated patients should be closely monitored for clinical worsening, and for the emergence of suicidal thoughts and behaviors. Use is contraindicated in patients receiving concomitant treatment with MAO-inhibitors, or within 14 days following discontinuation of an MAO-inhibitor, as well as in those receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range. The efficacy of Qelbree® for the treatment of ADHD in patients aged 6 to 17 years of age was assessed in 3 double-blind, placebo-controlled studies. All 3 studies demonstrated Qelbree® to have a statistically significantly greater change from baseline (reduction) in the ADHD-RS-5 total score as compared with placebo. Qelbree® is the first non-stimulant FDA approved in several years. Comparator trials with other agents approved for ADHD have not been found at this point.

Recommendation: Qelbree® be non-preferred.

Clinical Criteria:

- For pediatric patients 6 to 17 years of age
- DDI: Concomitant use of Qelbree® with an MAO inhibitor or within 2 weeks after discontinuing an MAO inhibitor is contraindicated.
- DDI: Concomitant use of Qelbree® significantly increases the total exposure, but not peak exposure, of sensitive CYP1A2 substates, which may increase the risk of adverse reactions associated with these CYP1A2 substrates. Coadministration of Qelbree® with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (e.g. alosetron, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline), is contraindicated.

Board Decision: The Board unanimously approved the above recommendation.

FDA SAFETY ALERTS

New FDA Drug Safety Communication on lamotrigine (Lamictal) – Drug Information Update
https://www.fda.gov/drugs/drug-safety-and-availability/studies-show-increased-risk-heart-rhythm-problems-seizure-and-mental-health-medicine-lamotrigine?utm_medium=email&utm_source=govdelivery

Board Decision: No formal action required

ADJOURNMENT: 8:30PM

The next meeting will be held on **September 14, 2021** 5:30pm –8:30pm at the Augusta Armory.