Department of Vermont Health Access
Pharmacy Benefit Management Program
DUR Board Meeting Minutes
June 18, 2019

Board Members:

Present:

Clayton English, PharmD	Jocelyn Van Opdorp, PharmD	Renee Mosier, PharmD
Zail Berry, MD	Margot Kagan, PharmD	Louise Rosales, NP
Joseph Nasca, MD	Marc Pasanen, MD	Claudia Berger, MD

Absent: Bill Breen, RPh, Patricia King, MD

Staff:

Laurie Brady, RPh, Change HealthCare	Mary Pion, RPh, Change HealthCare	Laureen Biczak, DO, Change Healthcare
Carrie Germaine, DVHA	Mike Ouellette, RPh, Change Healthcare	Lisa Hurteau, PharmD, DVHA
Jason Pope, DVHA	Nancy Hogue, PharmD, DVHA	Scott Strenio, MD, DVHA

Guests:

Bill Eicholzier, Alexion	Jeffery Olson, Gilead	Michael Armlin, Johnson &Johnson
Joseph Miller, Novo Nordisk	Karen Phillips, Amgen	

1. Executive Session:

- An executive session was held from 6:00 p.m. until 6:25 p.m.

2. Introductions and Approval of DUR Board Minutes:

- Introductions were made around the table.
- The May meeting minutes were accepted as printed.

3. DVHA Pharmacy Administration Updates: Nancy Hogue, PharmD DVHA

- New Conflict of Interest form will need to be signed yearly and an abbreviated version will need to be signed at each meeting.

4. Medical Director Update: Scott Strenio, MD, DVHA

- No update at this time.

5. Follow-up Items from Previous Meetings: Laurie Brady, RPh, Change Healthcare

- **Updated: Use of Opioids for Chronic Pain**

Additional data was collected. For members on 2 different short acting opioids, the medications being used in this situation were determined. The top three were Hydrocodone/acetaminophen and Tramadol, Oxycodone HCL and Tramadol and Oxycodone/acetaminophen and Tramadol. After reviewing the 2018 data for Essex county, it was determined only a select few members are bringing up the daily MME averages. A detailed look at the member profile was completed for those identified as being on 2 different long acting opioids. After reviewing the data it was found that some were not actually on 2 different long acting but were transiting or on a unique dosing.

Recommendation: No further action recommended at this time.

Public Comment: No public comment.

Board Decision: None needed.

6. RetroDUR/DUR: Laurie Brady, RPh, Change Healthcare,

- **Introduce: Appropriate Use of Asthma Controller Medications**

The National Heart, Lung and Blood Institute has published Guidelines for the Diagnosis and Management of Asthma. The treatment of asthma is done in a step-wise manner, and depending on disease severity, a combination of several agents may be needed. For anyone who requires use of a short acting agent > 2 days/week, a controller medication daily is recommended. The Guidelines state that the frequency of short acting beta-adrenergic inhaler (SABA) use can be clinically useful as a measure of disease activity since increased use of a SABA has been associated with increased risk for death or near death in patients who have asthma. Use of more than one SABA canister every one to two months is also associated with an increased risk of an acute exacerbation. Therefore, the use of more than one SABA canister (e.g., albuterol 200 puffs per canister) during a one-month period most likely indicates over reliance on this drug and suggests inadequate control of asthma. Additionally, inhaled corticosteroids (ICS) are the preferred long-term control therapy in asthma for all ages, although leukotriene receptor antagonists (LTRA) are listed as an alternative. Long-acting beta-adrenergic inhalers (LABAs) should never be used without first using ICS inhalers due to the increased risk of asthma exacerbations and death.

Change Healthcare will use paid, non-reversed Medicaid pharmacy claims from January 2018 through December 2018, excluding members with Part D, VMAP and Healthy Vermonters coverage. Change Healthcare will exclude members who had a diagnosis of cystic fibrosis, COPD or emphysema. Members will be stratified by age and the number of short acting inhalers used per year. In addition, the number of members in each group who had an ER visit or hospitalization associated with an asthma diagnosis during the study period will be reported. We will compare the rates of ER visits and hospitalizations to the rates seen in the 2015 analysis, examining whether the educational interventions provided by the Board had an impact in reducing rates of asthma exacerbations, understanding that the populations are not identical. Additional analysis will be done on those using more than 12 short acting inhalers/year and sorted geographically. The prescribers for these members will be identified to look at providers who are possibly practicing outside of guideline recommendations, perhaps identifying those who would be appropriate for more targeted education.

Recommendation: None at this time.

Public Comment: No public comment.

Board Decision: None needed.

- **Data presentation: Adherence to Anti-retroviral Therapy for HIV**

The use of antiretroviral therapy has changed HIV infection from a lethal diagnosis to a chronic condition. Since the discovery of the virus, scientific advancement in understanding viral components and mechanisms of infection has led the way to increasingly effective treatment. From single therapy AZT to now triple drug therapy, improvements in survival have been nothing short of miraculous. However, drug side effects remain a significant problem and are a barrier to compliance with therapy. Unfortunately, missing only a few doses can open the door for the development of drug resistance and studies suggest that adherence rates of at least 90-95% are required for optimal viral suppression. Given that HIV infected patients often have other health issues, including substance abuse and mental health diagnoses, that challenge compliance and given the expensive nature of the antiretroviral therapies, it is worth investigating medication compliance with the goal of working with providers to improve adherence in patients. The analysis identified members with at least one prescription for an anti-retroviral medication in 2017 and 2018. Those members were followed until the end of 2018 to evaluate how many were compliant with therapy using the Proportion of Days Covered (PDC) methodology. The formula is similar to the Medication Possession Ratio (MPR) but instead of simply adding the days supply in a given period, the PDC considers the days that are "covered".

PDC = (# of days in a period covered/# of days in a period) x 100
PDC is better suited for medication regimens consisting of multiple medications, such as antiretroviral therapy for HIV. PDC is not simply an average. Instead, it considers the days within a particular period when a patient is covered for all medications in a regimen. In other words, for a 3-drug regimen, a day is only considered "covered" when all 3 medications are available to the patient.

Note: Use of antiretrovirals for Pre-exposure prophylaxis (PrEP) was not the target of this intervention. Therefore, members on either Truvada® or Descovy® in the absence of another HIV medication in their profile were excluded from this analysis. Members on Viread in the in the absence of another HIV medication in their profile were also excluded as it was likely being used for Hepatitis B.

			Patients whose Proportion of Days Covered (PDC) >= 80%		Patients whose Proportion of Days Covered (PDC) >= 95%	
CY	Drug Class	Total Number of All FFS Patients who were Continuous Medicaid Eligible for CY	Number of Adherent Patients whose Proportion of Days Covered (PDC) >= 80%	% of Adherent Patients out of Total Number of All Patients	Number of Adherent Patients whose Proportion of Days Covered (PDC) >= 95%	% of Adherent Patients out of Total Number of All Patients
2017	HIV Meds	123	86	69.92%	42	34.15%
2018	HIV Meds	145	101	69.66%	48	33.10%

Recommendation: 5 patients identified in this report were on multiple HIV medications filled on a single day or over a few days then never filled again, and it is likely that this use was for post-exposure prophylaxis. While eliminating these patients would raise the adherence rates slightly, there appears to be room for improved adherence in this population. A targeted provider communication is recommended.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation. They asked that multiple patients for the same provider be combined into one provider notice. They also indicated that they would like the data shared with VCCI if possible.

7. Clinical Update: Drug Reviews: Laureen Biczak, DO, Change Healthcare and Laurie Brady RPh, Change Healthcare

Biosimilar Drug Reviews:

- None at this time

Full New Drug Reviews:

a) Krintafel® (tafenoquine succinate)

Tafenoquine succinate, the active ingredient of Krintafel®, is an 8-aminoquinoline antimalarial drug. It is active against the liver stages, including the hypnozoite (dormant stage) of *P. vivax*. It is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *P. vivax*. The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite prevents the development of the erythrocytic forms of the parasite, which are responsible for relapses in *P. vivax* malaria. In addition to its effect on the parasite, tafenoquine causes red blood cell shrinkage in vitro. The molecular target of tafenoquine is not known. A potential for development of resistance of *Plasmodium* species to tafenoquine was not evaluated. It is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection. Krintafel® is not indicated for the treatment of acute *P. vivax* malaria. The safety and efficacy of Krintafel® were assessed in a double-blind, controlled trial that included adults (N=522) positive for *P.vivax* across 3 regions (Asia, Africa, and Latin America). Compared with placebo plus chloroquine, Krintafel® plus chloroquine demonstrated a statistically significantly higher rate of recurrence-free efficacy. The control in study 1 was primaquine. The prescribing information did not have information regarding the active-control in the first study; however, in the full 2019 full-text article by Lacerda et al[2], the percentage of patients in the primaquine group who were free from recurrence at 6 months was 64.3%. This was statistically different from placebo (OR vs placebo 0.20; $p<0.001$). Note that this was an analysis in which patients with missing data were considered to have had recurrence and these results were consistent with the results of the primary analysis which included the intention-to-treat population (62.4% with tafenoquine vs 27.7% in the placebo group who were free from recurrence at 6 months. With primaquine, 69.6% were free from recurrence at 6 months.) Primaquine is a longer dosing regimen than tafenoquine. Avoid coadministration of Krintafel® with Organic Cation

Transporter 2 (OCT2) and Multidrug and Toxin Extrusion (MATE) substrates (e.g. dofetilide, metformin).

Recommendation:

- Re-name category Anti-Infectives Antimalarials.
- Add Krintafel® to preferred after clinical criteria are met.
- Add Atovaquone/Proguanil, Chloroquine, Coartem®, Daraprim®, Hydroxychloroquine sulfate, Mefloquine, Primaquine, and Quinidine sulfate to preferred.
- Add Malarone® to non-preferred.
    - Clinical criteria:
        - **Krintafel:** the patient is ≥ 16 years of age AND is receiving concurrent antimalarial therapy.
        - **Malarone:** patient has a documented intolerance to the generic equivalent
        - **Quinine sulfate, Qualaquin:** diagnosis or indication is for the treatment of malaria. (Use for leg cramps not permitted.) AND If the request is for brand Qualaquin, the patient has a documented intolerance to the generic equivalent.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation. Change Healthcare will see how Medispan ProDUR messages will be handled regarding the DDI with metformin.

b) Onpattro® (patisiran injection, lipid complex)

Patisiran, the active ingredient of Onpattro®, is a double-stranded small interfering ribonucleic acid (siRNA) formulated as a lipid complex for delivery to hepatocytes. Patisiran causes degradation of mutant and wild-type transthyretin (TTR) messenger RNA (mRNA) through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. It is indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. The safety and efficacy of Onpattro® were assessed in a randomized, double-blind, placebo-controlled, multicenter study that included adults with polyneuropathy caused by hATTR amyloidosis. All patients received pre-medications. In a clinical trial, Onpattro® was found to significantly improve the mNIS+7 and Norfolk QoL DN scales. Onpattro® is the first RNA interference (RNAi) therapy to be approved for the treatment of hATTR amyloidosis with polyneuropathy. It has been shown to provide some benefit to patients with this disease but is extremely costly (more than ten times the cost required to meet the ICER cost-effectiveness threshold).

Recommendation: Defer until review of Tegsedi.

Public Comments: None at this time.

Board Decision: None needed.

c) Tegsedi® (inotersen)

Inotersen, the active ingredient of Tegsedi®, is an antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) protein synthesis. It causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Serum TTR is a carrier of retinol binding protein, which is involved in the transport of vitamin A in the blood. Mean reductions in serum retinol binding of 71%, and serum vitamin A of 63%, were seen at week 65. It is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. The efficacy of Tegsedi® was assessed in a randomized, double-blind, placebo-controlled, multicenter study that included adults with polyneuropathy caused by hATTR amyloidosis. In a clinical trial compared with placebo, changes from baseline to week 66 on co-primary endpoints significantly favored Tegsedi®. Tegsedi® is the second RNA interference (RNAi) therapy, after Onpattro® (patisiran), to be approved for the treatment of hATTR amyloidosis with familial amyloidotic polyneuropathy. Both drugs have been shown to provide some benefit to patients with this disease, but both are extremely costly (more than ten times the cost required to meet the ICER cost-effectiveness threshold). Unlike Onpattro® (patisiran), Tegsedi® (the costlier of the two) has a box warning (for thrombocytopenia and renal toxicity) that requires additional monitoring. It is available through a REMS program and limited pharmacy network.

Recommendation:

- Add new category hATTR Treatments
- Add Onpattro® (patisiran) 10mg/5ml intravenous injection with the following limits to non-preferred: Weight < 100kg (0.3mg/kg every 3 weeks), Weight ≥ 100kg (30mg every 3 weeks).
- Add Tegsedi® (inotersen) 284mg/1.5ml injection for subcutaneous use with QL = 4 syringes/28 days to non-preferred.
- Clinical criteria:
- Add **Onpattro, Tegsedi:**
    - The patient is ≥ 18 years of age with a diagnosis of polyneuropathy of heredity transthyretin mediated (hATTR) amyloidosis (Documentation of TTR mutation by genetic testing and the presence of amyloid deposits via tissue biopsy has been submitted) AND
    - The medication is being prescribed by or in consultation with a neurologist AND
    - Clinical signs and symptoms of the disease (e.g., peripheral/autonomic neuropathy, motor disability, cardiovascular

dysfunction, renal dysfunction) are present and other causes of neuropathy have been excluded AND
- The patient has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from the tricyclic antidepressant (TCA) class and/or anticonvulsant class AND
- Patient is receiving vitamin A supplementation AND
- For approval of Tegsedi, the patient has had a documented side effect, allergy, or treatment failure with Onpattro AND the prescriber, patient, and pharmacy are registered with the REMS program.
- Initial approval will be granted for 3 months. For re-approval, the patient must have documentation of clinical improvement or slower progression of the disease than would otherwise be expected.

Public Comment: from: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

d) Sympazan® (clobazam)

Clobazam, the active ingredient of Sympazan®, is a benzodiazepine derivative. The exact mechanism of action is not fully understood, but it is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABA-A receptor. Sympazan® is a Schedule IV controlled substance. It can be abused in a similar manner as other benzodiazepines such as diazepam. It is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age and older. The efficacy of Sympazan® is based upon bioavailability studies comparing clobazam tablets with Sympazan® oral films. Apply Sympazan® on top of the tongue where it adheres and dissolves. The oral film can be taken with or without food, but do not administer with liquids. As the film dissolves, saliva should be swallowed in a normal manner, but the patients should refrain from chewing, spitting or talking. Only one film should be taken at a time; if a second film is needed to complete the dosage, it should not be taken until the first film has completely dissolved.

<u>Recommendation</u>:

- Add Sympazan® (clobazam) films to non-preferred.
  - Clinical criteria:
    - Add Sympazan to the Clobazam and Onfi criteria with the addition that for approval of Sympazan, prescriber must provide a clinically compelling reason why the patient is unable to use Clobazam tablets AND Clobazam suspension.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

e) Tolsura® (itraconazole)

Itraconazole, the active ingredient of Tolsura®, is an azole antifungal agent. It has been shown in vitro to inhibit the cytochrome P450-dependent, C-demethylation of ergosterol, which is a vital component of fungal cell membranes. Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated in vitro and from patients receiving prolonged therapy. It is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients:

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-fungal therapy should be adjusted accordingly. Tolsura® is not indicated for the treatment of onychomycosis. Tolsura® is not interchangeable or substitutable with other itraconazole products due to the differences in the dosing between Tolsura® and other itraconazole products. Therefore, follow the specific dosage recommendations for Tolsura®. Clinical studies in the clinical trials section of the prescribing information for Tolsura® were conducted with itraconazole 100mg capsules. Tolsura® is formulated to have greater bioavailability than itraconazole capsules, thus permitting use of a lower dose to obtain comparable drug levels. It has also been shown to provide more consistent drug levels, although there is no evidence showing improved outcomes with this formulation.

Recommendation:

- Defer until Antifungals, Oral class review.

Public Comment: No public comment.

Board Decision: None needed.

f) Ultomiris® (ravulizumab-cwvz)

Ravulizumab-cwvz, the active ingredient of Ultomiris®, is a complement inhibitor. It is a humanized monoclonal antibody produced in Chinese hamster ovary cells that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the pro-inflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex) and preventing the generation of the

terminal complement complex C5b9. Ultomiris® inhibits terminal complement-mediated intravascular hemolysis in patients with PHN. It is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). Patients should be vaccinated for meningococcal disease to reduce the risk of serious infection at least 2 weeks before the first dose of Ultomiris®. The safety and efficacy of Ultomiris® were assessed in two open-label, randomized, active-controlled, non-inferiority phase 3 studies. In phase 3 clinical trials, Ultomiris® was found to be non-inferior to eculizumab (brand name Soliris®).

Recommendation:

- Add Ultomiris® (ravulizumab-cwvz) to non-preferred.
  - Clinical criteria:
    - **Ultomiris:** The patient has a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) documented by flow cytometry AND The patient has received the meningococcal vaccine at least 2 weeks prior to therapy initiation. Authorization for continued use shall be reviewed to confirm that the patient has experienced an objective response to the therapy. Note: Dose requested must be within the weight based parameters for loading and maintenance dose

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

g) Yupelri® (revetenacin)

Revefenacin, the active ingredient of Yupelri®, is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits its pharmacological effects through inhibition of the M3 receptors at the smooth muscle, leading to bronchodilation. It is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Yupelri® should not be started in patients during acutely deteriorating or potentially life-threatening episodes of COPD. The safety and efficacy of Yupelri® were assessed in 2 dose-ranging studies, 2 replicate 12-week, phase 3 confirmatory studies, and a 52-week safety trial. The efficacy of Yupelri® is mainly based on the two replicate, phase 3 placebo-controlled confirmatory trials. Yupelri® has been found to be effective for COPD treatment as compared with placebo; however, no comparator trials with other active ingredients have been found.

Recommendation:

- Add Yupelri™ (revefenacin) inhalation solution with QL = 30 vials/30 days to non-preferred.
    - Clinical criteria:
        - Add Yuperlri to the Lonhala Magnair criteria.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

8. New Therapeutic Drug Classes

- None at this time.

9. Therapeutic Drug Classes- Periodic Review: Laureen Biczak, MD, Change Healthcare and Laurie Brady, RPh, Change Healthcare

a) Antifungals, Oral

- New drug Tolsura previously discussed as a New Drug Review.
- Isavuconazole and voriconazole are the preferred agents for first-line treatment of pulmonary IA.
- No new significant clinical changes

Recommendation:

- Add Tolsura® (itraconazole) caps with QL = 4 caps/day to non-preferred.
- Add Itraconazole solution to non-preferred.
- Remove Lamisil® tablets from the PDL.
    - Clinical criteria
        - **Tolsura:** patient has a diagnosis of aspergillosis intolerant of or refractory to Amphotericin B therapy AND patient has a documented intolerance to both generic itraconazole and voriconazole OR patient has a diagnosis of blastomycosis or histoplasmosis AND the patient has a documented intolerance to itraconazole capsules and solution.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

b) Antifungal, Topical

- No new drugs.
- No new significant clinical changes

Recommendation:

- Add Luliconazole 1% Cream and Miconazole w/ zinc oxide (compare to Vusion®) Ointment with QL=50 g/30 days to non-preferred.
    - Clinical criteria
        - Add Miconazole w/ Zinc Oxide to the Vusion criteria.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

c) Bone Resorption Suppression and Related Agents

- No new drugs.
- A 2019 systematic review and meta-analysis by Diez-Perez et al223 included 23 randomized controlled trials (N=8644) to assess the safety and efficacy of teriparatide in the reduction of hip and upper limb fractures in women and men with osteoporosis. Of the studies, 10 had an active control (including risedronate, alendronate, zoledronic acid, calcitonin, denosumab, strontium, abaloparatide, and romosozumab) and 11 were double-blind. The authors concluded that teriparatide had a significant effect on reducing hip fractures (by 56%) in patients with osteoporosis and a neutral effect on the pooled upper limb fractures reported.
- No new significant clinical changes.

Recommendation:

- Move Binosto® (alendronate) 70mg effervescent tablet with QL=4 tablets/28 days to non-preferred.
- Removed Zometa® (zoledronic acid) Injection 4mg/100ml or conc. 4mg/5ml from the PDL.
- Remove Miacalcin® (calcitonin) Nasal Spray from the PDL.
    - Clinical criteria:
        - Remove Zometa and Miacalcin nasal spray criteria.
        - Combine criteria **Evista and Fosamax:** patient has a documented intolerance to the generic formulation.
        - Combine criteria **Actonel, Atelvia, Boniva (oral), Ibandronate (oral), Risedronate:** patient has had a documented side effect, allergy, or treatment failure (at least a six-month trial) to generic alendronate tablets AND if the request is for brand, the patient has also had a documented intolerance to the generic equivalent.
        - Add Binosto to the Alendronate Oral Solution criteria.
        - Add multiple myeloma to diagnosis or indication criteria for Xgeva Injection.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

d) Hypoglycemics, Incretin Mimetics/Enhancers & SGLT-2 Inhibitors

- No new drugs.
- Canagliflozin (Invokana®) is also indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal MI, and non-fatal stroke) in adults with type 2 DM and established cardiovascular disease (CVD). While canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 DM and established CVD, the effectiveness of Invokamet®/Invokamet® XR on reducing the risk of major cardiovascular events in adults with type 2 DM and cardiovascular disease has not been established.
- In 2019, the ADA updated and published Standards of Medical Care in Diabetes. The recommendations include metformin as the preferred initial treatment for type 2 DM. The guidelines recommend a patient-centered approach to treatment, taking into consideration comorbidities (such as cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, side effects, and patient preferences. For those with type 2 DM and chronic kidney disease, it is recommended to consider an SGLT2 inhibitor or GLP-1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. In patients who need the greatest effect for glucose reduction of an injectable, the GLP-1 receptor agonists are preferred to insulin. Treatments should be re-evaluated at regular intervals and adjusted as needed. If after 3 months the target HbA1c is not achieved and the patient does not have atherosclerotic cardiovascular disease or chronic kidney disease, it is recommended to consider a combination of metformin with any of the preferred 6 treatment options, including sulfonylureas, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. The choice of which drug to should be based on drug-specific effects and patient factors.
- The AACE/ACE's 2019 statement is to individualize the goals but in adults with no clinically significant atherosclerotic cardiovascular disease, an HbA1c level ≤6.5% if obtained without substantial hypoglycemia or other unacceptable consequences, may reduce the lifetime risk of complications. An A1c >6.5% is appropriate for some patients with concurrent serious illness and at risk for hypoglycemia. Furthermore, the guidelines specify that certain GLP-1 receptor agonists and SGLT2 inhibitors have shown cardiovascular disease and chronic kidney disease benefits and are preferred in patients with those complications. In addition, if chronic heart disease is present, the guidelines recommend including either a GLP-1 receptor agonist or SGLT2

inhibitor. It is then recommended to use dual therapy if goal is not met after 3 months. Dual or triple therapy should be add-ons to metformin or another first-line agent.

Recommendation:

- No changes at this time.

Public Comment: Joseph Miller from Novo Nordisk: Highlighted the attributes of Ozempic.

Board Decision: None needed.

e) Hypoglycemics, Insulin and Related Agents

- In 2019, Hong et al[230] conducted a systematic review and meta-analysis of 22 randomized controlled trials (N=9,691). The purpose of this review was to compare the efficacy of basal insulin analogs (BA) including glargine U-100 and detemir to premixed insulins (PM) including human, lispro, and aspart biphasic. There was no significant difference in the primary efficacy outcome of mean change from baseline in HbA1C in the BA group compared to the PM group
- A 2019 Cochrane Review by Fullerton et al[233] included 10 randomized controlled trials to assess the efficacy of short-acting insulin analogues as compared with regular human insulin when used in adults with type 2 DM. No trials were blinded, and none looked at all-cause mortality as an outcome or were designed to investigate long-term effects. In conclusion, the authors stated there was no clear benefit of using short-acting insulin analogues over regular human insulin in adults with type 2 DM. Long-term efficacy and safety data are needed.
- In 2019, Holmes et al[236] conducted a systematic review and meta-analysis of 70 studies to compare the benefits and harms of long-acting insulins in patients with type 1 and 2 diabetes. Overall, the authors concluded that there was no difference in glycemic control between any of the long-acting insulins included; however, degludec was associated less incidence of hypoglycemia and detemir was associated with less weight gain.

Recommendation:

- Add Insulin Lispro (compare to Humalog®) and Toujeo® Max (insulin glargine) to non-preferred.
  - Clinical criteria:
    - Add Insulin Lispro to the Admelog, Fiasp criteria.
    - Update **Tresiba, Toujeo:** Patient has had a documented treatment failure of at least one preferred long-acting agent (Lantus or Levemir)

OR each Lantus or Levemir dose exceeds 80 units. **Note:** Pharmacy claims will be evaluated to assess compliance with insulin glargine or detemir U100 therapy prior to approval. Initial approval will be granted for 6 months. For re-approval after 6 months, the patient must have a documented improvement in hemoglobin A1c of ≥ 0.5% or decreased incidence of hypoglycemic events.

- **Toujeo Max:** The patient is currently using insulin glargine 300 units/mL AND the dose exceeds 160 units.
- Update **Basaglar:** Diagnosis of diabetes mellitus AND Lantus must be on a long-term backorder and unavailable from the manufacturer.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

f) Hypoglycemics, Meglitinides

- No new drugs.
- No new significant clinical changes
- A 2019 network meta-analysis (NMA) by Jia et al[54] included 75 randomized controlled trials (N=33,830) to assess the efficacy of hypoglycemic drugs for type 2 DM. The authors concluded that repaglinide and metformin would be the most efficacious oral drugs for first-line monotherapy of type 2 DM.

Recommendation:

Anti- Diabetics: Biguanides & Combinations

- Remove Glucovance® (glyburide/metformin) from the PDL.

Public Comment: from: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

g) Hypoglycemics, TZD Agents

- No new drugs.
- No new significant clinical changes.
- A 2018 systematic review and meta-analysis by Yan et al[134] included 12 randomized controlled and observational studies to identify a more precise relationship between pioglitazone use and risk of bladder cancer. The authors concluded that pioglitazone is associated with an increased risk of bladder cancer. Further research is needed.

Recommendation:

Anti-Diabetics: Thiazolidediones & Combinations

- Move Pioglitazone/Glimeperide (compare to Duetact®) with QL = 1 tab/day and Pioglitazone/Metformin (Compare to Actoplus Met) to non-preferred.
- Remove Actoplus Met XR (pioglitazone/metformin ER) from the PDL.
    - Clinical criteria:
        - Revise **Actos, Pioglitazone:** Patient has been started and stabilized on the requested medication OR patient has had a documented side effect, allergy, contraindication OR treatment failure with metformin AND for approval of Actos, the patient has a documented intolerance to the generic equivalent.
        - Revise **Actoplus Met, Duetact, Pioglitazone/Metformin, Pioglitazone/Glimepiride:** patient is unable to take as the individual separate agents AND if the request is for Actoplus Met or Duetact, the patient has had a documented intolerance to the generic equivalent.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

h) Immunologic Therapies for Asthma

- Dupilumab (Dupixent®) is an interleukin-4 (IL-4) receptor alpha antagonist. It is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits IL-4 and IL-13 signaling (by specifically binding the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes). It inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE; however, the exact mechanism of action in asthma has not been definitively established. It is indicated as an add-on maintenance, with an eosinophil phenotype or with oral corticosteroid dependent asthma. It is intended for use under the guidance of a healthcare provider, but a patient may self-inject after training in subcutaneous injection technique using the pre-filled syringe.
- The GINA guidelines recommend considering add-on biological treatments "...for patients with exacerbations and allergic/eosinophil biomarkers on high-dose ICS-LABA, with/without daily OCS." The guidelines also recommend considering cost, dosing frequency, route of administration, patient preference, and cost.

<u>Recommendation:</u>

- Add Dupixent® (dupilumab) subcutaneous injection with QL = 4 syringes the first 28 days then 2 syringes every 28 days thereafter to non-preferred.

- Clinical criteria:
    - Add to Xolair criteria that for approval of prefilled syringe, a clinically compelling reason must be provided detailing why vials cannot be used.
    - Add Dupixent to the Fasenra, Nucala, Cinqair criteria and limitations.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

i) Multiple Sclerosis Agents

- Cladribine (Mavenclad®) is a nucleoside metabolic inhibitor. The mechanism by which it exerts its therapeutic effects in MS has not been fully determined, but it is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. Cladribine (Mavenclad®) causes a dose-dependent reduction in lymphocyte count, and the lowest absolute lymphocyte counts occurred about 2 to 3 months after the start of each treatment cycle and were lower with each additional treatment cycle.No new significant clinical changes
- Siponimod (Mayzent®) is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which it exerts its therapeutic effects is MS is not known but may involve reduction of lymphocyte migration into the CNS. Siponimod (Mayzent®) induced a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues. Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping treatment.
- In a November 2018 FDA Safety Alert, the FDA warned that when fingolimod (Gilenya®) is stopped, the disease can be come much worse than before the medicine was started or while it was being taken. The MS worsening is rare but can result in permanent disability. It is recommended that healthcare professionals inform patients before starting treatment about the potential risk of severe increase in disability after stopping the treatment.
- The American Academy of Neurology published practice guidelines in 2018 for disease-modifying therapies (DMTs) in adults with MS. These guidelines also recommend that DMTs should be offered to patients with relapsing forms of MS with recent clinical or MRI activity. In addition, the guidelines recommend that alemtuzumab, fingolimod, or natalizumab should be prescribed to patients with MS with highly active MS. Ocrelizumab should be offered to patients with PPMS who are likely to benefit from this treatment.

Recommendation:

- Move Ampyra® (dalfampridine ER) tablet with QL = 2 tablets/day, maximum 30-day supply per fill to non-preferred.
- Add Dalfampridine ER tablet (compare to Ampyra®) with QL = 2 tablets/day, maximum 30-day supply per fill to preferred.
- Add Lemtrada® (alemtuzumab) intravenous and Avonex® (interferon B-1a) pre-filled syringe, auto-injector to non-preferred.
- Clarify Avonex® (interferon B-1a) vial will remain preferred.
    - Clinical criteria:
        - Add **Ampyra:** patient must have a documented intolerance to the generic equivalent.
        - Add **Avonex syringe, Avonex auto-injector**: patient has been started and stabilized on the medication (Note: samples are not considered adequate justification for stabilization) OR clinical justification has been provided detailing why the member cannot use Avonex vials or Rebif.
        - Add **Lemtrada**: Patient has a diagnosis of relapsing multiple sclerosis AND The prescriber, patient, and pharmacy are registered with the REMS program.

Public Comment: No public comment.

Board Decision: The Board unanimously approved the above recommendation.

11. General Announcements: Michael Ouellette, RPh, Change Healthcare

Selected FDA Safety Alerts

- None at this time.

Public Comment: No public comment.

Board Decision: No action is needed.

12. Adjourn: Meeting adjourned at 8:28 p.m.