In This Issue

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From the Department of Pharmacy

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Vibegron for Overactive Bladder

By: Maggie Segovia, Pharm.D.

Background: Overactive bladder (OAB) is a bothersome condition most commonly affecting women.[1] Its prevalence increases with advancing age. Overactive bladder is characterized by urinary urgency, frequent micturition, and nocturia, with or without urge urinary incontinence (UUI).[2] Historically, muscarinic antagonists have been the only oral pharmacologic option for the treatment of OAB.[3] These agents are commonly associated with unfavorable adverse effects, such as dry mouth, constipation, urinary retention, and blurred vision.[2] Furthermore, increasing evidence continues to emerge regarding a potential association between anticholinergic medications and the risk of severe cognitive impairment.[4] In light of these growing concerns regarding antimuscarinic medications, the beta-3 adrenergic agonists, a new class of OAB medications, have emerged.[5] In June 2012, the first beta-3 adrenergic agonist, mirabegron (Myrbetriq®; Astellas Pharma Inc.), gained approval from the Food and Drug Administration (FDA).[6,7] Eight years later, in December 2020, vibegron (Gemtesa®; Urovant Sciences) became the second beta-3 adrenergic agonist to gain FDA approval for the treatment of OAB.[8,9]

Mechanism of Action: Vibegron is a selective beta-3 adrenergic agonist.[8] Activation of the beta-3 receptor relaxes the detrusor smooth muscle, thus increasing bladder capacity.

Clinical Trial: The FDA approval of vibegron was based on the results of EMPOWUR, a phase III, randomized, double-blind, placebo, and active-controlled study which evaluated the safety and efficacy of vibegron for OAB.[10] Patients ≥18 years old with a history of OAB diagnosed at least 3 months before screening, and who

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Mirabegron for Overactive Bladder

By: Sarah Crisp, Pharm.D.

Background: Overactive bladder (OAB) is a syndrome of urinary urgency and frequency, with or without incontinence.[1,2] Treatment options described in the 2019 American Urological Association guidelines for OAB include behavioral therapy, anticholinergic medications, beta-3 adrenergic agonists, onabotulinumtoxinA injections, nerve stimulation, and/or surgery.[3] Mirabegron (Myrbetriq®; Astellas Pharma Inc.), a beta-3 adrenergic receptor agonist, was approved as monotherapy by the Food and Drug Administration in June 2012 and in combination with solifenacin in May 2018 for the treatment of OAB in adults with urge urinary incontinence, urgency, and urinary frequency.[4]

Mechanism of Action: By binding to the beta-3 adrenergic receptor, mirabegron relaxes the detrusor smooth muscle increasing bladder capacity during the urine storage phase of the bladder fill-void cycle.[4] At usual doses, mirabegron is selective for the beta-3 recep-

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met diary-based criteria for either wet (urinary incontinence) or dry (no urinary incontinence) OAB were included. Following a screening and washout period, patients (N=1518) were randomized in a 5:5:4 ratio to receive either vibegron 75 mg (n=547) once daily , placebo (n=540), or tolterodine extended-release (ER) 4 mg (n=431) once daily, respectively. Patients were instructed to maintain a voiding diary, in which they recorded micturitions, urgency, and incontinence at baseline and weeks 2, 4, 8, and 12. The two co-primary endpoints were change from baseline to week 12 in the average daily number of micturitions and change in the average daily number of UUI episodes. Patient demographics were similar between groups. The median age was 63 years old in the vibegron group, and 61 years old in both the placebo and tolterodine ER groups. Approximately 85% of patients were female across all groups. Most participants were Caucasian (~78%) and from the United States (~90%). At baseline, median micturitions per day ranged from 10.43 (vibegron and placebo groups) to 10.67 (tolterodine ER group). Of those with wet OAB, the median number of UUI episodes per day was 2.0 across all groups (vibegron, placebo, and tolterodine ER). At 12 weeks, the least-squares mean (LSM) change from baseline in micturitions was -1.8 episodes per day in the vibegron group compared to -1.3 episodes per day in the placebo group, demonstrating a difference of -0.5 (95% CI: -0.8, -0.2; p <0.001). The LSM change from baseline in UUI episodes was -2.0 episodes per day in the vibegron group compared to -1.4 episodes per day in the placebo group, demonstrating a difference of -0.6 (95% CI: -0.9, -0.3; p <0.001). Vibegron was not directly compared to tolterodine ER. However, compared to placebo, tolterodine ER showed statistically significant decreases in UUI episodes, but not in micturition frequency. Therefore, the EMPOWUR investigators concluded that vibegron 75 mg once daily provided a clinically significant improvement in OAB symptoms.

Safety: Vibegron was generally well tolerated among patients in the EMPOWUR trial.[10] Adverse events that occurred more frequently in the vibegron group compared to the placebo group included headache (2.4%,), nasopharyngitis (2.8%), diarrhea (2.2%), nausea (2.2%), upper respiratory tract infection (2%), constipation (1.7%), dry mouth (1.7%), and urinary retention (0.6%). Dry mouth occurred more frequently in the tolterodine ER group (6.5%) versus both the vibegron group (1.7%) and the placebo group (0.9%). Hypertension also occurred more frequently in the tolterodine ER group (2.6%) versus both the vibegron group (1.7%) and the placebo group (1.7%). Of note, eight patients in the vibegron group, six in the placebo group, and ten in the tolterodine ER group experienced serious adverse events.

Dosing and Administration: The recommended dose of vibegron is one 75 mg tablet by mouth once daily.[8] The tablet may be crushed and administered with applesauce, if necessary. There are no dosage adjustments recommended for renal or hepatic impairment. However, if the creatinine clearance is <15 mL/min or severe hepatic impairment exists, use is not recommended.

Cost and Availability: Vibegron is available as a 75 mg tablet (NDC 73336-0075-30) and has an average cost of $18.34/tablet.[9] The estimated annual cost of therapy is approximately $6,600.

Formulary Status: Vibegron is not currently on the CCHS Formulary.

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tor, however, higher doses (e.g., 200 mg) can cause stimulation of beta-1 receptors.

Clinical Trials: The safety and efficacy of mirabegron were evaluated in a double-blind randomized, placebo-controlled, parallel-group trial.[5] Patients ≥18 years old with OAB symptoms for ≥3 months who experienced an average of ≥eight micturitions/24 hours and ≥three urgency episodes, with or without urgency incontinence, over a 3-day micturition diary period were included. Eligible patients (N=1305) were randomized to receive placebo (n=433), mirabegron 25 mg (n=432), or 50 mg (n=440) once daily for 12 weeks. The co-primary endpoints were change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 hours. The adjusted mean change from baseline to the final visit of incontinence episodes per 24 hours was -0.96 in the placebo group, -1.36 (95% CI: -0.74, -0.06; p=0.005) in the mirabegron 25 mg group, and -1.38 (95% CI: -0.76, -0.08; p=0.001) in the mirabegron 50 mg group. The adjusted mean change from baseline to final visit in the number of micturitions per 24 hours was -1.18 in the placebo group, -1.65 (95% CI: -0.82, -0.13; p=0.007) in the mirabegron 25 mg group, and -1.60 (95% CI: -0.76, -0.08; p=0.015) in the mirabegron 50 mg group. Based on these results, the authors concluded that mirabegron significantly improved symptoms of OAB. Another clinical trial using a similar design, inclusion criteria, and co-primary efficacy endpoints evaluated the use of mirabegron in combination with solifenacin.[6] Patients (N=3527) were randomized to placebo (n=447), solifenacin 5 mg (n=434), mirabegron 25 mg (n=441), mirabegron 50 mg (n=437), solifenacin 5 mg plus mirabegron 25 mg (n=885), or solifenacin 5 mg plus mirabegron 50 mg (n=883). The adjusted changes from baseline in the mean number of incontinence episodes per 24 hours in the mirabegron 25 mg and 50 mg monotherapy groups were –1.70 (95% Cl: –1.90, -1.51) and -1.76 (95% Cl: –1.93, -1.59), respectively, versus the mirabegron 25 mg and 50 mg combination groups which were -2.04 (95% CI: -2.18, -1.90) and -1.98 (95% CI: -1.98, -1.85), respectively. The adjusted changes from baseline in the mean number of micturitions per 24 hours in the mirabegron 25 mg and 50 mg monotherapy groups were –2.00 (95% CI: –2.23, -1.78) and –2.03 (95% CI: –2.26, -1.80), respectively, versus the mirabegron 25 mg and 50 mg combination groups which were -2.49 (95% CI: -2.65, -2.33) and -2.59 (95% CI: -2.75, -2.43), respectively. The authors concluded that combination therapy of solifenacin and mirabegron provided a beneficial additive effect in controlling symptoms of OAB.

Safety: The most common adverse events observed in patients treated with mirabegron 25 mg compared to placebo were hypertension 11.3%), urinary tract infection (4.2%), nasopharyngitis (3.5%), and headache (2.1%). The most common adverse events observed in patients treated with mirabegron 25 mg in combination with solifenacin 5 mg were dry mouth (9.3%), urinary tract infections (7.0%), constipation (4.2%), and tachycardia (2.2%).

Dosing and Administration: Mirabegron may be used as monotherapy or in combination with solifenacin 5 mg once daily.[4] The recommended initial dose of mirabegron is 25 mg once daily. If symptoms of OAB have not improved after 4 to 8 weeks of treatment, mirabegron may be increased to 50 mg once daily. The maximum recommended dose of mirabegron in patients with severe renal impairment is 25 mg daily and it is not recommended in patients with end-stage renal disease or those on hemodialysis (CrCl <15 mL/min). Mirabegron's maximum daily dose is 25 mg in patients with moderate hepatic impairment (Child-Pugh Class B), and it is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). There is no dosage adjustment for patients with mild-to-moderate renal impairment (CrCl=30-89 mL/min) or those with mild hepatic impairment (Child-Pugh Class A). Mirabegron should be swallowed whole and should not be chewed, divided, or crushed. It may be given with or without food.

Cost and Availability: Mirabegron is an extended-release tablet available in 25 mg (NDC 0469-2601-30) and 50 mg (NDC 0469-2601-30) strengths.[4] Each tablet has an average wholesale price of $16.69.[7] The estimated annual cost of treatment is approximately $6,091.

Formulary Status: Mirabegron is not currently on the CCHS Formulary.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Acetazolamide Extended-Release Capsules	Carbonic Anhydrase Inhibitor	Idiopathic Intracranial Hypertension	No restrictions
Amivantamab (Rybrevant®)	EGFR	NSCLC*	Restricted to the Department of Hematology/Oncology for outpatient use only
Artesunate	Antimalarial Agent	Severe Malaria	Restricted to the Department of ID for patients with severe malaria
Asparaginase Erwinia Chysanthemi (Recombinant)-rywn (Rylaze®)	Antineoplastic Agent	ALL LBL	Restricted to the Department of Hematology/Oncology
Dalbavancin (Dalvance®)	Glycopeptide	SSTI	Restricted as follows: 1. For the inpatient setting, restricted to the Department of ID for pathogen-directed osteoarticular and endovascular infections as a bridge to outpatient therapy 2. For the outpatient setting, restricted to the Department of ID for pathogen-directed treatment of ABSSSI, osteoarticular and endovascular infections in patients who are not candidates for formulary CCHS agents and with insurance approval
Elexacaftor, Tezacaftor,and Ivacaftor (Trikafta®)	CFTCRC	CF	Restricted to continuation of home therapy†

*For NSCLC which is locally advanced or metastatic, with epidermal growth factor receptor exon 20 insertion mutation
† Patients will need to use home supply, since this medication cannot be obtained by Cleveland Clinic pharmacies
EGFR=Epidermal Growth Factor Receptor NSCLC=Non-small Cell Lung Cancer ID=Infectious Diseases
ALL=Acute Lymphoblastic Leukemia LBL=Lymphoblastic Lymphoma SSTI=Skin Soft Tissue Infection
ABSSSI=Acute Bacterial Skin and Skin Structure Infections CFTCRC=Cystic Fibrosis Transmembrane Conductance Regulator Corrector
CF=Cystic Fibrosis

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Mag Plus Protein	Electrolyte	Hypomagnesemia	No restrictions*
Oxcarbazepine Extended-Release (Oxtellar XR®) Topiramate Extended-Release (Trokendi XR®)	Antiepileptic	Seizures	Restricted to continuation of home therapy

*This oral magnesium product is being added to help patients with short bowel syndrome

Denials to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Isatuximab (Sarclisa®)	Monoclonal Antibody	Multiple Myeloma	Not added to the CCHS Formulary due to no clear role or place in therapy at this time
Sodium Zirconium Cyclosilicate (Lokelma®)	Potassium Binder	Hyperkalemia	Not added to the CCHS Formulary since it is not an ideal medication for inpatients due to time constraints around dosing to avoid drug interactions

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bevacizumab (Avastin®)	Monoclonal Antibody	HHT	Modified restrictions to include use by Cleveland Clinic HHT Clinic (Main Campus A90)
Chemotherapy Agents (Oral and Parenteral)	Anticancer Agents	Various Cancers	Modified restrictions to allow select APPs to order subsequent doses of chemotherapy in the inpatient and outpatient settings
Hypertonic Saline 3%	Electrolyte	Severe Hyponatremia Cerebral Edema	Modified restrictions to allow CCT ACNPs and physicians to order hypertonic 3% for severe hyponatremia or cerebral edema
Hydroxocobalamin for Injection (Cyanokit®)	Antidote	Cyanide Toxicity Refractory Vasoplegic Shock Vasodilatory Shock	Restriction was modified as follows: 1. Treatment of suspected or known cyanide toxicity 2. Treatment of refractory vasoplegic shock after cardiothoracic surgery in patients unable to receive methylene blue (e.g., active use of SSRIs, SSNRIs, MAOIs, tricyclic antidepressants or patients with known G6PD deficiency) 3. Treatment of vasodilatory shock during abdominal transplantation refractory to three or more vasopressor agents
Orphenadrine Injection	Skeletal Muscle Relaxant	Muscle Spasms	All restrictions have been removed

HHT=Hereditary Hemorrhagic Telangiectasia APPs=Advanced Practice Practitioners CCT=Cleveland Clinic Transport
ACNP=Advanced Care Nurse Practitioners SSRIs=Selective Serotonin Reuptake Inhibitors
SSNRIs=Selective Serotonin Norepinephrine Reuptake Inhibitors MAOIs=Monoamine Oxidase Inhibitors
G6PD=Glucose-6-Phosphate Dehydrogenase Deficiency

Product Standardization and Process Changes to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Bivalrudin	Anticoagulant	Suspected or Confirmed HIT	A new dosing nomogram was created for patients with suspected or confirmed HIT*
Cefpodoxime	Antibiotic	Various Infections	The cefpodoxime therapeutic interchange will specify cefixime for UTIs and cefdinir for non-UTIs *
Pentamidine Oral Inhalation	Antiprotozoal Agent	PJP Prevention	Pharmacists will be allowed to autonomously update the administration date of inhaled pentamidine orders to be timed 4 weeks from the previous dose
Posaconazole DR Tablets (Noxafil®)	Antifungal Agent	Antifungal Prophylaxis	Lung transplant patients who remain on IV posaconazole at 7 days may be transitioned to posaconazole DR tablets
Tenecteplase (TNKase®)	Thrombolytic Agent	Acute Ischemic Stroke	Alteplase will be replaced by tenecteplase 0.25 mg/kg with doses rounded to the nearest 1 mg (maximum dose of 25 mg) as the IV fibrinolytic for the treatment of acute ischemic stroke
Tocilizumab (Actemra®)	Monoclonal Antibody	COVID-19 Infection	An automatic dose rounding for tocilizumab for the treatment of COVID-19 will be instituted*

*Details are in Lexicomp
HIT=Heparin-Induced Thrombocytopenia UTI=Urinary Tract Infection PJP=Pneumocystis Jirovecii Pneumonia
IV=Intravenous COVID-19=Corona virus disease 2019

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Asparaginase Erwinia Chysanthemi (Recombinant)-rywn (Rylaze®)	Antineoplastic Agent	ALL	Restricted to the Department of Pediatric Hematology/ Oncology for outpatient use only in pediatric patients with ALL who have developed hypersensitivity to E. coli-derived asparginase, when Erwinaze® is not available. Inpatient use will be limited to not more than two doses per cycle
Dabigatran Etexilate (Pradaxa®)	Direct Thrombin Inhibitor	VTE	Restricted as follows: 1. Initiation is restricted to the Departments of Pediatric Hematology/ Oncology or Pediatric Cardiology for the treatment of active VTE after initial treatment with an injectable anticoagulant or for the prevention of VTE 2. Continuation of home therapy
Elexacaftor, Tezacaftor,and Ivacaftor (Trikafta®)	CFTCRC	CF	Restricted to continuation of home therapy*

*Patients will need to use home supply, since this medication cannot be obtained by Cleveland Clinic pharmacies
ALL=Acute Lymphoblastic Leukemia VTE=Venous Thromboembolism
CFTCRC=Cystic Fibrosis Transmembrane Conductance Regulator Corrector CF=Cystic Fibrosis

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Fentanyl Intranasal	Opioid	Analgesic	Restricted as follows: 1. Use is restricted to the ED only (including Free-standing EDs) 2. For use in patients ≥ 1 year of age 3. Dosing: 1 to 2 mcg/kg/ dose (maximum single dose: 100 mcg: divide to-tal volume evenly be-tween nares) 4. May give up to one repeat dose of 0.5 to 1.5 mcg/kg 10 to 20 minutes after the initial dose 5. Only recommended in patients that do not have IV access 6. Patients receiving in-tranasal fentanyl should have pulse oximetry mon-itoring and observation for at least 60 minutes after the last dose
Lurasidone (Latuda®)	Atypical Antipsychotic	Bipolar Depression Schizophrenia	Restricted for use to children ≥10 years of age as follows: 1. Initiation is restricted to the Department of Child and Adolescent Psychia-try 2. Continuation of therapy from home is not restricted

ED=Emergency Department IV=Intravenous

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Rivaroxaban (Xarelto®)	Direct Oral Anticoagulant	VTE	Modified restrictions as follows: 1. Initiation is restricted to the Departments of Pediatric Hematology/ Oncology or Pediatric Cardiology for the treatment of active VTE after initial treatment with an injectable anticoagulant or for the prevention of VTE 2. Continuation of therapy is not restricted

VTE=Venous thromboembolism

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Glutamine Powder Packets (Glutasolve®)	Supplement	Oral Mucositis/ Stomatitis	Removed due to the following: 1. Wholesaler no longer carries this product 2. Low use in the last 5 years 3. No longer included in Beacon protocols 4. Pediatric Oncology providers are in agreement with removal 5. Use has transitioned to Healios™ Glutamine Complex by Nutrition

Process Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Acetylcysteine IV (Acetadote®)	Antidote	Acetaminophen Overdose	Only the three-bag dosing of IV acetylcysteine will be permitted for the treatment of acetaminophen overdose toxicity
Vancomycin IV	Antibiotic	Various Infections	The Pediatric Vancomycin Dosing Service Dosing and Monitoring Guideline will be updated as follows: 1. Added more restrictive serum creatinine ranges to allow for more conservative dosing in patients postnatal age 7 days to 2 months 2. Added recommendation to obtain pre-dialysis level that may be extrapolated to estimate the post-IHD trough 3. Added more criteria for patients on CRRT

IV=Intravenous IHD=Intermittent Hemodialysis CRRT=Continuous Renal Replacement Therapy