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Formulary Update

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From the Department of Pharmacy

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AbobotulinumtoxinA for Neurogenic Detrusor Overactivity

By: Andrew Vandermause, Pharm.D.

Background: Neurogenic detrusor overactivity (NDO) is described as an inability to hold urine, bladder stiffness, and bladder shrinking due to nervous system detrusor muscle overactivity that usually results from nervous system disorder or injury.[1] Neurogenic detrusor overactivity is different than overactive bladder in that NDO is associated with an alteration of the electromechanical properties of the detrusor smooth muscle.[1,2] Due to the nature of the disease, the prevalence of NDO is difficult to estimate as there is not a clearly defined age during which it develops. Use of botulinum toxin A (BTA) is third line in therapy for treatment of NDO behind behavioral therapy and use of oral antimuscarinics or beta-3 adrenoreceptor agonists.[3] There are three commercially available formulations of BTA: onabotulinumtoxinA (Botox®;Allergan), abobotulinumtoxinA (Dysport®;Ipsen), and incobotulinumtoxinA (Xeomin®;Merz). Each of these BTA formulations have different neurotoxin A protein contents and are not interchangeable.[4] In August 2011, Botox® was approved by the Food and Drug Administration (FDA) to treat NDO, and it is currently the only BTA approved to treat NDO in the U.S.[5] Dysport® is not FDA-approved to treat NDO, and it is not included in any NDO guidelines.[3] In the event of Botox® failure as determined by the patient's physician, most patients will undergo bladder augmentation, which is a surgery that increases the total volume of the bladder to allow for storage of larger amounts of urine.[6]

Mechanism of Action: Botulinum toxin A inhibits the release of the neurotransmitter, acetylcholine, from the pe-

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Dapagliflozin for Heart Failure with Reduced Ejection Fraction

By: Richa Shah, Pharm.D.

Background: An estimated 6 million individuals in the U.S. have heart failure (HF), and the prevalence is expected to continue to increase.[1] Heart failure with reduced ejection fraction (HFrEF) is defined as having a left ventricular ejection fraction (LVEF) of ≤ 40% and is associated with higher in-hospital mortality than those with preserved LVEF. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are oral antidiabetic agents indicated to improve glycemic control in adult patients with type 2 diabetes (T2DM) and have been associated with cardiovascular (CV) disease protection in patients with T2DM and risk factors for or established CV disease.[2] The Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial found that dapagliflozin (Farxiga®;AstraZeneca) was associated with a lower rate of CV death or hospitalization for heart failure (HHF) than placebo, which was driven primarily by a lower rate of HHF.[3] Based on these results, dapagli-

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ripheral cholinergic nerve endings.[5] The primary pharmacodynamic effect of Botox® is due to the reversible chemical denervation of the treated muscle resulting in a measurable decrease of the compound muscle action potential, causing a localized reduction of muscle activity.

Key Clinical Trial: Bottet and colleagues conducted a retrospective multicenter study in France between 2007 and 2015 comparing the number of urinary incontinence episodes per day in patients initially treated with Botox® who underwent a switch to Dysport®.[6] Patients (N=57) with NDO refractory to anticholinergics who received intradetrusor injections (IDI) of Dysort® following failure of first or subsequent doses of Botox® were included in the study. The definition of failure was determined by physicians' discretion. The primary outcome was assessed utilizing a bladder diary and four urodynamic parameters: maximum cystomanometric capacity, detrusor maximum pressure, presence or not of uninhibited detrusor contraction, and the volume at the first uninhibited detrusor contraction. The success of the switch was subjectively defined as improvement in the number of urinary incontinence episodes per day lasting >12 weeks and/or significant changes in the four urodynamic parameters. A time lapse of 3 months or longer was maintained between repeat injections of BTA. The median number of Botox® IDI was five before failure (range of 1 to 17); 38.6% (22/57) of patients were considered primary non-responders. The first dose of Botox® was 200 units (12/57 patients) or 300 units (42/57 patients), and there was a dose escalation to 400 units in some patients. The dose of Dysport® in 75.4% of patients was 750 units (with a range of 500 to 1000 units) and the injections were spread out evenly over the bladder wall. Thirty patients (52.6%) reported a significant reduction in the number of urinary incontinence episodes per day. Thirty-two patients experienced clinical and/or urodynamic benefits from the botulinum toxin switch and matched success criteria. The switch to Dysport® failed in 25 patients, resulting most commonly in surgery. The authors concluded that botulinum toxin switch from Botox® to Dysport® was beneficial in 56% of patients who failed a first or subsequent trial of Botox®, and this should be considered as a treatment option in refractory patients with NDO.

Safety: The most frequent adverse reaction reported was urinary tract infection occurring in 35.7% of those treated.[7] The product may contain milk protein and thus is contraindicated in patients with a milk protein allergy.[5]

Dosing and Administration: Based on information presented in the clinical trials, doses of 250-, 300-, 500-, 750-, and 1000-units of Dysport® were dissolved in 20 milliliters of saline.[1,6,7] Equal volumes were partitioned and roughly one milliliter was injected into 20 different sites of the patient's detrusor muscle and suburothelium every 12 weeks.

Cost and Availability: Dysport® is available in 300- and 500-unit vials.[5] Dysport® has an average wholesale price of $619 per 300 unit vial and $1031 per 500 unit vial.[8] With one treatment cycle occurring roughly every 12 weeks, the annual cost of therapy could range from $2682 to $8935.

Formulary Status: The restrictions for Dysport® were modified on CCHS Formulary to include the Department of Urology for outpatient use only in patients with NDO that have failed oral anticholinergic and Botox® therapy.

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flozin received approval by the Food and Drug Administration in October 2019 for its use in patients with T2DM and CV disease or multiple risk factors to reduce the risk of HHF.[4,5] Following this trial, investigators sought to determine if the use of these agents in HF showed similar benefits regardless of the presence of T2DM in the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial.[6]

Mechanism of Action: The exact mechanism of SGLT2 inhibitors providing CV protection and reducing HHF is unknown.[7-9] Proposed mechanisms include reducing CV risk factors such as blood pressure, hemoglobin A1c, and body fat. Additionally, SGLT2 inhibitors may increase cardiac efficiency by reducing preload through diuresis and afterload by decreasing arterial stiffness. These postulated mechanisms would benefit patients with HF, regardless of their T2DM status.

Key Clinical Trial: The DAPA-HF trial was a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of SGLT2 inhibitors in patients with HFrEF irrespective of diagnosis for T2DM.[6] Patients were randomized 1:1 to receive dapagliflozin 10 mg daily (n=2373) or placebo (n=2371), stratified based on the presence of T2DM at screening. Dose reduction to 5 mg daily was permitted in the setting of renal dysfunction, volume depletion, or hypotension. The primary endpoint was a composite of death from CV causes or worsening HF, defined as an unplanned hospitalization or urgent visit for HF resulting in intravenous therapy. Secondary endpoints included a composite of HHF or CV death, total number of HHF, change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, a composite of worsening renal failure, and death from any cause. Dapagliflozin was found to confer a statistically significant reduction in the primary outcome of composite of CV death or worsening HF (HR:0.74;P<0.001). Patients in the dapagliflozin group had lower rates of CV death or HHF (HR:0.74;P<0.001), decreased total number of hospitalizations (RR:0.75;P<0.001), and greater change in KCCQ score (HR:1.18;P<0.001). Death from any cause occurred in 11.6% and 13.9% of patients in the dapagliflozin and placebo groups, respectively. In a subgroup analysis of the primary outcome no difference in treatment effect was seen with age, cause of HF, or T2DM status at baseline. However there was a difference in patients based on NYHA class, with class II deriving greater benefit than class III or IV (HR:0.63; 95%CI 0.52-0.75 vs. HR:0.9; 95%CI 0.74-.09). The authors concluded that in patients with HFrEF dapagliflozin use resulted in a lower risk of worsening HF or death from CV causes and better symptom scores compared to placebo, regardless of the presence of T2DM.

Safety: The most common adverse events in the dapagliflozin arm in DAPA-HF were volume depletion (7.5%), renal adverse event (6.5%), and fracture (2.1%), which did not differ from placebo.[6] Amputation, urinary tract infection, and major hypoglycemia occurred in <0.5% of patients in both groups.

Dosing and Administration: The recommended dose of dapagliflozin to reduce the risk of HHF is 10 mg by mouth daily with eGFR ≥45 mL/min/1.73 m^2.[5] The manufacturer does not recommend use in patients with eGFR <45 mL/minute/1.73 m^2. Dapagliflozin is contraindicated in patients with eGFR <30 mL/minute/1.73 m^2, severe renal impairment, or those receiving dialysis.

Availability and Cost: Dapagliflozin is available as 5 mg and 10 mg oral tablets.[10] The average wholesale price for both tablet strengths is $20.29 per tablet.

Formulary Status: Dapagliflozin will be evaluated for formulary addition the second quarter of 2020. Currently, patients admitted on an SGLT2 inhibitor are automatically converted to an equivalent dose of empagliflozin (Jardiance®).

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Clorazepate (Tranxene®)	Anticonvulsant	Epilepsy	Restricted to Epilepsy/Neurology for initiation of therapy Continuation of therapy from home is not restricted Clorazepate will be removed from any CCHS therapeutic interchanges for the indication of epilepsy
Crizanlizumab-tmca (Adakveo®)	P-Selectin Inhibitor	Sickle Cell Disease	Restricted to Department of Hematology/Oncology for outpatient use only
Enfortumab vedotin (Padcev®)	Monoclonal Antibody	Urothelial Cancer	Restricted to Hematology/Oncology for outpatient use only in patients with urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor or a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting
Fam-traztuzumab deruxtecan (Enhertu®)	Monoclonal Antibody	Metastatic Breast Cancer	Restricted to Department of Hematology/Oncology for outpatient use only in patients who have failed ≥ two prior anti-HER2-based regimens in the metastatic setting
Imipenem cilastatin/ relebactam (Recarbrio™)	Antibiotic	Pneumonia Complicated Abdominal and UTI infections	Restricted to Infectious Diseases
Luspatercept-aamt (Reblozyl®)	Recombinant Fusion Protein	Beta-thalassemia MDS	Restricted to the Department of Hematology/Oncology for outpatient use only in patients with beta-thalassemia and in patients with MDS
N-acetylcysteine (NAC) oral capsules	Antidote Mucolytic	Substance Use Disorder	Note: Oral NAC capsules should not be used for other indications such as acetaminophen overdose/ toxicity, acute alcoholic hepatitis, or non-acetaminophen induced acute liver failure.

PD1=Programmed death receptor 1 PD-L1=Programmed death-ligand1 HER2=Hormone estrogen receptor 2
UTI= Urinary tract infection MDS=Myelodysplastic syndrome FDA=Food and Drug Administration
NAC=N-acetylcysteine

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Nifedipine immediate-release capsules	Dihydropyridine Calcium Channel Blocker	Acute-Onset, Severe Hypertension during Pregnancy and Postpartum Period	Restricted to use by Labor and Delivery for urgent blood pressure control
Spironolactone Oral Suspension (CaroSpir®)	Potassium Sparing Diuretic	Diuresis	This suspension is not therapeutically equivalent to spironolactone tablets as CaroSpir® results in 15% to 37% higher serum concentrations compared to spironolactone tablets; doses of CaroSpir® ≥ 100 mg per day will be reduced by 25% per CCHS P&T Committee
Tildrakizumab (Ilumya®)	Monoclonal Antibody	Plaque Psoriasis	Restricted to the Department of Dermatology for outpatient use only

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction/ Comments**
AbobotulinumtoxinA (Dysport®)	Botulinium Toxin Type A	NDO OAB	Modified restrictions to include use by Urology in patients with NDO and OAB after onabotuliniumtoxinA (Botox®) failure
Aztreonam (Azactam®)	Antibiotic	Surgical Prophylaxis in Aortic and LVAD Surgery	Modified restrictions to include prophylaxis for cardiothoracic surgery (aortic and LVAD cases)
Brentuximab vedotin (Adcetris®)	Monoclonal Antibody	ALCL	Modified restrictions to include Hematology/Oncology for inpatient use in newly diagnosed ALCL who cannot be discharged due to disease burden

NDO=Neurogenic detrusor overactivity OAB=Overactive bladder LVAD=Left ventricular assist device
ALCL=Anaplastic large cell lymphoma

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction/ Comments**
Flucytosine	Antifungal	Fungal Infections	Modified restrictions to Infectious Diseases Service/ Restriction was due to the drug's toxicity profile, limited role in treatment, and need for therapeutic drug monitoring for dosage adjustment
Foscarnet (Intravenous)	Antiviral Agent	CMV HSV	Modified restrictions to Infectious Diseases Service/ Restriction was due to adverse effect profile, limited application in HSV– and CMV–resistant infections, and complex dosing*
Intravenous Immune Globulin (IVIG;Gammagard®)	Immunoglobulin	STSS	Modified restrictions to include Department of Infectious Diseases for the treatment of suspected or confirmed STSS based on CDC case definition
Pegfilgrastim (Neulasta®)	CSF	Prevention of chemotherapy-induced neutropenia	Modified restrictions to include Hematology/Oncology inpatients if ALL of the following criteria are met: 1) Emergent new start chemotherapy (new diagnosis or new relapse; not planned chemotherapy admissions) 2) Receiving a regimen that requires growth factor support 3) Lacks access to outpatient growth factor (unable to afford/no coverage for filgrastim or unable to coordinate outpatient pegfilgrastim due to insurance or facility) 4) Inability to coordinate growth factor will delay discharge Note: If a patient is to be discharged within 24 hours of chemotherapy, pegfilgrastim on-body injector (Neulasta OnPro®) should be used to prevent administration of GF within a 24 hour window of chemotherapy

*This restriction does not apply to intravitreal foscarnet use.
CMV=Cytomegalovirus HSV=Herpes simplex virus STSS=Streptococcal toxic shock syndrome
CDC=Centers for Disease Control and Prevention CSF=Colony stimulating factor GF=Growth factor

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction/ Comments**
Ramucirumab (Cyramza®)	Monoclonal Antibody	Gastric or gastro-esophageal junction adenocarcinoma Non-small cell lung cancer	Modified restrictions to Hematology/Oncology for treatment of HCC for outpatient use only in second-line setting after progression or unacceptable toxicity on sorafenib
Ravulizumab (Ultomiris®)	Monoclonal Antibody	aHUS	Modified restrictions to include use by Hematology/ Oncology and Nephrology for outpatient use only for the indication of aHUS in either patients who are complement inhibitor therapy naïve or those who are clinically stable on eculizumab. 1) A new inpatient diagnosis of aHUS will be initiated on eculizumab with a plan to transition to ravulizumab as an outpatient. Efforts should be made to initiate insurance coverage for ravulizumab as soon as possible. 2) Inpatient use of ravulizumab for aHUS will be evaluated for approval on a case by case basis for continuation of therapy only. Patients admitted to the hospital when they are due ravulizumab (whether for PNH or aHUS) who cannot be discharged within ± 7 day window of ravulizumab administration, will receive a one-time dose of ravulizumab inpatient to avoid the need to re-load as an outpatient.

HCC=Hepatocellular carcinoma aHUS =Atypical hemolytic uremic syndrome PNH=Paroxysmal nocturnal hemoglobinuria

Therapeutic Interchange on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Cefadroxil	Antibiotic	Various Infections	Conversion to cephalexin; dosage based on renal function Therapeutic Interchange details are available on Pharmacy SharePoint site

Product Standardization to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Warfarin (generic)	Anticoagulant	Thromboembolism	Due to contracting issues with the brand manufacturer, CCHS will be switching to generic warfarin. Inpatient and outpatient pharmacies will carry the same generic product.

Denials to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Lefamulin (Xenleta™)	Antimicrobial Agent	CAP	Due to its significantly higher cost and lack of advantage over standard CAP therapy, it was recommended not to add this agent to the CCHS formulary.
Patiromer (Veltassa®)	Potassium Binder	Hyperkalemia	Due to its delayed onset of action and the availability of a less expensive alternative (sodium polystyrene sulfate) to treat hyperkalemia, it was recommended not to add patiromer to the CCHS formulary.*
Sodium zirconium cyclosilicate (Lokelma®)	Potassium Binder	Hyperkalemia	Due to lack of evidence of benefit over sodium polystyrene sulfonate, it was recommended not to add sodium zirconium cyclosilicate to the CCHS formulary.*

*This medication is non-formulary for both initiation and continuation of therapy
CAP=Community acquired pneumonia

Removal from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Tacrolimus extended-release capsules (Astagraf®XL)	Calcineurin Inhibitor	Prevention of organ rejection	Envarsus®, another extended-release formulation of oral tacrolimus, was recently added to the CCHS Adult Formulary. Due to very low use of Astagraf®XL for inpatients and the potential medication safety concerns with having multiple long-acting tacrolimus formulations, it was determined that Astagraf® XL should be removed from the CCHS Formulary.

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Belimumab (Benlysta®)	Monoclonal Antibody	Autoantibody-Positive SLE	Restricted to the Department of Pediatric Rheumatology for outpatient use only
Crizanlizumab-tmca (Adakveo®)	Monoclonal Antibody	Sickle Cell Disease	Restricted to the Department of Pediatric Hematology/Oncology for patients aged 16 years and older with sickle cell disease for outpatient use only with insurance coverage verification prior to starting. Initiation and continuation while inpatient will not be permitted.
Gemtuzumab Ozogamicin (Mylotarg®)	Monoclonal Antibody	Relapsed and Refractory CD33 Positive AML	Restricted to the Department of Pediatric Hematology/Oncology and BMT
Imipenem cilastatin/ relebactam (Recarbrio™)	Antibiotic	Pneumonia Complicated Abdominal and UTI infections	Restricted to Pediatric Infectious Diseases
Prothrombin Complex Concentrate (Human) (Kcentra®)	Blood Factor	Warfarin Reversal Non-warfarin related refractory coagulopathic bleeding associated with cardiac surgery	Restricted to: 1) The Department of Neurology and Neurosurgery, Emergency Room physicians, Intensivists for intracranial bleeds secondary to warfarin 2) The reversal of warfarin for urgent/emergent surgeries. Kcentra® should not be used to reverse warfarin for elective or non-invasive procedures. 3) The reversal of warfarin prior to heart transplant 4) Non-warfarin related refractory coagulopathic bleeding associated with cardiac surgery under specific criteria* 5) Life-threatening bleeds secondary to warfarin

*Specific criteria is listed in Lexicomp
SLE=Systemic lupus erythematosus AML=Acute myeloid leukemia BMT=Bone marrow transplant UTI=Urinary tract infection

Denial to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Lefamulin (Xenleta™)	Antimicrobial Agent	CAP	Refer to Adult Formulary section for details

CAP=Community acquired pneumonia

Changes to Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Aztreonam (Azactam®)	Antibiotic	Surgical Prophylaxis in Aortic and LVAD Surgery	Modified restrictions to include prophylaxis for cardiothoracic surgery (aortic and LVAD cases)
Bevacizumab (Avastin®)	Monoclonal Antibody	RRP	Modified restrictions to include the treatment of RRP
Flucytosine	Antifungal	Fungal Infections	Modified restrictions to Pediatric Infectious Diseases/Refer to Adult Formulary section for details
Foscarnet (Intravenous)	Antiviral Agent	CMV HSV	Modified restrictions to Pediatric Infectious Diseases/Refer to Adult Formulary section for details
Intravenous Immune Globulin (IVIG; Gammagard®)	Immunoglobulin	STSS	Modified restrictions to include Pediatric Infectious Diseases for the treatment of suspected or confirmed STSS based on CDC case definition
Palonosetron (Aloxi®)	Antiemetic	Prevention of chemotherapy-induced nausea and vomiting	Modified restrictions to the Department of Pediatric Hematology/ Oncology and BMT for the prevention of chemotherapy-induced nausea and vomiting from moderately- and highly-emetogenic chemotherapy (as defined by COG supportive care guidelines) in inpatients and outpatients with these caveats: 1) Patients 18 years and older who receive palonosetron should not receive ondansetron for 72 hours following palonosetron dose 2) Patients less than 18 years of age who receive palonosetron should not receive ondansetron for 48 hours following palonosetron dose*

*If another 5HT-3 receptor antagonist is ordered prior to 48 hours, another antiemetic class should be utilized.
LVAD=Left ventricular assist device RRP=Recurrent respiratory papillomatosis CMV=Cytomegalovirus HSV=Herpes simplex virus
STSS=Streptococcal toxic shock syndrome CDC=Centers for Disease Control and Prevention BMT=Bone marrow transplant
COG=Children's Oncology Group

Product Standardization to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Warfarin (generic)	Anticoagulant	Thromboembolism	Refer to Adult Formulary section for details