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Formulary Information

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FDA Medication Safety Alert: Risk of VTE with Testosterone

By: Libby Herman, Pharm.D.

Introduction: Testosterone is indicated for use in males with hypogonadism, in females with inoperable metastatic breast cancer, and in adolescent males with hypogonadism or delayed puberty.[1] Testosterone is also used off-label to treat sexual dysfunction in certain women.[1] Use of testosterone therapy in men increased more than 3-fold from 2001-2011, largely due to the discovery that, after age 40, testosterone levels in men begin to decrease.[2-3] This decline, referred to as andropause, may account for a number of pathophysiologic changes associated with aging including sexual dysfunction, depression, changes in body composition, and male osteoporosis.[3]

Thrombosis Risk and Testosterone Therapy: Increases in hematocrit, red blood cell volume, and blood viscosity are predictable effects of exogenous testosterone administration.[3] Testosterone therapy also increases circulating estrogens that may play a role in increasing thrombotic and cardiovascular-related events , due to resistance to activated protein C.[2] These pathophysiologic changes are purported to increase the risk of thromboembolic disease.[3] In contrast to exogenous testosterone, elevated endogenous levels of testosterone have not been associated with similar risks.[4] Likewise, Glueck and colleagues reported an aggregate of 42 patients who experienced thrombotic events during treatment with testosterone, none of whom had underlying polycythemia.[2] A 2013 meta-analysis of randomized controlled trials conducted in men receiving testosterone therapy revealed an increased risk of cardiovascular-related events (OR 1.54;95% CI:1.09-2.18).[5] The increased risk of cardiovascular-related events is compounded by the fact that typical users of testosterone therapy (e.g., men or women over age 40) have an elevat-

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Does Olmesartan Use Increase CV Risk for Diabetics?

By: Maya Wai, Pharm.D.

Introduction: Since 2010, the Food and Drug Administration (FDA) has been reviewing evidence and releasing drug safety communications (DSC) to the public regarding the use of olmesartan (Benicar®), an angiotensin receptor blocker (ARB) antihypertensive medication, and its association with cardiovascular (CV) events. These reviews began after the publication of two randomized controlled trials, **R**andomized **O**lmesartan **a**nd **D**iabetes **M**icro**a**lbuminuria **P**revention (ROADMAP) and **O**lmesartan **R**educing **I**ncidence of **E**nd-stage Renal Disease in Diabetic **N**ephropathy **T**rial (ORIENT). These two trials evaluated the use of olmesartan in delaying the progression of kidney disease in type II diabetic patients.[1,2] ROADMAP evaluated time to microalbuminuria in diabetics with other CV risk factors who were treated with olmesartan 40 mg daily or placebo.[1] ORIENT evaluated the use of olmesartan (10-40 mg) or placebo with concomitant angiotensin-converting-enzyme inhibitors (ACEI) in time to worsening renal function in diabetic patients with no prior CV event histo-

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ed baseline risk. Women and men over the age of 40 have a 27-36% lifetime risk of cardiovascular events with optimal risk factors.[6]

FDA Medication Safety Alert: On June 16th, 2014, the Food an Drug Administration (FDA) issued a mandate to manufacturers of all approved testosterone products to include a warning about the risk of venous thromboembolism(VTE).[7] Traditionally the risk of VTE with testosterone therapy was associated with polycythemia, but recent reports have demonstrated an increased risk of VTE independent of polycythemia.[2] This new warning is unrelated to the ongoing investigation of the risk of arterial thromboembolism.[7] To further ensure safe use, various FDA-approved testosterone products also have Risk Evaluation and Mitigation Strategies (REMS) requirements ranging from a medication guide for most topical gel products to other elements to assure safe use including an implementation system for the injectable formulation.[8]

Conclusion: The FDA's warning highlights the fact that testosterone therapy is not without significant risks and the decision to initiate therapy should be individualized, particularly if the indication is not FDA-approved. It is prudent to identify health conditions that benefit most from testosterone therapy and weigh those outcomes against the risk of VTE and other serious consequences. Moreover, concomitant medications and comorbidities that further increase the risk of VTE should be considered prior to initiation of testosterone therapy. If the risk of VTE is low and the benefit is high, testosterone therapy may be a reasonable option with appropriate monitoring.

References:

1. Testosterone. Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc. Updated September 5, 2014. http://www.crlonline.com/lco/action/doc/retrieve/docid/patch f/7742#, Accessed: September 6, 2014.
2. Glueck CJ, Wang P. Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. Metabolism 2014;63(8): 989-94.
3. Myers JB, Meacham RB. Androgen replacement therapy in the aging male. Rev Urol 2003;5(4):216-26.
4. Holmegard HN, Nordestgaard BG, Schnohr P, Tyjaerg-Hansen A, Benn, M. Endogenous sex hormones and the risk of venous thromboembolism in women and men. J Thromb Haemost 2014;12:297-305.
5. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013;108:1-12.
6. D'Agostino RB, Vasan RS, Pencian MJ, Wolf PA, Cobain M, Massarn JM et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117:743-53.
7. United States Food and Drug Administration. FDA added general warning to testosterone products about potential for venous blood clots. Food and Drug Administration website: http://www.fda/gov/drugs/drugsafety/ucm401746.htm. Accessed: September 4, 2014.
8. United States Food and Drug Administration. Approved risk evaluation and mitigation strategies. Food and Drug Administration website: http://www.fda.gov/Drugs/Drug Safety/PostmarketDrug SafetyInformation for Patients and Providers/ucm111350.htm. Accessed: September 4, 2014.

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ry.[2] An unexpected finding of an increase in fatal CV deaths in the patients receiving olmesartan raised concern and prompted the FDA to review the data and issue the initial DSC in 2010.[1-3] Of particular concern are diabetics who have been using high-dose olmesartan (40 mg) for greater than 6 months. A follow-up DSC was issued by the FDA on April 14, 2011, which determined that the benefits outweigh the risk when olmesartan is used to treat high blood pressure; however, olmesartan use is not recommended to delay or prevent microalbuminuria in diabetic patients.[4]

FDA's Latest Statement Regarding Olmesartan CV Risk in Diabetics: The latest DSC released by the FDA was on June 24, 2014, which stated that it "has found no clear evidence of increased CV risks associated with use of (…) olmesartan in diabetic patients. As a result, our recommendations for use of olmesartan (…) will remain the same, but we will require information about some of the studies to be included in the drug labels." The FDA re-reviewed the results from the ORIENT study and reviewed the data from three additional retrospective studies before drawing this conclusion.[5]

FDA's Interpretation of Olmesartan Studies: When the FDA re-reviewed the results from the ORIENT study, they concluded that the association of olmesartan use and CV risk was not strong. There was no difference in mortality between the olmesartan and placebo groups when the causes of death and deaths that occurred greater than 30 days after last dose were excluded.[2,5] One of the studies that was evaluated by the FDA was a large retrospective study of Medicare patients (n=882,727) who were treated with olmesartan or another ARB for CV and mortality risk.[6] Researchers found that a lower dose (<40 mg/day) of olmesartan was not associated with an increased risk of acute myocardial infarction (AMI), stroke, or death, regardless of duration of use. One subgroup of diabetic patients (6.2%) who took high-dose olmesartan (40 mg/day) for greater than 6 months was associated with a two-fold increased risk of death.[6] However, non-diabetic patients on high-dose olmesartan for greater than 6 months were associated with a 54% decreased risk of death.[6] The FDA concluded that "the conflicting results in diabetics and non-diabetics are difficult to reconcile and raise uncertainty about the credibility of the findings in either group."[5]

Conclusion: Of all the data that are currently available, the Medicare study is the only study that specifically examined the subgroup of interest: diabetics using high-dose olmesartan. The FDA concluded that the association of high-dose olmesartan with a decrease in survival for diabetics and an increase in survival for non-diabetics from the Medicare study is "not a plausible finding" and therefore, did not substantiate the findings from ROADMAP and ORIENT.[1,2,5] The FDA states that they found no clear evidence of increased CV risk associated with diabetics using olmesartan, and therefore, their recommendations remain the same: "the benefits of Benicar continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the drug label."[4,5] Clinical judgment should be exercised when deciding to prescribe high-dose olmesartan in diabetic patients.

References:

1. Haller H, Ito S, Izzo JL, Januszeica A, Katayam S, Menne J et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes N Engl J Med 2011;364:907-17.
2. Imai E, Chan JC, Ito S, Yamsaki T, Kobayashi F, Haneda M et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicenter, randomized, placebo-controlled study. Diabetologia 2011; 54: 2978-86.
3. FDA Drug Safety Communication: Ongoing safety review of Benicar (olmesartan) and cardiovascular events. Food and Drug Administration [Internet] Rockville , MD June 11, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm215222htm. Accessed: July 23, 2014.
4. FDA Drug Safety Communication: Safety Review Update of Benicar (olmesartan) and cardiovascular events. Food and Drug Administration [Internet] Rockville MD. April 14, 2011. Available at: http://www.fda.gov/Drugs/Drug Safety/ucm251268.htm. Accessed: July 23, 2014.
5. FDA Drug Safety Communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesaratan not conclusive: label updates required. Food and Drug Administration [Internet] Rockville MD. June 24, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm402323.htm. Accessed: July 23, 2014.
6. Graham DJ, Zhou EH, McKean S, Levenson M, Calia K, Gelperin K et al. Cardiovascular and mortality risk in elderly Medicare beneficiaries treated with olmesartan versus other angiotensin receptor blockers. Pharmacepidemiol Drug Saf 2014;23:331-9.

Pharmacological Considerations Following Bariatric Surgery

By: Kent Wilin, Pharm.D. Candidate

Introduction: Between 2003-2011, the number of bariatric surgeries performed worldwide has been estimated to have increased from 146,301 to over 340,000.[1,2] As the prevalence of this surgery grows, it is important for clinicians to be aware of its effect on the pharmacokinetic profile of various medications. Obesity is a risk factor for many disease states such as hypertension, cardiomyopathy, hyperlipidemia, diabetes, and major depressive disorder.[3,4] As one can expect, bariatric surgery candidates often need multiple maintenance medications. After surgery, these maintenance medications may require modifications in dosage and/or formulation, and in some cases substitution to an agent from another pharmacologic class may be necessary.

Roux-en-Y Gastric Bypass: The most commonly performed bariatric procedure is Roux-en-Y gastric bypass (RYGB).[2,4-6] In a RYGB procedure, stomach volume is reduced to a small pouch.[5,6] This limits the amount of food a patient can eat at one time, as well as restricts the number of parietal cells available to secrete acid. The small pouch is then directly connected to the jejunum bypassing the duodenum.

How Does Bariatric Surgery Affect Drug Therapy?: The main mechanism of malabsorption in RYGB stems from the decreased intestinal surface area available for drug absorption.[3,5-6] Along with less surface area available for passive diffusion, there are also less transporter proteins available to actively transport drugs across intestinal cell membranes. An example of a drug transporter protein is oligopeptide transporter (PEPT-1).[5] A reduction in PEPT-1 can lead to an impaired absorption of drugs such as β-lactam antibiotics and angiotensin-converting-enzyme inhibitors. In addition to a lower surface area, RYGB yields a shorter transit time through the gastrointestinal (GI) tract.[3,5-7] The resulting consequence is a decreased bioavailability of certain products which require a longer duration of GI exposure for optimal absorption such as enteric-coated, delayed- or extended-release formulations.[7] Following RYGB surgery, it is advised that patients be switched to immediate-release formulations. While a change to immediate-release will likely not require a different daily dose, the administration frequency may increase. In some cases, switching to a liquid formulation may reduce pill burden and GI irritation; however, if oral administration cannot be tolerated alternative dosage forms (e.g., parenteral, transdermal, sublingual) may need to be utilized.[6,7] Prior to converting a patient to a liquid formulation, an important factor to consider is the formulation's hyperosmolality. Administration of high volumes of hypertonic solutions can cause GI intolerance. The hyperosmolality of liquid formulations can be reduced by diluting them with 10-30mL of water prior to administration. Also of concern with commercially available liquid preparations are the inactive ingredients such as sorbitol, an artificial sweetener known to cause GI intolerance, especially diarrhea.[8] Limiting the number of sorbitol-containing agents is a step that can be taken to prevent such side effects. Due to a reduction in parietal cells, the pH of the stomach may be elevated affecting medications which depend on an acidic environment for solubility, activation, and absorption.[5-7] Notable drugs affected by reduced acidity include simvastatin, ketoconazole, and enalapril; alternative agents should be considered.[6] As bariatric surgery often modifies mesenteric circulation, so the absorption of medications that depend on enterohepatic recycling can be disrupted.[5] An important medication that could undergo unpredictable pharmacokinetic changes due these alterations in mesenteric circulation is warfarin.[9] Cautious monitoring should be done when initiating or continuing warfarin therapy in a post-bariatric surgical patient.

Pharmacological Considerations: Some maintenance medications warrant caution when restarting postoperatively.[7] Bariatric surgery can lead to improvement in some disease states like hypertension and type 2 diabetes.[5] Therefore, drugs used to treat these conditions may require dose reductions or in some cases may be discontinued.[7] Following bariatric surgery, food intake including carbohydrate consumption is restricted; therefore, type 2 diabetic patients who are subsequently restarted on their antidiabetic medications at preoperative doses may be at risk for hypoglycemia. Therefore, blood glucose levels of type 2 diabetic patients should be carefully monitored after bariatric surgery; antidiabetic therapy may need to be adjusted. Furthermore, these patients may also experience an increase in metformin absorption which could potentially increase the risk of Vitamin B12 deficiency.[10-11] A high proportion of bariatric surgery patients receive psychotropic therapy which needs to be continued after surgery.[4,7] One complication of disrupting antidepressant therapy is discontinuation syndrome.[7,12] This syndrome manifests as "flu-like"

symptoms, imbalance, sensory disturbances, and hyperarousal.[11] Fortunately, many psychotropic medications are available as liquid formulations, but resorting to sublingual, intramuscular or intravenous injectable dosage forms may be necessary in the event of oral intolerance.[7] Although the absorption of bisphosphonates may not be altered by bariatric surgery, oral formulations should be avoided due to their propensity to cause gastric ulcers.[6,13] Ulcers are especially concerning in the bariatric surgical population as they can lead to reoperations.[5] Since bariatric surgery patients are at a high risk for osteoporosis due to impaired calcium absorption, clinicians may need to turn to alternatives such as calcitonin, teriparatide, or raloxifene.[6] Other agents that can cause ulceration such as nonsteroidal anti-inflammatory drugs should be avoided.[5,6] For pain relief, acetaminophen, opioids, or tramadol could be considered.

Conclusion: Bariatric surgery can greatly affect drug absorption. It is imperative that pharmacists be aware of the physiological impact this type of surgical procedure has on the bioavailability of various medications. Post-operative assessment of each bariatric patient's medication profile is essential to determine whether drug therapy needs to be modified.

References:

1. Buchwald H, Williams SE. Bariatric surgery worldwide 2003. Obes Surg 2004;14(9):1157-64.
2. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obes Surg 2013;23(4):427-36.
3. Geraldo Mde S, Fonseca FL, Gouveia MR, Feder D. The use of drug in patients who have undergone bariatric surgery. Int J Gen Med 2014;7:219-24.
4. Hamad GG, Helsel JC, Perel JM, Kozak GM, McShea MC, Hughes C et al. The effect of gastric bypass on the pharmacokinetics of serotonin reuptake inhibitors. Am J Psychiatry 2012;169 (3):256-63.
5. Smith A, Henriksen B, Cohen A. Pharmacokinetic considerations in Roux-en-Y gastric bypass patients. Am J Health Syst Pharm 2011; 68(23):2241-7.
6. Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. Am J Health Syst Pharm 2006; 63(19):1852-7.
7. Quidley AM, Bland CM, Bookstaver PB, Kuper K. Peripoerative management of bariatric surgery patients. Am J Health Syst Pharm 2014;71(15):1253-64.
8. Beckwith MC, Fedderma SS, Barton RG, Graves C. A guide to drug therapy in patients with enteral feeding tubes: dosage form selection and administration methods. Hosp Pharm 2004;39:225-37.
9. Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin Pharmacokinet 2002;41(10):751-90.
10. Padwaj RS, Gabr RQ, Sharma AM, Langkaas,, LA, Birch DW, Karmali S et al. Effect of gastric bypass surgery on the absorption and bioavailability of metformin. Diabetes Care 2001;34 (6):1295-1300.
11. Langan RC, Zawistoski KJ. Update on vitamin B12 deficiency. Am Fam Physician 2011;83(12):1425-30.
12. Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. Am Fam Physician 2006;74 (3):44-56.
13. Fosamax® [product insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; May 2014.

Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ezogabine (Potiga®)	Neuronal Potassium Channel Opener	Adjunct treatment for refractory partial-onset seizures	Restriction: Restricted to Epilepsy for continuation of therapy Comment: Ezogabine is designated as a Schedule V Controlled Substance
Memantine Extended-Release (Namenda XR™)	N-Methyl-D Aspartate Receptor Antagonist	Treatment of moderate-to severe Alzheimer-type dementia	Comment: Namenda® is being discontinued but will remain on CCHS Formulary until commercially available stock is depleted. Formulary status of Namenda XR™ will be re-evaluated once generic immediate-release memantine is on the market.
Simeprevir (Olysio™)	Antihepaciviral	Treatment of chronic hepatitis C infections in combination with peginterferon alfa and ribavirin	Restriction: For initiation of therapy restricted to Hepatology Comments: Drug is extremely expensive. Will obtain on an as-needed basis or patient will use own supply.
Sofosbuvir (Sovaldi™)	Antihepaciviral	Treatment of chronic hepatitis C infections in combination with antiviral regimen for patients with select genotypes including those with hepatocellular carcinoma awaiting liver transplant and those co-infected with HIV-1	Restriction: For initiation of therapy restricted to Hepatology Comments: Drug is extremely expensive. Will obtain on an as-needed basis or patient will use own supply.
Vedolizumab (Entyvio®)	Integrin Receptor Antagonist	Treatment of moderate-to-severe active ulcerative colitis	Restriction: Restricted to Gastroenterology for outpatient use only in patients who have failed at least one TNF blocker or are positive for JC virus on natalizumab therapy

HIV=Human Immunodeficiency Virus JC=John Cunningham TNF=Tumor Necrosis Factor

Restriction Changes and Other Updates to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
IV Acetaminophen (Ofirmev®)	Analgesic	Pain-reliever	Restriction: **May be prescribed only by Staff Physicians from General Anesthesia, CT Anesthesia, or Pain Management; no other services can prescribe it. PAs, NPs, and other mid-level providers cannot prescribe it.** Comments: **One-time doses prescribed by non-staff will no longer be allowed.** IV acetaminophen should only be used in patients who have a documented opioid tolerance or in patients who cannot take NSAIDs. It will be removed from all automated dispensing machines. The rest of the restrictions are still in place. Please see Lexicomp for the complete list of restrictions.
Tirofiban (Aggrastat®)	GPIIb/IIIa Inhibitor	Antiplatelet Agent	Comment: Tirofiban will replace eptifibatide (Integrilin®) on the CCHS Formulary
Ciprofloxacin and dexamethasone (Ciprodex®)	Antibiotic/ Corticosteroid Otic	Acute Otitis Media	**Removed from Formulary** Comment: Ciprodex® will be replaced with *ophthalmic* ciprofloxacin 0.3% solution and *ophthalmic* dexamethasone sodium phosphate 0.1% solution administered in the ear at the same dose and frequency as Ciprodex®.

CT=Cardiothoracic NSAIDS=Nonsteroidal Anti-inflammatory Drugs NP= Nurse Practitioner PA=Physician Assistant

Adult CCHS Formulary Therapeutic Interchange			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Mesalamine Extended-Release (Apriso®)	5-Amino Salicylic Acid Derivative	Maintenance of remission of ulcerative colitis	The following will be converted to Apriso® 1.5 grams a day: • Asacol® HD 1.6 grams three times a day • Lialda® 2.4 grams once daily • Pentasa® 1 gram four times a day • Delzicol® 800 mg three times a day

Formulary Update

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Alteplase (Activase®)	Thrombolytic Agent	Intra-pleural use for treating loculated pleural effusion/empyema	Comment: Alteplase 4 mg in 40 mL of 0.9% NaCl syringe can be ordered in Epic (pediatric drug file) for intra-pleural administration; this can be instilled via chest tube every 12 hours and allowed to dwell for 1 hour. Treatment duration is no more than 3 days.
Dexmedetomidine (Precedex®)	Selective alpha$_{2}$-adrenergic agonist	Sedation of intubated and mechanically ventilated patients within the intensive care unit	Restriction: Use within the Neonatal and Pediatric Intensive Care Units
Intravenous Immune Globulin 10% (Oral Administration)	Blood Product Derivative	Viral Enteritis	Restriction: Pediatric Bone Marrow Transplant Service and Pediatric Infectious Disease Service; both services must agree therapy is warranted and both must approve its use. Oral therapy is for pediatric hospital inpatients only. Comment: Oral IVIG dose of 20 mg/kg/dose four times a day for a total duration of 7 days. The Epic file is available through Database Look-up only and must be entered via CPOE by a pharmacist.

IVIG=Intravenous Immune Globulin

Formulary Update

Restriction Changes and Other Updates to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Alglucosidase Alfa (Lumizyme®)	Enzyme	Enzyme replacement therapy for adult and pediatric patients of all ages with Pompe disease.	Restriction: Outpatient use only Comment: The REMS requirement for Lumizyme® has been removed by the FDA. Pediatric patients less than 8 years of age on Myozyme® therapy will be transitioned to Lumizyme® therapy. Genzyme, the manufacturer of both products, has stopped producing Myozyme®.
Ciprofloxacin and dexamethasone (Ciprodex®)	Antibiotic/ Corticosteroid Otic	Acute Otitis Media	**Removed from Formulary** Comment: Ciprodex® will be replaced with *ophthalmic* ciprofloxacin 0.3% solution and *ophthalmic* dexamethasone sodium phosphate 0.1% solution administered in the ear at the same dose and frequency as Ciprodex®.
Vitamin A Injection (Aquasol® A)	Vitamin	Prevention and treatment of Vitamin A deficiency	**Removed from Formulary** Comment: The newly FDA-approved product was recently re-released in the US market at a significantly increased cost.
Algucosidase Alfa (Myozyme®)	Enzyme	Treatment of infantile-onset Pompe Disease	**Removed from Formulary** Comment: Manufacturer discontinued this product. Patients will be converted to Lumizyme®.
Desvenlafaxine succinate extended-release (Pristiq®)	Serotonin/ Norepinephrine Reuptake Inhibitor	Antidepressant	**Removed from Formulary** Comment: All orders for Pristiq® will be converted to Khedezla® via therapeutic interchange.

FDA=Food and Drug Administration REMS=Risk Evaluation and Mitigation Strategies

Pediatric CCHS Formulary Therapeutic Interchange			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Desvenlafaxine fumarate (Khedezla®)	Serotonin/ Norepinephrine Reuptake Inhibitor	Antidepressant	All orders for desvenlafaxine succinate (Pristiq®) will be converted to Khedezla®. The dose conversion from Pristiq® to Khedezla® is a one-to-one conversion.