# In This Issue





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## Ravulizumab-cwvz for Paroxysmal Nocturnal Hemoglobinuria

**By: Ramara E. Walker, Pharm.D.**

**Background:** Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, rare bone marrow disorder characterized by hemolytic anemia, thrombosis, and peripheral blood cytopenias.[1] Its pathophysiology is attributed to a deficiency of complement-regulating CD55 and CD59 proteins on red blood cells which increases the risk of chronic, complement-mediated hemolysis. Eculizumab (Soliris®; Alexion Pharmaceuticals), approved by the Food and Drug Administration (FDA) for the treatment of PNH in 2007 has been the gold standard therapy for this disease state.[2] However ravulizumab (Ultomiris®; Alexion Pharmaceuticals), a derivative of eculizumab approved by the FDA for the same indication in December 2018, may be a viable alternative.[3]

**Mechanism of Action:** Ravulizumab inhibits terminal complement-mediated intravascular hemolysis in patients with PNH by binding with high affinity to complement protein C5.[3] This action prevents the cleavage of C5 to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complex) interfering with the production of the terminal complement complex C5b9. Eculizumab has the same mechanism of action, however ravulizumab's half-life is four times longer.[2-4]

**Key Clinical Trial:** A phase 3, multicenter, randomized, active-controlled study determined whether ravulizumab was noninferior to eculizumab in treating complement inhibitor-naïve adults with PNH. Patients (N=246) were randomized 1:1 to receive ravulizumab (n=125) or eculizumab (n=121) for a 26-week treatment period.[4] The patients in the ravulizumab group received a weight-based loading dose on day 1 and a weight-based maintenance dose on day 15 and every 8 weeks

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## Risk for Lower Limb Amputations with Canagliflozin

**By: Chandni Patel, Pharm.D.**

**Background:** The sodium glucose cotransporter type 2 (SGLT-2) inhibitors are a newer class of oral antidiabetic agents that are favored due to their metabolic and cardiovascular (CV) benefits.[1,2] The antiglycemic effect of these agents is attributed to the inhibition of glucose reabsorption in the proximal tubules of the kidney.[3] Canagliflozin (Invokana®; Janssen Pharmaceuticals), a SGLT-2 inhibitor, gained Food and Drug Administration (FDA) approval for the treatment of type 2 diabetes mellitus (T2DM) in March 2013 and for reduction in the risk of major adverse CV events in adults with T2DM and established CV disease in October 2018.[3-5] Canagliflozin is also available in combination with metformin as Invokanet® and Invokanet® XR.[6] Other agents in the SGLT-2 inhibitor class include dapagliflozin (Farxiga®; AstraZenaca Pharmaceuticals) and empagliflozin (Jardiance®; Boehringer Ingelheim Pharmaceuticals).[7,8] Recently, it has been reported that the use of SGLT-2 inhibitors, especially canagliflozin, have

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thereafter. Patients in the eculizumab group received four weekly, standard loading doses on days 1, 8, 15, and 22 followed by a standard maintenance dose on day 29 and every 2 weeks thereafter. The co-primary endpoints of this study were: 1) transfusion avoidance (TA) defined as the proportion of patients who remained transfusion-free or did not require a transfusion per protocol-specified guidelines through day 183 and 2) lactate dehydrogenase (LDH) normalization reflecting the degree of hemolysis from day 29 through 183. Ravulizumab met noninferiority criteria compared to eculizumab for both co-primary endpoints. Regarding TA, 73.6% vs 66.1% of patients in the ravulizumab and eculizumab groups, respectively, avoided transfusion with a between-group difference of 6.8% ($p_{inf}$ <0.0001). Moreover, the prevalence of LDH normalization was 53.6% and 49.4% for the ravulizumab and eculizumab groups, respectively ($p_{inf}$ <0.0001). The safety and tolerability of ravulizumab and eculizumab were comparable. The authors concluded that ravulizumab, administered every 8 weeks, achieved noninferiority for efficacy endpoints and had a similar safety profile to eculizumab administered every 2 weeks.

**Safety and Immunogenicity:** The most frequent adverse effects that occurred in >10% of those who received ravulizumab in clinical trials were upper respiratory tract infection and headache.[3] Treatment-emergent antibodies developed in 0.5% of those receiving ravulizumab. It is important to note that like eculizumab, ravulizumab carries a black box warning regarding increased risk of serious meningococcal infections.

**REMS and Vaccination Requirements:** Healthcare professionals prescribing ravulizumab must be certified and enrolled in the Ultomiris™ Risk Evaluation and Mitigation Strategy (REMS) program which educates healthcare professionals and patients about the increased risk of meningococcal infection; patients are not required to enroll in this program.[5,6] Prior to receiving ravulizumab, patients should be vaccinated with two doses of MenACWY (Menactra®) at least 8 weeks apart followed by one dose every 5 years if ravulizumab is to be continued. Furthermore, patients should also receive two doses of MenB-4C (Bexsero®) at least 1 month apart. If the first vaccine doses have not be administered within 2 weeks prior to initiation of ravulizumab, antibacterial prophylaxis with oral amoxicillin, azithromycin (for penicillin allergy), or ciprofloxacin should be administered for 2 weeks after the vaccines are given.

**Dosing and Administration:** Weight-based loading and maintenance doses of ravulizumab as well as the recommended maximum infusion rates can be found in the package insert.[3] The first maintenance dose is given 2 weeks after the loading dose, while subsequent maintenance doses are given every 8 weeks. The day of administration of a maintenance dose (with the exception of the first maintenance dose) may vary within a 7 day window, but the subsequent dose needs to be timed according to the original schedule. The drug is diluted in 0.9% sodium chloride to a final concentration of 5 mg/mL and must be administered through a 0.22 micron filter. For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab dose.

**Cost and Availability:** Ravulizumab is available as a 300 mg/30 mL (10 mg/mL) single-dose vial NDC 25682-022-01 with an average wholesale price (AWP) of about $7600.[3,7] Similarly, eculizumab is available as a 300 mg/30mL (10 mg/mL) single-dose vial NDC 25682-001-01 with an AWP of about $7800.[2,7] Even though the AWPs of these drugs are comparable, the overall cost of therapy with ravulizumab is less than eculizumab due to its less frequent maintenance dosing schedule (every 8 weeks vs every 2 weeks, respectively).

**Formulary Status:** Ravulizumab is restricted to REMS-certified prescribers from Hematology/ Oncology for outpatient use ONLY for the treatment of PNH.

**References:**


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been associated with an increased risk of lower extremity amputations.[1,2]

**CANVAS and CANVAS-R Studies:** Canagliflozin was approved for reducing CV events in patients with T2DM and established CV disease based on the combined results from the CANVAS (Canagliflozin Cardiovascular Assessment Study) (conducted November 2009 to March 2011) and the CANVAS-R (CANVAS-Renal) (conducted January 2014 to May 2015) studies.[9,10] Although canagliflozin demonstrated cardiovascular benefit in the CANVAS and CANVAS-R trials, the use of this SGLT-2 inhibitor was associated with a two times higher risk of lower extremity amputations compared to placebo (6.3 vs 3.4 patients per 1000 patient-years, respectively; HR 1.97 (95% CI, 1.41-2.75;P<0.001).[9] The highest risk of amputations occurred in patients with a history of amputation or peripheral vascular disease (PVD).

**Black Box Warning and FAERS Report:** In May 2017, the FDA released a statement confirming an increased risk of lower leg and foot amputations with canagliflozin based on the results from the CANVAS and CANVAS-R trials.[11] As a result, the package inserts for canagliflozin and canagliflozin combination products now include a black box warning about lower extremity amputation risk.[3,6] The package inserts for the other SGLT-2 inhibitors do not contain this warning.[7,8] Data from the FDA Adverse Event Reporting System (FAERS) involving SGLT-2 inhibitors and amputations were published in September 2017.[12] Of over 9 million adverse event reports submitted to FAERS, 66 cases were for SGLT-2 inhibitor-associated amputations and 57 of these cases were specifically attributed to canagliflozin use with an average treatment duration of approximately 1.5 years. Most of the affected patients were men about 60 years of age. In this FAERS analysis, the frequency of amputation reports for canagliflozin was significantly higher than for non-SGLT inhibitors with a proportional reporting ratio of 1.59 (95% CI, 1.12-2.30; P=0.009). However the FAERS analysis did not link the use of other SGLT-2 inhibitors with an increased risk of amputation. It is not known why canagliflozin specifically increases amputation risk; further research is needed to determine the mechanism behind this adverse event.[13,14] Additionally, while the majority of the data suggest that canagliflozin is the main causative agent among SGLT-2 inhibitors, there is some research indicating that this may be a class effect.[1]

**Counseling Points:** Based on current evidence and the FDA Drug Safety Communication, canagliflozin and combination canagliflozin products should not be started in patients with a history of prior amputation, PVD, diabetic neuropathy, and diabetic foot ulcers.[3,6] Furthermore, patients who are already taking an agent with canagliflozin should contact their healthcare provider if they develop new onset pain, sores, ulcers, or infections in their lower extremities. At this time, there is no consensus whether lower extremity amputation is a class effect of SGLT-2 inhibitors.[1]

**Formulary Status:** Canagliflozin is not on the CCHS Formulary. Currently, empagliflozin is the preferred SGLT-2 inhibitor on the CCHS Formulary.

**References:**


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2. Filippas-Ntekouan S, Filippatos TD, Elisaf MS. SGLT2 inhibitors: are they safe? Postgraduate Medicine. 2018; 130(1):72-82.
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| Additions to the Adult CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Restrictions/Comments** |
| Cannabidiol Oral Solution (Epidiolex®)* | Cannabinoid | Antiepileptic Agents | Restricted to the Department of Neurology Division of Epilepsy for initiation of therapy<br>No restrictions for continuation of therapy |
| Caplacizumab-yhdp (Cablivi®) | Monoclonal Antibody | aTTP | Restricted to Benign Hematology as second-line treatment for aTTP |
| Doravirine (Pifeltro™) | Antiretroviral | HIV infection | No restrictions |
| Droperidol† | Antiemetic | Antiemetic | Restricted to ICU-designated areas and Radiology areas<br>EKG monitoring should be considered due to risk of QT interval prolongation |
| Eravacycline (Xerava™) | Antibiotic | Bacterial Infection | Restricted to Infectious Diseases Physicians |
| Hydrogen Peroxide 40% Topical Solution | Karyolytic Agent | Raised Seborrheic Keratosis | Restricted to the Department of Dermatology for outpatient use only |
| Romosozumab-aqqg (Evenity®) | Monoclonal Antibody | Osteoporosis | Restricted to outpatient use only |
| SUBA-itraconazole (Tolsura™) | Antifungal Agent | Fungal Infection | Restricted to second-line therapy for transplant patients (i.e., patient needs to be tried on itraconazole first) |
| Tagraxofusp-erzs (Elzonris™) | Antineoplastic Agent | BPDCN | Restricted to Hematology/Oncology<br>Insurance coverage must be verified prior to pharmacy ordering in the medication |
| Urea Oral Powder | Medical Food | Hyponatremia | Restricted to patients who have failed fluid restriction for management of hyponatremia |

aTTP=Acquired Thrombotic Thrombocytopenic Purpura HIV=Human Immunodeficiency Virus ICU=Intensive Care Unit EKG=Electrocardiogram BPDCN=Blastic Plasmacytoid Dendritic Cell Neoplasm

*Cannabidiol oral solution (Epidiolex®) is an FDA-approved medication and does not violate the CCHS Medical Marijuana Policy.

†The addition of droperidol has been delayed due to insufficient commercial availability. A communication regarding the implementation date of this product will be sent out once it is available.

| Changes to Restrictions of Medications on the Adult CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Changes to Restrictions** |
| Dexmedetomidine (Precedex®) | Sedative | Procedural and Surgical Sedation | Removed all restrictions<br>Note: The use of dexmedetomidine as an adjuvant for perineural blockade was approved. |
| Dupilumab (Dupixent®) | Monoclonal Antibody | Eosinophilic Asthma<br>Atopic Dermatitis | Modified restrictions to include use by Staff Physicians from the Departments of Allergy/ Immunology and Pulmonary/ Critical Care Medicine for use in the outpatient setting |
| Levothyroxine Injection | Thyroid Hormone | Hypothyroidism | Restricted to:<br>1) Organ Donation/Life Banc<br>2) Patients with Myxedema Coma<br>3) Patients who are NPO ≥ 7 days and no enteral levothyroxine<br>4) Recommended by Department of Endocrinology |
| Palonosetron (Aloxi®) | 5-HT3 Receptor Antagonist | Antiemetic | Modified restrictions to include inpatient Hematology/Oncology patients for the prevention of CINV |
| Rituximab (Rituxan®) | Monoclonal Antibody | Various Indications (e.g., CLL, NHL, TTP) | Modified restriction to allow for rapid rate administration (over 90 minutes) for all indications within Adult Hematology/ Oncology |
| Sacubitril/Valsartan (Entresto®) | Neprilysin Inhibitor/Angiotensin II Receptor Blocker | Heart Failure | Removed all restrictions |

NPO= Nothing by Mouth  CINV= Chemo-induced Nausea and Vomiting  CLL=Chronic Lymphocytic Leukemia
NHL=Non-Hodgkin's Lymphoma  TTP=Thrombotic Thrombocytopenic Purpura

| Denials to the Adult CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Reason for Denial** |
| Andexanet alfa (Andexxa®) | Antidote | Reversal Agent for Rivaroxaban and Apixaban | After consideration of published literature and CCHS data summarizing the oral anti-Xa reversal with FEIBA®, the CCHS Specialty Panels (Emergency Medicine, Neurosciences, Cardiovascular , Hematology/Oncology, and Critical Care) decided to recommend against the addition of andexanet alfa to the CCHS Adult Formulary at this time until further comparative data are available for review. |
| Brivaracetam (Briviact®) | Anticonvulsant | Partial Onset Seizures | The CCHS Neurosciences Specialty determined that brivaracetam does not offer any significant advantages over levetiracetam and is more expensive.<br>However brivaracetam may be stocked to allow for continuation of home therapy. |
| Omadacycline (Nuzyra®) | Antibiotic | CAP<br>Skin and skin structure infections | Omadacycline has a similar spectrum of action as tigecycline but is more expensive and only available through specialty pharmacies. |

CAP=Community Acquired Pneumonia

| Product Standardizations and Therapeutic Interchange on the Adult CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Action/Rationale** |
| Erlotinib (Tarceva®) | Antineoplastic Agent | NSCLC Pacreatic Cancer | CCHS will standardize to generic formulation/Cost Savings |
| Fulvestrant (Faslodex®) | Antineoplastic Agent | Breast Cancer | CCHS will standardize to generic formulation/Cost Savings |
| Glipizide/ Glimepiride | Sulfonylureas | Diabetes | All orders for sulfonylureas will be converted to either glipizide (for immediate-release agents) or glimepiride (for extended-release glipizide formulations)/ Cost Savings<br><br>A conversion table is available in Lexi-Comp and the Therapeutic Interchange List on the Drug Information SharePoint site |

NSCLC=Non-small Cell Lung Cancer

| Additions to the Pediatric CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Restrictions/Comments** |
| Cannabidiol Oral Solution (Epidiolex®)* | Cannabinoid | Anticonvulsant | Restricted to the Department of Pediatric Epilepsy for initiation of therapy<br>There are no restrictions on continuation of therapy |
| Treprostinil Injection (Remodulin®) | Prostaglandin | PAH | Restricted as follows:<br>1) Subcutaneous/IV treprostinil initiation and titration are restricted to the ICUs Continuation of therapy at a straight rate may occur on M30/M40<br>2) Ordering of SQ/IV treprostinil is restricted to:<br>a) Staff Physicians from Pediatric Pulmonology<br>b) Staff Physicians from Pediatric Cardiology<br>c) Staff Physicians from ICUs with Pulmonology or Cardiology consult |
| Ziprasidone Intramuscular Injection (Geodon®) | Atypical Antipsychotic | Acute Agitation Psychosis | Restricted to Pediatric Psychiatry and Emergency Medicine |

PAH=Pulmonary Arterial Hypertension IV=Intravenous ICU=Intensive Care Unit SQ=Subcutaneous
*Cannabidiol oral solution (Epidiolex®) is an FDA-approved medication and does not violate the CCHS Medical Marijuana Policy.

| Changes to Restrictions of Medications on the Pediatric CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Restrictions/Comments** |
| Epoprostenol Intravenous Infusion (Veletri®) | Prostacyclin | PAH | Modified restrictions as follows:<br>1) IV epoprostenol initiation and titration are restricted to ICUs. Continuation of therapy at a straight rate may occur on M30/40<br>2) Ordering of IV epoprostenol is restricted to:<br>a) Staff Physicians from Pediatric Pulmonology<br>b) Staff Physicians from Pediatric Cardiology<br>c) Staff Physicians from ICUs with Pulmonology or Cardiology consult |
| Hydroxyurea (Droxia®) | Antineoplastic Agent | Sickle Cell Disease | Modified restrictions as follows:<br>For patients with sickle cell disease continuing hydroxyurea home therapy, any provider may order a single dose<br><br>Subsequent doses must be entered by a Staff Physician only |
| Iloprost Inhalation Solution (Ventavis®) | Prostacyclin | PAH | Modified restrictions as follows:<br>1) Inhaled iloprost initiation and titration are restricted to ICUs. Continuation of home dose/straight dose may occur on M30/40.<br>2) Ordering of inhaled iloprost is restricted to:<br>a) Staff Physicians from Pediatric Pulmonology<br>b) Staff Physicians from Pediatric Cardiology<br>c) Staff Physicians from ICUs with Pulmonology or Cardiology consult |
| Meningococcal ACYW-135 (Menveo®) | Vaccine | Prevention of Meningococcal Disease | Modified restrictions as follows:<br>1) Pediatric patients aged 2 months-23 months with anatomical or functional asplenia, including patients with sickle cell anemia, complement component deficiency, or at risk from meningococcal disease outbreaks<br>2) Pediatric patients <9 months traveling to areas where meningococcal disease is endemic<br>3) Patients requiring co-administration of meningococcal ACYW-135 and pneumococcal conjugate vaccine (Prevnar 13®) within 4 weeks<br>4) Patients receiving eculizumab (Soliris®) |

PAH=Pulmonary Arterial Hypertension IV=Intravenous ICU=Intensive Care Unit

| Medication Removals from the Pediatric CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Comments** |
| Cisatracurium (Nimbex®) | Neuromuscular Blocking Agent | Neuromuscular Blockade | Removed as a cost-savings measure (Previously removed from the CCHS Adult Formulary in January 2019) |
| Lorazepam Continuous Infusion | Benzodiazepine | Anticonvulsant Sedation | ASHP recommends not to use lorazepam continuous infusions in pediatric patients due to its long half-life and potential for propylene glycol toxicity.<br><br>Other formulations of lorazepam will remain on the Pediatric Formulary. |

ASHP=American Society of Health-System Pharmacists

| Restrictions Removed from Medications on the Pediatric CCHS Formulary | | | |
|---|---|---|---|
| **Drug** | **Pharmacologic Class** | **Formulary Use** | **Comments** |
| Meningococcal B Vaccine (Bexsero®) | Vaccine | Prevention of Meningococcal Disease | All restrictions have been removed/ Previously restricted to only ACIP criteria for use but no other vaccines on CCHS Formulary were restricted to solely ACIP criteria |
| Zoledronic Acid (Zometa®) | Bisphosphonate | Bone metastases from solid tumors<br><br>Multiple myeloma osteolytic lesions | All restrictions have been removed/Generic zoledronic acid is available |

ACIP=Advisory Committee for Immunization Practices