In This Issue

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Cleveland Clinic Clinical Rx Forum

From the Department of Pharmacy

March/April Issue **2022 Volume 10, Issue 2**

Amisulpride for Postoperative Nausea and Vomiting

By: Marina Capitanov, Pharm.D.

Background: Postoperative nausea and vomiting (PONV) occurs in 30-80% of patients and is reported to be the postsurgical outcome least desired by patients.[1,2] It often impedes discharge and is one of the leading causes of unexpected admission after ambulatory surgery.[3,4] There are several detriments to PONV including wound opening, dehydration, electrolyte imbalance, and aspiration.[5] The Apfel risk score is a validated tool that quantifies the risk for PONV, and includes the risk factors female sex, non-smoker, PONV history, and postoperative opioids.[6] An Apfel score of 0 or 1 indicates low risk, a score of 2 indicates medium risk, and a score of 3 or 4 indicates high risk.[1] According to the 2020 PONV treatment guidelines, patients classified as low to medium and high risk are recommended to prophylactically receive one to two or three to four antiemetics, respectively. Current prophylaxis commonly comprises 5-hydroxytryptamine (5-HT3) antagonists, such as ondansetron, with or without dexamethasone. An antiemetic from a different class than the prophylactic agent is recommended as rescue treatment for refractory PONV.[1] Droperidol is a dopamine antagonist that may be utilized, but it is less desirable due to its black box warning of QT prolongation.[1,7] Amisulpride (Barhemsys®; Acacia Pharma Inc.) is a comparable agent that was approved by the Food and Drug Administration (FDA) in February 2020 for the prevention of PONV, as monotherapy or in combination with an antiemetic of a different class, and for treatment in adults who did not receive prophylaxis with a dopamine antagonist.[8]

Mechanism of Action: Amisulpride is a selective dopamine-2 and dopamine-3 (D-3) receptor antagonist.[8] Dopamine-2 and D-3 receptors are located in the chemoreceptor trigger zone (CTZ) and

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Anifrolumab for Systemic Lupus Erythematosus

By: Alexsandra Nilges, Pharm.D. , MBA

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease estimated to affect nearly 205,000 Americans.[1] It disproportionately impacts Black and Hispanic populations, and its prevalence is nine times higher in women than men. The autoimmune dysfunction in SLE results from dysregulation of both the innate and adaptive immune systems and can be inherited and/or triggered by both hormonal and environmental factors.[2] There are a variety of scales used to assess the severity and treatment effects of SLE, including the SLE Disease Activity Index-2000 (SLEDAI-2K) which drives the composite SLE Responder Index-4 (SRI-4), and the British Isles Lupus Assessment Group (BILAG) which drives the BILAG-based composite lupus assessment (BICLA).[3-6] While the SRI-4 response requires complete resolution of an SLE-affected organ system, a BICLA response encompasses both partial and complete improvement.[6] First-line treatment for SLE includes hydroxychloroquine and glucocorticoids

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respond to dopamine released from nerve endings. Amisulpride's antagonism of the dopamine receptors is thought to prevent CTZ stimulation of the vomiting center.

Clinical Trials: The FDA approval of amisulpride was based on two clinical trials.[9,10] Gan and colleagues evaluated the efficacy of amisulpride for PONV prophylaxis in two multicenter, double-blind, randomized control trials (RCTs).[9] In the U.S. study, patients received monotherapy with amisulpride,. However patients received amisulpride combined with one additional intravenous (IV), non-dopaminergic antiemetic (ondansetron, dexamethasone, or betamethasone) in the European study. Patients were included if they were ≥ 18 years old, scheduled for elective surgery with general anesthesia, expected to last at least 1 hour from anesthesia induction to wound closure, required overnight hospitalization, and had at least two Apfel risk factors. In total, 689 patients were included, with 342 in the U.S. study and 347 in the European study. Patients were randomized to receive amisulpride 5 mg IV or placebo in a 1:1 fashion. The primary endpoint was complete response (CR), defined as no vomiting/retching and no use of antiemetic rescue medication in the 24-hour postoperative period. In the U.S. study, 46.9% of patients achieved CR in the amisulpride group compared to 33.8% in the placebo group (P=0.026). In the European study, CR rates were 57.4% for amisulpride and 46.6% for placebo (P=0.07). The most frequent adverse events (AEs) of flatulence, nausea, and infusion-site pain had similar incidences in the two arms. There were no significant differences in electrocardiographic parameters between groups. The authors concluded that amisulpride was safe and superior to placebo in reducing PONV when given prophylactically. Candiotti and colleagues conducted a double-blind RCT that evaluated amisulpride for the treatment of PONV in patients who did not receive antiemetic prophylaxis.[10] The inclusion and exclusion criteria were similar to that of the studies conducted by Gan and colleagues. Patients (N=568) were randomized in a 1:1:1 fashion to receive amisulpride 5 mg (n=191) or 10 mg (n=188) or a matching placebo (n=181). The primary endpoint of CR, defined as no emesis 30 minutes to 24 hours after study drug administration and no rescue medication, occurred in 60 (31.4%) amisulpride patients compared to 39 (21.5%) in the placebo group (P=0.015). The only AEs in ≥5% of any treatment group were flatulence, nausea, constipation, and infusion-site pain. This study demonstrated a benefit for both 5 mg amisulpride (P=0.014) and 10 mg amisulpride (P=0.014) over placebo, concluding that both doses were safe and superior in the treatment of PONV in patients undergoing general anesthesia with no prior PONV prophylaxis.

Safety: Amisulpride is associated with infusion-site pain (6%), increased serum prolactin (5%), hypokalemia (4%), chills (4%), procedural hypotension (3%), and abdominal distention (2%).[8] According to the package insert, amisulpride may cause dose- or concentration-dependent QTc prolongation and should be avoided in patients with congenital long QT syndrome.

Dosing and Administration: Amisulpride is given as a single 5 mg IV dose at anesthesia induction to prevent PONV or as a single 10 mg IV dose after surgery to treat PONV in patients who did not receive prophylaxis or received an agent of a different class.[8] It should be infused over 1-2 minutes, and the line should be flushed before and after administration with dextrose 5% in water or normal saline. It is recommended to avoid use in patients with an eGFR <30 mL/minute/1.73 m^2.

Cost and Availability: Amisulpride is currently available as an IV solution in two strengths: 5 mg/2 mL (NDC 71390-125-21) and 10 mg/4 mL (NDC 71390-125-51).[8] The average wholesale price per mL is $25.50. The cost of a course of therapy per patient is $51 for prevention (5 mg) and $102 for treatment (10 mg).[11]

Formulary Status: Amisulpride is not currently on the Cleveland Clinic Health-System formulary.

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with or without additional immunosuppressants.[4] Belimumab (Benlysta®; GlaxoSmithKline) was the first monoclonal antibody approved by the Food and Drug Administration (FDA) in 2011 to treat SLE.[7] Anifrolumab-fnia (Saphnelo™; AstraZeneca) , another monoclonal antibody product, was granted FDA approval in July 2021 for adults with moderate-to-severe SLE receiving standard therapy.[8]

Mechanism of Action: Anifrolumab is a recombinant, human monoclonal antibody that inhibits the type I interferon (IFN) receptor (IFNAR).[8] Type I IFN is a central mediator in SLE, with approximately 60-80% of SLE patients overexpressing type I IFN genes, also known as a high type I gene signature, which is associated with increased immune activity.[9]

Clinical Trials: The safety and efficacy of anifrolumab were evaluated in two phase 3 trials, TULIP-1 and TULIP-2.[5,6] The first trial, TULIP-1, was a double-blind, randomized, controlled, phase 3 trial conducted in patients with moderate-to-severe SLE on stable treatment.[5] This trial compared anifrolumab 150 mg versus 300 mg versus placebo (PBO) administered intravenously (IV) every 4 weeks for 48 weeks in patients ages 18-70 years old with SLE (N=457). Groups were stratified based on baseline SLEDAI-2K, steroid dose, and type I IFN gene signature (high or low), and then randomized 2:1:2 to PBO (n=184) or anifrolumab 150 mg (n=93), or 300 mg (n=180), respectively. The primary efficacy endpoint of the proportion of patients who achieved an SRI-4 response at 52 weeks was not met with 36% for the anifrolumab 300 mg group compared to 40% for the PBO group (P=0.41). However, the authors concluded that anifrolumab was associated with improvements in the BICLA response and certain organ systems (e.g., skin and joints) as well as a reduction in corticosteroid dose. The next trial, TULIP-2 (N=362), was a double-blind, randomized, placebo-controlled, parallel-group, phase 3 trial comparing anifrolumab 300 mg IV every 4 weeks to PBO for 48 weeks with the same inclusion criteria as TULIP-1.[6] Unlike TULIP-1 which utilized the more stringent SRI-4 assessment to evaluate response, the primary efficacy endpoint in TULIP-2 used the BICLA scale to determine the comparative response rate between the treatment and PBO groups at week 52. At week 52, 47.8% of patients receiving anifrolumab demonstrated a BICLA response compared to 31.5% of those who received PBO (P=0.001). The authors concluded that in contrast to the findings in TULIP-1, TULIP-2 which used a different primary endpoint demonstrated that anifrolumab was significantly more effective than PBO.

Safety: The most common adverse events of anifrolumab (incidence ≥2%) were upper respiratory tract infections, bronchitis, infusion-related reactions, herpes zoster, and cough.[8] In a pooled analysis of all clinical trials, herpes zoster was more commonly reported in the treatment group versus the placebo group (6.1% versus 1.3%, respectively).

Dosing and Administration: The recommended dose of anifrolumab is 300 mg IV over 30 minutes every 4 weeks.[8] There should be a minimum of 14 days between infusions. Anifrolumab is administered via a 0.2-micron in-line filter. After completion of the infusion, the line should be flushed with 25 mL of 0.9% sodium chloride. There are no pre-medications required before the infusion. However, in patients with a history of hypersensitivity or infusion-related reactions, it is recommended to consider pre-medication.

Cost and Availability: Anifrolumab is available as a 300 mg/2 mL vial (NDC: 00310-3040-00) and has an average cost of $5,521 per vial.[10] The estimated annual cost of drug therapy is about $66,248.

Formulary Status: Anifrolumab-fnia is restricted to the Department of Rheumatology for outpatient use only in patients with active, moderate-to-severe systemic lupus erythematosus not controlled on current therapy.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Avacopan (Tavneos®) Capsules	Complement C5a Receptor Inhibitor	ANCA-associated Vasculitis	Restricted to Nephrology and Rheumatology for initiation of ANCA-associated vasculitis Continuation of therapy is not restricted
Bebtelovimab Injection	Monoclonal Antibody	COVID-19 Treatment	Restricted for outpatient and inpatient adults following the same restriction criteria as COVID-19 treatment as all other COVID-19 monoclonal antibodies Inpatient bebtelovimab will be restricted to Infectious Diseases*†
Bimatoprost (Durysta®) Implant	Prostaglandin	Glaucoma	Restricted to Ophthalmology for outpatient use only
Brivaracetam (Briviact®) Injection	Antiepileptic Agent	Epilepsy	Restrictions as follows: 1) Initiation of therapy is restricted to Epilepsy or Neurology (if the hospital does not have an Epilepsy Consult Service) and patients must have an intolerance (severe behavioral reaction) to levetiracetam 2) If patients are on oral brivaracetam prior to admission and need IV therapy, they are permitted to receive IV brivaracetam 3) Continuation of therapy is not restricted
Efgartigimod Alfa (Vyvgart®) Injection	Neonatal Fc Receptor Antagonist	Refractory Generalized MG	Restricted to Neurology (Neuromuscular) for outpatient use only in patients with refractory, generalized MG positive for anti-acetylcholine receptor antibodies
Hyaluronic Acid/ Silk Particles (Silk Voice®)	Viscoelastic Agent	VCP	Restricted to Otolaryngology for use in VCP for outpatient use only
Inclisiran (Leqvio®) Injection	Antilipemic sRNA agent	HFH	Restricted to outpatient use only

*It is recommended to continue to allow the COVID-19 Monoclonal Antibody Taskforce to determine the preferred COVID-19 monoclonal antibody for Cleveland Clinic locations based on supply and currently circulating SARS-CoV-2 variants.

†It is recommended to update the restriction criteria for utilization of COVID monoclonal antibodies for treatment of COVID-19 infection at Cleveland Clinic to be within 7 days of symptom onset to align with sotrovimab and bebtelovimab EUA requirements.

ANCA=Antineutrophil cytoplasmic antibody COVID-19=Coronavirus Disease 2019 IV=Intravenous MG=Myasthenia gravis VCP=Vocal cord paralysis Srna=Small interfering ribonucleic acid HFH=Heterozygous familial hypercholesterolemia

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Margetuximab (Margenza®) Injection	Monoclonal Antibody	HER–2 positive Metastatic Breast Cancer	Restricted to Hematology/ Oncology for outpatient use only
Maribavir (Livtencity®) Tablets	Antiviral Agent	Refractory/Resistant CMV (Post-transplant)	Restricted to Infectious Diseases for the treatment of refractory or resistant CMV infection/disease in post-transplant patients
Meningococcal (Groups A,C,Y,W) Conjugate Vaccine (MenQuadFi™)	Vaccine	Protection Against Meningitis	
Pneumococcal conjugate-20 (Prevnar-20®)	Vaccine	Protection Against Pneumonia	For adult patients ≥19 years of age
Ranibizumab (Susvimo®) Implant	Monoclonal Antibody	AMD Neuovascular (Wet)	Restricted to Ophthalmology for outpatient use only
Tebentafusp (Kimmtrak®) Injection	Antineoplastic Agent	Uveal Melanoma Unresectable/Metastatic	Restricted to Hematology/ Oncology

HER2=Human epidermal growth factor receptor-2 CMV=Cytomegalovirus AMD=Age-related macular degeneration

Denials to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial/Removal**
Bupivacaine/ meloxicam extended-release solution (Zynrelef™)	Analgesic	Post-surgical Analgesia	Data did not strongly support the clinical benefit of this medication over other formulary agents. R.E.C.K. or immediate-release bupivacaine is preferred.
Darbepoetin (Aranesp®) Epoetin Alfa (Epogen®, Procrit®)	ESA	Anemia	The request to modify the current ESA formulary restriction criteria to include use in acute, post-transplant setting for kidney and/or liver patients who otherwise do not meet restriction criteria was denied due to lack of evidence supporting therapeutic benefit (e.g., reduced transfusion rates, significant increase in hemoglobin levels) and concern for ESA-related adverse events (e.g., thrombosis)

R.E.C.K= Ropivacaine, epinephrine, clonidine, ketorolac ESA=Erythropoiesis stimulating agent

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Omacetaxine (Synribo®)	Antineoplastic Agent	CML	Due to its administration schedule requiring14 consecutive dosing days that currently cannot be accommodated, as well as the availability of TKIs for CML, omacetaxine was removed from the CCHS Formulary

TKI=Tyrosine kinase inhibitor CML=Chronic myelogenous leukemia

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Albumin 5%	Blood Product Derivative	Plasma Volume Expander	Modified restrictions to include use by Critical Care Transport
Bortezomib (Velcade®)	Proteasome Inhibitor	Antibody-Mediated Rejection	Modified restrictions to include use for the treatment of antibody-mediated rejection in lung transplant recipients
Indomethacin Suppositories	NSAID	Prevention of PEP	Added restriction as follows: Restricted for prevention of PEP
Nelarabine (Arranon®) Injection	Antineoplastic Agent	T-cell Acute Lymphoblastic Leukemia/Lymphoma	Modified restrictions to state: Restricted to Hematology/ Oncology *for outpatient use only*
Voriconazole	Antifungal Agent	Antifungal Prophylaxis and Treatment	Modified restrictions as follows: 1) Department of Infectious Diseases 2) Department of Hematology/Oncology *3) Lung Transplant for antifungal prophylaxis up to 3 months post-lung transplant*

NSAID=Nonsteroidal anti-inflammatory agent PEP=Post-endoscopic retrograde cholangiopancreatography pancreatitis

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Standardization**
Insulin Lispro (Admelog®)	Insulin	Diabetes	A therapeutic interchange for insulin lispro products from Humalog® (Eli Lilly) to Admelog® (Sanofi) was approved and supported by Endocrinology.
Pramipexole	Dopamine Agonist	Parkinson's Disease Restless Leg Syndrome	A therapeutic interchange from pramipexole ER daily to pramipexole IR divided into three times daily dosing was approved.*
Ropinirole	Dopamine Agonist	Parkinson's Disease Restless Leg Syndrome	A therapeutic interchange from ropinirole extended-release daily to ropinirole immediate-release divided in three times daily dosing was approved.*

*Details in Lexicomp.

Process Changes of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Process Change**
Levetiracetam (Keppra®) Injection	Antiepileptic	Seizures	The administration of undiluted levetiracetam doses ≤ 1500 mg via IV Push will be allowed.
Levetiracetam (Keppra®) Injection	Antiepileptic	Seizures	Pharmacists will be allowed to automatically round levetiracetam loading doses up to the next 250 mg (e.g., dose of 1100 mg will be rounded to 1250 mg). These loading doses are typically weight-based. Maintenance doses will not be rounded.
Recombinant Zoster Vaccine (Shingrix®)	Vaccine	Preventions of Herpes Zoster (Shingles)	Recombinant zoster vaccine will be used in adult patients 19-49 years of age who are or will be immunodeficient because of disease or therapy
Treprostinil	Prostaglandin	Pulmonary Arterial Hypertension	Generic treprostinil (PAR Pharmaceuticals) may be used for subcutaneous pumps

IV=Intravenous

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bebtelovimab	Monoclonal Antibody	COVID-19 Treatment	Restricted for outpatient and inpatient pediatrics ≥ 12 years of age and ≥ 40 kg following the same restriction criteria as COVID-19 treatment as all other COVID-19 monoclonal antibodies. Inpatient bebtelovimab will be restricted to Infectious Diseases*†
Fenoldopam (Corlopam®) Injection	Antihypertensive	Severe Hypertension	Restricted to Staff Physicians from the ICU or Cardiology and in patients meeting the following criteria: Criteria for use (must meet all all three) 1) Post-operative congenital heart surgery AND 2) Already receiving conventional diuretics including furosemide and chlorthiazide AND 3) Urine output <1 mL/kg/hr
Meningococcal (Groups A,C,Y,W) Conjugate Vaccine (MenQuadFi™)	Vaccine	Protection Against Meningitis	For patients ≥ 2years of age
Methylphenidate Hydrochloride (Metadate® CD) Capsules	CNS Stimulant	ADHD Narcolepsy	

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†It is recommended to update the restriction criteria for utilization of COVID monoclonal antibodies for treatment of COVID-19 infection at Cleveland Clinic to be within 7 days of symptom onset to align with sotrovimab and bebtelovimab EUA requirements.

COVID-19=Coronavirus Disease 2019 ICU=Intensive care unit CNS=Central nervous system
ADHD=Attention deficit hyperactivity disorder

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Naxitamab-gpgk (Danyelza®) Injection	Monoclonal Antibody	Relapsed or Refractory Neuroblastoma	Restricted to the Department of Pediatric Hematology/ Oncology and Bone Marrow Transplant
Tolvaptan (Samsca®) Tablets	Vasopressin Antagonist	Hyponatremia	Restricted to Staff Physicians from the ICU or Cardiology and in patients meeting the following criteria: 1) Criteria for use: Cardiac patients with hypervolemia and hyponatremia (serum sodium <130 mMol/L , independent of sodium supplementation) on maximized conventional diuretic therapy (2 mg/kg/dose of PO furosemide equivalent, max of 80 mg furosemide equivalent + thiazide) 2) Criteria for discontinuation: Serum sodium > 135 mMol/L and euvolemic

ICU=Intensive care unit

Change in Restriction to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Menveo®)	Vaccine	Protection Against Meningitis	Modified restriction to use in patients < 2years of age

Removal from Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Methylphenidate Hydrochloride (Metadate® ER) Tablets	CNS Stimulant	ADHD Narcolepsy	Product was discontinued. Metadate® CD was added to the formulary.

CNS=Central nervous system ADHD=Attention deficit disorder

Product Standardization and Process Change to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comment**
Insulin Lispro (Admelog®)	Insulin	Diabetes	A therapeutic interchange for insulin lispro products from Humalog® (Eli Lilly) to Admelog® (Sanofi) was approved and supported by Endocrinology.
Polyethylene Glycol 3350 (MiraLAX®) Oral Powder	Laxative	Constipation Bowel Preparation	Pharmacy may automatically round oral doses of polyethylene glycol 3350 as follows: For constipation: • 0 g to 6.375 g rounds to: 4.25 g (1/4 packet) • 6.376 g to 10.625 g rounds to: 8.5 g (1/2 packet) • 10.626 g to 14.875 g rounds to: 12.75 g (3/4 packet) • 14.876 g and up rounds to: 17 g (full packet) For bowel preparation: • Doses > one 17 g packet will round to the next full packet (e.g., dose=24.5 g rounds up to 34 g or 2 full packets)