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Cleveland Clinic Clinical Rx Forum

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Benralizumab for Severe Eosinophilic Asthma

By: James Blackmer, Pharm.D., MPA

Background: Eosinophilic asthma is characterized by increased numbers of circulating and airway eosinophils, accompanied by more frequent asthma exacerbations and declines in lung function.[1] This form of severe asthma typically affects less than 5% of the total cases of adult-onset asthma.[2] Mepolizumab (Nucala®; GlaxoSmithKline) and reslizumab (Cinqair®; Teva) are monoclonal antibodies approved by the Food and Drug Administration (FDA) as add-on therapies for the treatment of eosinophilic asthma.[3,4] Benralizumab (Fasenra™; AstraZeneca), a monoclonal antibody preparation with a unique mechanism of action, was FDA-approved in November 2017 as add-on maintenance therapy for patients aged ≥ 12 years with severe asthma with an eosinphilic phenotype.[5]

Mechanism of Action: Benralizumab, a humanized afucosylated monoclonal antibody, directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα).[1,5] The IL-5Rα receptor is expressed on the surface of eosinophils. By binding to this receptor, benralizumab reduces the number of eosinophils by causing apotosis through a process called antibody-dependent cell-mediated cytotoxicity (ADCC). Benralizumab differs from the other medications in its class by its specificity to the IL-5 receptor. However, its exact mechanism of action in the treatment of eosinophilic asthma has not been clearly established.[5]

Key Clinical Trial: Benralizumab's FDA approval was based on a randomized, double-blind, placebo-controlled trial. Patients (N=220) underwent randomization in a 1:1:1 ratio to receive either benralizumab 30 mg subcutaneously every 4 weeks (n=72), benralizumab 30 mg subcutaneously every

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Buprenorphine Extended-Release Depot for Opioid Use Disorder

By: Hanjie Mo, Pharm.D.

Background: Opioid use disorder (OUD), characterized by an addiction to opioids, is a chronic, relapsing disease which adversely affects neurological function.[1] The 2013 National Survey on Drug Use and Health (NSDUH) indicated that 4.5 million Americans abused prescription opioid medications with 1.9 million diagnosed with OUD. Buprenorphine and buprenorphine/naloxone sublingual and buccal dosage forms are often used to treat OUD; potential disadvantages of these agents are the requirement for daily dosing and the possibility of misuse. Buprenorphine extended-release depot injection (Sublocade™; Indivior Inc.), a Schedule III Controlled Substance, was approved by the Food and Drug Administration (FDA) in November 2017 for the treatment of moderate-to-severe OUD in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by dose adjustment for a minimum of 7 days.[2,3] It must be used as part of a complete treatment program that includes coun-

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4 weeks for the first three doses and then every 8 weeks (n=73), or placebo administered every 4 weeks (n=75) for 28 weeks.[1] The primary endpoint was the percentage reduction in the oral glucocorticoid dose from baseline to the final dose at the end of the maintenance phase while asthma control was maintained. Select secondary endpoints included the annual asthma exacerbation rate and the forced expiratory volume in 1 second (FEV_1) before bronchodilation. The median reduction from baseline in the final oral glucocorticoid dose was 75% in patients who received either of the benralizumab regimens compared to a 25% reduction in the placebo group (P<0.001). In 33% of patients who received benralizumab every 4 weeks and 37% of patients who received benralizumab every 8 weeks, there was a reduction of 90% or more from baseline in their final oral glucocorticoid dose, compared to 12% in the placebo group. The annual asthma exacerbation rate for the benralizumab every 4 week group and every 8 week group was 55% lower (P=0.003) and 70% lower (P<0.001) respectively, compared to the placebo group. The FEV_1 before bronchodilation at week 20 was significantly higher in both treatment groups than in the placebo group. However, by week 28, patients who received benralizumab in either group did not demonstrate a significant improvement in the FEV_1. From these results, the authors concluded that for patients with severe eosinophilic asthma, benralizumab demonstrated a significant reduction in glucocorticoid use and asthma exacerbation rates, but without a sustained improvement in FEV_1.

Safety: Hypersensitivity reactions (e.g., anaphylaxis, angioedema, uticaria, rash) may occur within hours of administration of benralizumab, but in some cases, the reaction may take days to develop.[5] While benralizumab has glucocorticoid-sparing effects, it is important to gradually taper steroids, if appropriate. Due to eosinophilic involvement in the immune response to parasitic (i.e., helminth) infections, patients should discontinue benralizumab if they become infected and do not respond to anti-helminth therapy. The most common adverse reactions were headache (8%), pharyngitis (5%), pyrexia (3%), and hypersensitivity reactions (3%).

Dosing and Administration: The recommended dose of benralizumab is 30 mg administered subcutaneously into the upper arm, thigh, or abdomen once every 4 weeks for the first three doses and then once every 8 weeks thereafter.[5] The dose must be given by a healthcare professional. It is recommended that the patient be monitored for adverse events after administration. Prior to administration, benralizumab may be warmed to room temperature in its original carton for about 30 minutes; afterwards, it must be given within 24 hours.

Availability and Cost: Benralizumab is available as a 30 mg/mL single-dose prefilled syringe.[5] The product has an average wholesale price (AWP) of approximately $5,702 per syringe.[6] Therefore, the cost of 12 months of therapy would be about $40,000.

Formulary Status: The formulary status of benralizumab for the treatment of severe asthma is currently under review by the Cleveland Clinic Health-System (CCHS) Pharmacy and Therapeutics Committee.

References:

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seling and psychosocial support. This new long-acting formulation, which allows for once-monthly administration by a healthcare professional, may help improve adherence and mitigate misuse.[4]

Mechanism of Action: Buprenorphine provides analgesia by binding with high affinity mu-opioid receptors in the central nervous system.[3,5] It exhibits partial mu-opioid agonist and weak kappa-opioid antagonist effects. Buprenorphine's high affinity to mu-opioid receptors enables it to block other mu-opioid agonists which reduces opioid withdrawal.[6]

Key Clinical Trial: Buprenorphine extended-release depot injection received FDA approval based on a randomized, double-blind, placebo-controlled, 24-week trial that included 504 treatment-seeking adults with moderate-to-severe OUD.[3,7] Prior to the first dose of buprenorphine extended-release depot injection, patients were initiated on sublingual film buprenorphine/naloxone to control cravings and withdrawal symptoms. Afterwards they were randomized to the following dosing regimens: 1) six once-monthly 300 mg doses of buprenorphine extended-release depot injection (n=201), 2) two once-monthly 300 mg doses followed by four once-monthly 100 mg doses of buprenorphine extended-release depot injection (n=203), 3) six once-monthly subcutaneous injections of placebo matching the volume of active treatment groups 1 or 2 (n=100). All doses were given by a qualified healthcare professional and separated by 28 ± 2 days. Patients in both treatment groups showed statistically significant differences in the primary outcome of opioid abstinence rate defined as the proportions of negative urine samples for opioids and self-reports negative for illicit opioid use; opioid abstinence rates were significantly higher in the treatment groups compared to placebo ($p<0.0001$ for both).

Dosing and Administration: Buprenorphine extended-release depot injection should only be administered subcutaneously in the abdomen by a healthcare provider.[3] It cannot be administered intramuscularly or intravenously. Administration sites should be rotated. After treatment and dose adjustment with transmucosal buprenorphine for a minimum of 7 days, buprenorphine extended-release depot injection 300 mg is administered monthly for 2 months. Afterwards, maintenance doses of 100 mg are administered monthly. Patients who do not have a satisfactory response to the 100-mg maintenance dose, as evidenced by self-reported illicit drug use or a positive opioid urine screen, may have their maintenance dose increased to 300 mg monthly. There should also be a minimum of 26 days between doses. Occasional delays in administration for up to 2 weeks is not expected to affect treatment efficacy. No dosage adjustments are recommended with renal or mild hepatic impairment. However, it is not recommended in moderate-to-severe hepatic impairment.

Risk Evaluation and Mitigation Strategy (REMS): Since serious harm or death may occur from inadvertent intravenous administration, buprenorphine extended-release depot injection is part of a detailed REMS program and is only available through REMS certified pharmacies.[3,5] Key elements of this program are summarized in the Buprenorphine Extended-Release Injection (Sublocade™) document in the REMS section of the CCHS Pharmacy SharePoint site.

Availability and Cost: Buprenorphine extended-release depot injections are available as a single-dose, prefilled syringe with safety needle in the following doses: 100 mg/0.5 mL and 300 mg/1.5 mL.[3] The average wholesale price (AWP) is $1896 per 100 mg syringe and $1264 per 300 mg syringe. with an estimated yearly cost of about $22,000.[5]

Formulary Status: Buprenorphine extended-release depot injection was added to the CCHS Formulary restricted to physicians certified in Addiction Medicine for the use in adult outpatients for the management of moderate-to-severe OUD. All Sublocade™ REMS requirements must be met prior to dispensing.

References:

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bictegravir, emtricitabine, and tenofovir alafenamide (Biktarvy®)	Antiretroviral	HIV-1 infection	No restrictions
Buprenorphine extended-release subcutaneous injection (Sublocade™)	Opioid Partial Agonist	Opioid Use Disorder	Restricted to physicians certified in Addiction Medicine for the use in adult outpatients for the management of moderate to severe opioid use disorder All Sublocade™ REMS requirements must be met prior to dispensing
Epidural clonidine (Duraclon® Epidural) for OB Anesthesia	$Alpha_2$-Adrenergic Agonist	Pain Management in Opioid-Addicted OB and Postpartum Patients	Restricted to OB Anesthesia for opioid-addicted (i.e., on buprenorphine or methadone maintenance therapy) OB patients
Ketamine mouthwash	General Anesthetic	Severe Mucositis	Restricted to Palliative Medicine and Hematology/ Oncology for the treatment of severe mucositis
Letermovir (Prevymis®)	Antiviral Agent	CMV Infection	Restricted to: 1) Infectious Diseases physicians for the treatment of CMV infection 2) Infectious Disease and BMT for the prophylaxis of CMV infection in hematopoietic stem cell transplant patients

HIV=Human Immunodeficiency Virus REMS=Risk Evaluation Mitigation Strategy OB=Obstetrics CMV=Cytomegalovirus BMT=Bone Marrow Transplant

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Celecoxib	NSAID	Pain Reliever	Removed the current CCHS Formulary restrictions and added creatinine clearance to the order verification screen for pharmacists in order to facilitate review of renal function prior to verification of NSAID orders
Dexmedetomidine (Precedex®)	Sedative	Procedural and Surgical Sedation	Removed the restriction stating that only Staff Physicians may order. All other restriction criteria still apply
Herpes zoster subunit vaccine (Shingrix®)	Vaccine	Prevention of Shingles	Removed the CCHS Formulary restrictions for herpes zoster subunit vaccine Herpes zoster subunit vaccine is non-formulary for pediatric patients
Hepatitis B adjuvant vaccine (Heplisav B™)	Vaccine	Prevention of Hepatitis B	Removed CCHS Formulary restrictions for hepatitis B adjuvant vaccine Hepatitis B adjuvant vaccine is non-formulary for pediatric patients
Hypertonic 23.4% Saline	Hypertonic Agent	Traumatic Brain Injury	Modified restrictions to allow hypertonic 23.4% saline in traumatic brain injury
Naltrexone extended-release injection (Vivitrol®)	Opioid Antagonist	Alcohol and Opioid Addiction	Restricted to physicians certified in Addiction Medicine for the management of alcohol and opioid dependence
Rituxmab subcutaneous injection (Rituxan Hycela™)	Monoclonal Antibody	FL DLBCL CLL	Modified restrictions to the Department of Hematology and Medical Oncology for: 1) FDA-labeled indications: • FL • DLBCL • CLL 2) Off-label use for B-cell lymphomas (adults only) 3) Off-label use for CLL in non-Medicare patients only (adults only and must submit prior authorization before initiating treatment) The restriction for outpatient use only was removed

NSAID= Non-steroidal Anti-inflammatory Drug FL= Follicular Lymphoma DLBCL=Diffuse Large B-cell Lymphoma
CLL=Chronic Lymphocytic Leukemia

Removal and Denials for the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/ Comments**
Clevidipine (Cleviprex®)	Calcium Channel Blocker	Alternative to Nitroprusside	Reason for removal: The cost of nitroprusside has significantly decreased
Oral benzocaine (e.g., Anbesol®)	Local Anesthetic	Dental Pain	Reason for removal: The FDA released a Drug Safety Communication regarding the use of OTC topical benzocaine products. This Drug Safety Communication was used as a basis for formulary removal of benzocaine gels and liquid in pediatrics. After additional review, low utilization of these products in adults was identified. Due to low utilization and potential for use in pediatric patients, these products were removed from the adult formulary and will not be stocked in inpatient areas. This removal of benzocaine 10% and 20% topical gels and liquids for dental pain does not affect formulary status of other benzocaine-containing products such as benzocaine-menthol lozenges (e.g., Cepacol®) or anesthetic sprays (e.g., Topex®)
Pamidronate (Aredia®)	Bisphosphonate	CRPS (off-label indication)	Reason for denial of off-label indication: Lack of evidence to support use for CRPS, no clear dosing, frequency or duration of therapy for consistent benefit. Adverse reactions including flu-like symptoms and infusion reactions were reported Please note: Pamidronate remains on the CCHS Formulary for other indications
Secnidazole (Solosec™)	Nitroimidazole	BV	Reason for denial: Metronidazole also used for BV has similar activity and a significantly lower cost

FDA=Food and Drug Administration OTC=Over-the-Counter CRPS=Complex Regional Pain Syndrome BV= Bacterial Vaginosis

Product Standardizations on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Standardization**
Beclomethasone (Qvar® RediHaler®)	Corticosteroid	Asthma COPD	Teva discontinued the 8.7 gram Qvar® HFA® inhaler and has replaced it with the Qvar® RediHaler® 10.6 gram products with 40 mcg or 80 mcg per actuation Therapeutic interchange was updated for inhaled corticosteroids to include Qvar® RediHaler®
Bendamustine	Antineoplastic Agent	CLL NHL HL MM	Switching to Eagle Pharmaceutical brand bendamustine 100 mg/4 mL vial from the Teva brand Bendeka® due to cost savings **Differences in products:** **Eagle bendamustine:** 1) Diluted in 500 mL of 0.9% NaCl 2) Final concentration 0.2 mg/mL to 0.7 mg/mL 3) Infused over 30 minutes **Teva Brand Bendeka®** 1) Diluted in 50 mL of 0.9% NaCl 2) Final concentration 1.85 mg/mL to 5.6 mg/mL 3) Infused over 10 minutes
Infliximab Biosimilar (Renflexis®)	Monoclonal Antibody	Crohn's Disease Ulcerative Colitis Rhematoid Arthritis Psoriatric Arthritis Ankylosing Spondylitis	Switching from: Remicade® to the biosimilar agent Renflexis® due to cost savings.
Tiotropium bromide inhalation (Spiriva® Respimat®)	Anticholinergic Agent	Asthma COPD	Switching from: Spiriva® HandiHaler® to Spiriva® Respimat® due to cost savings **Differences in products:** **Spiriva® Respimat®:** 1) Inhalation spray 2) 2 puffs (5 mcg) once daily for COPD 3) 2 puffs (1.25 mcg) once daily for asthma **Spiriva® HandiHaler®** 1) Dry powder capsule for inhalation 2) 1 capsule (18 mcg) once daily for COPD 3) Not FDA-approved for asthma There is a new therapeutic interchange for Spiriva® HandiHaler® to Spiriva® Respimat® and a new Spiriva® Respimat® Asthma Interchange

COPD=Chronic Obstructive Pulmonary Disease CLL=Chronic Lymphocytic Leukemia NHL=Non-Hodgkin's Lymphoma
HL=Hodgkin's Lymphoma MM=Multiple Myeloma

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Erythropoietin alfa (Procrit®)	Colony Stimulating Factor	Hypoxic Ischemia Encephalopathy	Eligibility criteria for erythropoietin include: 1) Gestational age > 36 weeks 2) Birth weight > 1800 grams 3) Admitted to the NICU within the first 6 hours of life An order set has been developed with dosing recommendations.
Letermovir (Prevymis®)	Antiviral Agent	CMV Infection	Restricted to: 1) Infectious Diseases physicians for the treatment of CMV infection 2) Infectious Disease and BMT for the prophylaxis of CMV infection in hematopoietic stem cell transplant patients
Sildenafil PO and IV (Revatio®)	Phosphodiesterase-5 inhibitor	Pulmonary Hypertension Facilitate Weaning of Inhaled Nitric Oxide	Restrictions: 1) IV sildenafil is restricted to the NICU and PICU providers (Staff, Fellows, NPs, PAs) in consultation with Cardiology or Pulmonology and Cardiac Stepdown providers (Staff, Fellows, NPs, PAs). IV sildenafil can only be administered in the ICUs and Cardiac Stepdowns 2) Oral sildenafil: a) Initiation is restricted to NICU and PICU providers (Staff, Fellows, NPs, PAs) in consultation with Cardiology or Pulmonology and Cardiac Stepdown Providers (Staff, Fellows, NPs, PAs) b) Continuation of therapy from home is not restricted
Sugammadex (Bridion®)	Selective Relaxant Binding Agent	Reversal Agent for Rocuronium and Vecuronium	Restricted to reversal of rocuronium and vecuronium only

CMV=Cytomegalovirus BMT=Bone Marrow Transplant NICU=Neonatal Intensive Care Unit PO=Oral IV=Intravenous
PICU=Pediatric Intensive Care Unit NP=Nurse Practitioner PA=Physician's Assistant ICU=Intensive Care Unit

Changes to Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Smoflipid®	Fat Emulsion	Short Bowel Syndrome TPN Cholestasis	Modified the current Formulary restrictions to the following: 1) Initiation is restricted to Pediatric Gastroenterology 2) Continuation (e.g., transferred from inpatient to Shaker Rehab Campus) is not restricted

TPN=Total Parenteral Nutrition

Product Standardization for the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Spironolactone (CaroSpir®)	Diuretic	Heart Failure Hypertension	Spironolactone suspension had been previously compounded as a 5 mg/mL and 25 mg/mL suspension Because it is preferable to use a commercially available product, CaroSpir® a brand name spironolactone 5 mg/mL suspension will replace the 5 mg/mL compounded product The 25 mg/mL suspension will still be compounded.

Formulary Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Oral benzocaine (e.g., Anbesol®)	Local Anesthetic	Teething Pain	The FDA released a Drug Safety Communication stating that OTC oral drug products containing benzocaine should not be used to treat infants and children < 2 years of age for any indication and should not be used for teething pain regardless of the age due to concerns with the development of methemoglobinemia Due to these safety concerns, these products were removed from the Pediatric Formulary and will not be stocked in any inpatient areas or at the CCHS Ambulatory Family Health Centers

FDA=Food and Drug Administration OTC= Over-the-Counter