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Rezafungin for Invasive Fungal Infections

By: Kata Bes, Pharm.D.

Background: Invasive candidiasis (IC) is a systemic fungal disease that can include candidemia, one of the most common healthcare-associated bloodstream infections.[1,2] Over 95% of IC infections are due to six common pathogens: *C. albicans, C. glabrata*, *C. tropicalis, C. parapsilosis*, and *C. krusei* and in some regions, *C. auris*.[1] Invasive candidiasis is a very difficult disease to treat with a mortality rate as high as 50%.[3] The echinocandins which include micafungin (Mycamine®), caspofungin (Cancidas®), and anidulafungin (Eraxis®) are recommended first-line by the Infectious Diseases Society of America for the management of most types of IC due to their superior efficacy and tolerability over other antifungal agents.[4] However these medications must be administered daily via intravenous (IV) infusion, a difficult regimen to maintain outside of the hospital necessitating in some cases a prolonged hospital stay.[3] Furthermore, treatment failure occurs in approximately 40% of patients signaling a need for another echinocandin therapeutic option.[5] Consequently, rezafungin (Rezzayo®; Melinta Therapeutics), a new echinocandin, was approved in March 2023 by Food and Drug Administration (FDA) for the treatment of candidemia and IC in adult patients who have limited or no alternative therapeutic options.[6] Unlike the other echinocandins, rezafungin has a long half-life of >130 hours, making it the first once-weekly antifungal agent that could easily be given on an outpatient basis.[2]

Mechanism of Action: Rezafungin inhibits the 1,3-beta-D-glucan synthase enzyme complex within fungal cell walls to prevent the formation of the essential cell wall component, 1,3-beta-D-glucan.[6] Rezafungin demonstrates concentration-dependent fungicidal activity against *Candida* species.[5] A unique aspect of rezafungin is its wide spectrum of activity, which includes a subset of echinocandin-resistant *C. auris* and azole-resistant *Aspergillus* isolates.[3]

Clinical Trial: ReSTORE was a multicenter, double-blind, double-dummy, phase 3 randomized, noninferiority trial evaluating the safety and efficacy of rezafungin in candidemia and IC compared to caspofungin.[7] A total of one-hundred ninety-nine patients age 18 years or older with systemic signs and mycological confirmation of candidemia and/or IC were randomized to receive either rezafungin 400 mg as a one-time IV loading dose, followed by 200 mg IV weekly (n=100) for a total of two to four doses or caspofungin 70 mg IV as a one-time loading dose, followed by 50 mg IV once daily (n=99) up to 4 weeks for the treatment of candidemia or IC. Patients were stratified based on their diagnosis (candidemia only or IC), modified Acute Physiology and Chronic Health Evaluation (APACHE) II score, and absolute neutrophil count. There were two primary efficacy outcomes, one mandated by the European Medicines Agency (EMA) and the other

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by the FDA. The EMA outcome evaluated global cure, which was based on clinical cure as assessed by the investigator, radiological cure (for patients with IC diagnosed by radiological or imaging evidence), and mycological eradication. The FDA outcome evaluated all-cause mortality up to day 30. These efficacy endpoints were assessed in a modified intention-to-treat population (those with a documented Candida infection who received at least one dose of study drug). Safety was assessed by the incidence and type of adverse events and deaths in the safety population. About 70% of patients had candidemia only and 30% of patients had an IC infection with or without candidemia. *Candida albicans* and *C. glabrata* were the most commonly isolated species in this study. For the EMA endpoint, global cure was found in 59% of patients in the rezafungin group compared to 61% of the caspofungin group (treatment difference of -1.1; 95% confidence interval (CI) -14.9 to 12.7). For the FDA endpoint, the 30-day mortality was observed among 24% of patients in the rezafungin group compared to the 21% in the caspofungin group (treatment difference of 2.4; 95% CI –9.7 to 14.4). Rezafungin met the non-inferiority margin of 20% for both endpoints. In the safety analysis, the most commonly reported adverse events with rezafungin compared to caspofungin were pyrexia (14% vs 5%, respectively), hypokalemia (13% vs 9%, respectively), pneumonia (10% vs 3%, respectively), septic shock (10% vs 9%, respectively), and anemia (9% vs 9%, respectively). The authors concluded that rezafungin was non-inferior to caspofungin for the co-primary endpoints and that there were no concerning trends for treatment-emergent adverse events.

Safety: The most common side effects of rezafungin with an incidence ≥5%, are electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypophosphatemia), pyrexia, gastrointestinal disorders, and anemia.[6] Rezafungin may cause photosensitivity, therefore, protection against sun exposure and other sources of ultraviolet radiation is recommended. Patients who develop abnormalities in liver function tests while receiving rezafungin should be monitored.

Dosing and Administration: Rezafungin is administered once weekly by IV infusion with an initial loading dose of 400 mg, followed by a 200 mg dose once weekly.[6] The safety of rezafungin has not been established beyond four weekly doses. The 200 mg and 400 mg doses are diluted in 250 mL of 0.9% Sodium Chloride or 5% Dextrose Injection and administered over 1 hour (~250 mL/hr). Rezafungin may cause infusion-related reactions; if this occurs the infusion should be slowed or paused and restarted at a slower rate. If a scheduled dose is missed, the missed dose should be given as soon as possible. If the dose was missed within 3 days of the assigned day, the next weekly dose may be on schedule. If it is missed by more than 3 days, the dosing schedule would need to be revised to ensure that there are at least 4 days between doses. If the drug needs to be restarted after at least 2 weeks of the missed dose, a loading dose of 400 mg would need to be readministered.

Cost and Availability: Rezzayo® (NDC: 70842-240-01) is available as a single-dose vial that contains 200 mg of rezafungin.[6] When stored at 5°C to 25°C (41°F to 77°F), the stability of the reconstituted single-dose vial and the IV infusion is 24 hours and 48 hours, respectively. The average wholesale price is $2,340 per vial.[7] The cost for a 4-week course of rezafungin including the loading dose is approximately $11,700.

Formulary Status: Rezafungin (Rezzayo®) is on the CCHS Adult Formulary restricted to the Department of Infectious Diseases for outpatient use only.

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What are the Key Differences between Respiratory Syncytial Virus Vaccines?

By: Jack Dykema, Pharm.D.

Some key differences between respiratory syncytial virus (RSV) vaccines are listed in Table 1.

Table 1: Key Characteristics of FDA-approved RSV Vaccines

	Abrysvo™ (RSVpreF)	Arexvy® (RSVPreF3)	mResvia® (mRNA-1345)
Manufacturer	Pfizer	GlaxoSmithKline	Moderna
Approval Date	May 2023	May 2023	June 2024
FDA-Approved Indications	1) Individuals age 60+ 2) Pregnant individuals at 32 through 36 weeks gestational age*	1) Individuals age 60+ 2) Individuals aged 50-59 who are at increased risk for RSV	1) Individuals age 60+
Type of Vaccine	Bivalent Recombinant Protein Vaccine	Adjuvanted Recombinant Protein Vaccine	Messenger RNA Vaccine
Dosage Form/ Administration	Supplied in two vials: a lyophilized powder and sterile water for reconstitution. It is also available as an Act-O-Vial and prefilled syringe. It is administered as a 0.5 mL intramuscular injection	Supplied in two vials: a lyophilized powder and accompanying adjuvant suspension. After reconstitution, it is to be administered as a 0.5 mL intramuscular injection	0.5 mL pre-filled syringe that must be thawed prior to administration as an intramuscular injection
Vaccine Efficacy**	85.7%	82.6%	82.4%
Rate of Injection Site Pain	11%	61%	56%

*Pregnant individuals are only eligible for vaccination September through January.
**Efficacy rates were based on comparison to placebo in older adult patients with at least three signs/symptoms of lower respiratory tract infection. No head-to-head studies between the vaccines were performed.
RSV=Respiratory syncytial virus FDA=Food and Drug Administration

The Advisory Committee on Immunization Practices (ACIP) released an updated guidance statement in June 2024 regarding RSV vaccination of older adults. Currently a single dose of RSV vaccine is recommended for all adults age 75+ and adults aged 60-74 who are at an increased risk of severe RSV disease.±
±*Risk factors for severe RSV disease can be found on the Centers for Disease Control and Prevention (CDC) website at:* https://www.cdc.gov/vaccines/vpd/rsv/hcp/older- adults.html

As of September 2024, Abrysvo™ is the preferred RSV vaccine on the CCHS formulary.

References:

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Imetelstat (Rytelo®) Intravenous Injection	Telomerase Inhibitor	Low-to Intermediate-1 Risk MDS	Restricted to the Department of Hematology/Oncology for outpatient use only
Nogapendekin alfa inbakicept-pmln (Anktiva®) Intravesical Solution	Interleukin-15R Agonist	BCG-unresponsive NMIBC	Restricted to the Department of Urology for outpatient use only
Remimazolam (Byfavo®) Intravenous Injection	Benzodiazepine	Procedural Sedation	Restricted to the Department of Gastroenterology (specifically for A3 Endoscopy at Main Campus)

MDS=Myelodysplastic syndrome BCG=Bacillus calmette-guerin NMIBC=Non-muscle invasive bladder cancer

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Esketamine (Spravato®) Nasal Spray	NMDA Receptor Antagonist	TRD	Modified restrictions to include use at Akron General Hospital
Obinutuzumab (Gazyva®) Intravenous Injection	Monoclonal Antibody	ANCA-Associated Vasculitis	Modified restrictions to include the Department of Rheumatology and the Department of Nephrology for use in patients with ANCA-associated vasculitis, who have failed rituximab, for use in the inpatient or outpatient setting.
Olanzapine (Zyprexa®) Intravenous/ Subcutaneous Injection	Atypical Antipsychotic	Psychiatric Disorders Agitation	Modified restrictions to add intravenous and subcutaneous injections as routes of administration for parenteral olanzapine. 1) Intravenous olanzapine will be restricted to the Departments of Emergency Medicine and Psychiatry for use in ICU-designated areas. 2) Subcutaneous olanzapine will be restricted to the Departments of Psychiatry and Palliative Medicine.
Paliperidone (Invega®) Oral Tablets	Atypical Antipsychotic	Psychiatric Disorders	Modified restrictions to use in patients with a contraindication to risperidone due to severe hepatic impairment. Note: If the patient does not meet the restriction criteria, paliperidone will be automatically interchanged to risperidone.

NMDA=N-methyl-D-aspartate TRD=Treatment resistant depression ANCA=Anti-neutrophil cytoplasmic antibody
ICU=Intensive care unit

Change to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Ravulizumab (Ultomiris®) Intravenous Injection	Monoclonal Antibody	NMOSD	Modified restrictions to include use by REMS-certified Staff prescribers from the Department of Neurology (Neuroimmunology) for outpatient use in patients with NMOSD
Tarlatamab-dlle (Imdelltra™) Intravenous Infusion	Antineoplastic Agent	ES-SCLC	Modified restrictions to state: Restricted to the Department of Hematology/Oncology as follows: 1) C1D1 and C1D8 must be administered at Main Campus or Weston in an outpatient setting followed by hospitalization under observation status for 22-24 hours from the start of the infusion. Patients must stay within 1-hour of an appropriate healthcare setting for 48 hours from the start of the infusion following these two doses, accompanied by a caregiver. 2) Starting C1D15 and beyond, administration may occur at any outpatient location without the need for hospitalization for observation if the local facility has a contingency plan in place for cytokine release syndrome.*

*Note: It was recommended to modify the Formulary restriction verbiage for all other bispecific antibody therapies to include location restrictions to Main Campus and Weston (as appropriate) during the initial ramp up period. This includes teclistamab, elranatamab, talquetamab, epcoritamab, mosunetuzumab, and tebentafusp.
NMOSD=Neuromyelitis optica spectrum disorder REMS=Risk evaluation mitigation strategy
ES-SCLC=Extensive stage small cell lung cancer C1D1=Cyle 1 Day 1 C1D8= Cyle 1 Day 8 C1D15=Cyle1 Day 15

Product Standardizations to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Lanreotide Product Standardizations	Somatostatin Analog	Acromegaly GEP Neuroendocrine Tumors Carcinoid Syndrome	It was recommended to approve the use of generic or 505 (b)(2) FDA-approved lanreotide product.
Leuprolide Product Standardization	Gonadotropin-Releasing Hormone Agonist	Prostate Cancer Ovarian Function Suppression Hormonal Targeted Therapy	Leuprolide acetate for depot suspension (Lupron® Depot) will automatically interchange to leuprolide acetate subcutaneous injection (Eligard®) for patients with prostate cancer in the outpatient setting. Leuprolide acetate for depot suspension (Lupron® Depot) will automatically interchange to goserelin acetate (Zoladex®) in the outpatient setting for management of ovarian function suppression and hormonal targeted therapy in gynecological and breast cancer indications; and for the inpatient setting restricted to Endocrinology, Rheumatology, Oncology, and Obstetrics/Gynecology for ovarian suppression. Lupron® Depot will continue to be available for insurance mandates only.

GEP=Gastroenteropancreatic FDA=Food and Drug Administration

Removal from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Apomorphine Subcutaneous Injection	Dopamine Agonist	Parkinson's Disease	Due to low usage and availability issues, it was recommended to remove apomorphine from the CCHS Formulary. Inpatients and outpatients requiring outpatient monitoring for initial dose and dose titrations must use home supply.

Process Changes to the Adult CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Daptomycin Intravenous Injection Dose Rounding	Anti-infectives	Various Infections	Dose rounding was changed to accommodate the use of daptomycin pre-mixed bags. Details are in Up-to-Date® Lexi Drug™
Golimumab (Simponi®) Intravenous Injection	TNF Blocker	Various Indications	Golimumab intravenous injection doses will be rounded down to the nearest 50 mg vial size if the dose falls within 10% (e.g., golimumab 156 mg will round down to 150 mg).
Inpatient Antimicrobial Dosing Pharmacist Consult Agreement	Antimicrobial Agents	Various Infections	The Antimicrobial Dosing and Monitoring for Pharmacist Consult Agreement SOP consolidates the previously approved Vancomycin Dosing and Monitoring SOP and Aminoglycoside Dosing and Monitoring SOP. These agreements remain largely unchanged and include updates to the quality assurance and continuous quality improvement components. Program effectiveness evaluations will be extended from yearly to every other year*
Pulmonary SOP for Pharmacist Consult Agreements	Pulmonary Agents	Asthma COPD Smoking Cessation	An outpatient consult agreement has been created to allow expanded roles of the pharmacist practicing in outpatient pulmonary clinics. The Managing Pharmacist will have the authority to manage medication therapy and laboratory or point-of-care testing related to treatment and management of asthma, COPD, and smoking cessation.
Psychiatry SOP For Pharmacist Consult Agreements	Antipsychotics	Various Psychiatric Disorders	The Psychiatry SOP for Pharmacist Consult Agreements allows pharmacists to perform medication monitoring for certain psychiatric mediations. Under this consult agreement, pharmacists may place specified laboratory and monitoring orders. Additionally, pharmacists may place orders for polyethylene glycol as part of bowel movement monitoring for clozapine treatment. Pharmacists must complete training and pass the post-training assessment to be eligible to participate in this monitoring service. Designees will review a selection of five patient cases annually to assess: scope of service, clarity and completeness of documentation, and appropriateness of actions taken.

*This policy would exclude Nevada and Florida practice sites.
TNF=Tumor necrosis factor SOP=Standard operating procedure COPD=Chronic obstructive pulmonary disease

Denials to the Adult CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Pemivibart (Pemgarda™) Intravenous Injection	Monoclonal Antibody	Pre-exposure Prophylaxis To COVID-19 Infection	Reasons for denial to add drug to the CCHS Adult Formulary: 1) Anaphylaxis and hypersensitivity/ infusion related reactions rates were higher than with other monoclonal antibodies approved for COVID-19 treatment or prevention. 2) Pemivibart requires a 1-hour infusion with a 2-hour observation period following completion of the infusion.
Tocilizumab (Actemra®) for ICI-induced Pneumonitis	Interleukin-6 Receptor Antagonist	Pneumonitis Secondary to ICIs	Reason for denial to expand the restriction criteria for treatment of drug-induced ILD secondary to ICIs 1) A literature review provided only limited data to support this indication in case reports and case series with mixed patient populations. 2) The 2024 NCCN Guidelines, 2021 ASCO Guidelines, and 2017 SITC Toxicity Management Working Group do not include tocilizumab for ICI-related ILD.

COVID-19=Corona virus disease 2019 ICI=Immune checkpoint inhibitors ILD=Interstitial lung disease
NCCN=National Comprehensive Cancer Network ASCO=American Society of Clinical Oncology SITC=Society of Immunotherapy of Cancer

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Macitentan (Opsumit®) Oral Tablet	Endothelin Receptor Antagonist	PAH	Restricted to: 1) Initiation is restricted to patients with recommendation from the Pediatric Pulmonary Hypertension Team. The prescriber must be registered with the REMS program. 2) For continuation of therapy: a) For those receiving medication supplied by a CCHS inpatient pharmacy, the prescriber must be registered with the REMS program. b) If a patient brings in a home supply of their medication (i.e., the medication is is not supplied by a CCHS inpatient pharmacy), then the inpatient order may be written by any prescriber, including those not registered with the REMS program. This is permitted by the REMS program.

PAH=Pulmonary arterial hypertension REMS=Risk Evaluation Mitigation Strategy

Process Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Daptomycin Intravenous Injection Rounding	Antimicrobial Agent	Various Infections	Please refer to the Process Changes to the Adult CCHS Formulary Table and Up-to-Date® Lexidrug™ for further details. Daptomycin dose rounding will apply to any pediatric orders meeting the minimum dosing criteria in the dose rounding scheme.
Hydroxocobalamin (Cyanokit®) Intravenous Injection Dose Rounding	Antidote	Cyanide Poisoning	In order to improve accuracy of doses, hydroxocobalamin (Cyanokit®) intravenous injection doses will be rounded to the nearest 25 mg . Details will be in Up-to-Date® Lexidrug™ .
Inpatient Antimicrobial Dosing Pharmacist Consult Agreement	Antimicrobial Agents	Various Infections	Please refer to the Process Changes to the Adult CCHS Formulary Table for further details.

Changes to Restrictions of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Emapalumab-lzsg (Gamifant®) Intravenous Injection	Monoclonal Antibody	sJIA with MAS	Modified restrictions to include Staff Physicians from the Department of Pediatric Rheumatology
Iloprost (Ventavis®) Inhalation	Prostaglandin	PAH	Modified restrictions to the following: 1) Physicians and fellows from Pediatric Pulmonology 2) Staff Physicians and fellows from Pediatric Cardiology 3) Staff Physicians, fellows, and APPs from NICU/PICU/ PCICU with Pulmonary Hypertension Team approval 4) Pediatric Pulmonary Hypertension Nurse Practitioners*
Lipid Injectable Emulsion [fish and plant based] (SMOFlipid®)	Caloric Agent	Parenteral Nutrition	Modified restrictions to the following: 1) Initiation of SMOFlipid® in the NICU, PICU, and PCICU is not restricted 2) Initiation of SMOFlipid® in the non-ICU areas is restricted to Pediatric Gastroenterology.
Nıcardipine Intravenous Injection	Calcium Channel Blocker	Blood Pressure Control	Restriction criteria for nicardipine injection have been removed to allow for ordering by any provider specialty

*Nurse practitioners will be permitted to order for initiation and continuation, including dose titrations.
sJIa=Systemic onset juvenile idiopathic arthritis MAS=Macrophage activation syndrome PAH=Pulmonary arterial hypertension
APP=Advanced practice practitioners NICU=Neonatal intensive care unit PICU=Pediatric intensive care unit
PCICU=Pediatric cardiology intensive care unit ICU=Intensive care unit