PMMC Executive Summary

Title: isavuconazonium sulfate (ISAV) injection and capsules (Cresemba®); Astellas Pharmaceuticals

Formulary recommendation: The Antimicrobial Stewardship and Formulary Evaluation Team recommends ISAV to the Duke Health System Formulary with Restrictions. Restrictions will be determined by each hospital P&T Committee. DUH use is restricted to ID consult.

The following points were considered for this recommendation:

1. **FDA Approved Recommendation**[1]: treatment of invasive aspergillosis and invasive mucormycosis caused by the following organisms: *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Rizopus oryzae*, and Mucormycetes spp in patients 18 years of age or older
2. **Anticipated Off-label Uses at Duke**: treatment of invasive Candida infections, Cryptococcus, or other invasive infections caused by rare fungi
3. **Efficacy Information**[1]:
    a. Treatment of invasive aspergillosis: The SECURE trial was a phase III, randomized, double-blind, noninferiority, comparative group-study of ISAV and voriconazole (VORI). The all-cause mortality rate through day 42 in the intent to treat (ITT) population was 18.6% for ISAV and 20.2% for VORI, meeting the study's primary objective of noninferiority. Treatment emergent adverse events related to study drug administration were significantly more common among VORI vs ISAV patients. The VITAL study was a multicenter, open-label, non-comparative study of ISAV in the treatment of patients with aspergillosis and renal impairment. Results revealed that ISAV was effective as assessed by mortality (3 of 20 subjects died) and overall response (success occurred in 6 of 20 subjects). Overall, ISAV was well tolerated.
    b. Treatment of mucormycosis: The VITAL study mentioned above also included 37 subjects with proven or probable invasive mucormycosis. Of the 35 subjects with an end of therapy (EOT) assessment, 31.4% had a successful overall response with ISAV. Complete and partial responses were achieved in 14.3% and 17.1% of subjects with stable disease and disease progression reported in 28.6% and 40% of subjects, respectively. The most common treatment-emergent adverse events were vomiting (32.4%) and diarrhea, nausea, and pyrexia (27% for each).
4. **Safety Information**[1]: side effects may include gastrointestinal discomfort. Severe or life-threatening effects have not shown to be common with this use of this medication. Monitor liver function tests.
5. Risk Evaluation and Mitigation Strategies (REMS) is not required for this medication.
6. No special resources are needed to obtain, dispense, or administer this medication.
7. Black Box Warning: No black box warnings are included with this medication.
8. Isavuconazole is a pregnancy category C.
9. Education Plan Level 1: Requires a "read only" approach. Monographs posted on the Pharmacy intranet accessible to all hospital personnel
10. There is no known research being conducted at Duke at this time.

Pharmacology[1]: isavuconazonium sulfate is the prodrug of isavuconazole, an azole antifungal. Like other azole antifungals, ISAV inhibits the synthesis of ergosterol, and essential component of the fungal cell membrane. Azole antifungals block ergosterol synthesis by inhibiting 14-alpha demethylase which is needed to convert lanosterol to ergosterol. The depletion of ergosterol results in increased cellular permeability causing leakage of cellular contents.

Spectrum of Activity[1]: *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, and Mucorales such as *Rizopus oryzae* and Mucormycetes species

Table 1. Formulary Product(s) in similar therapeutic/drug class:

Medication Name	Brand Name	Manufacturer	Formulary Status		
			DUH	DRaH	DRH
Posaconazole	Noxafil	Merck	F*	F	F
Voriconazole	Vfend	Pfizer/generic	F*	F	F
Amphotericin	Ambisome	Astellas	F*	F	F

*Formulary, restricted to ID consult. Exceptions to ID approval: HOA, 9200, and lung transplant anti-fungal prophylaxis protocols

Nursing Implications[1]:

- **Drug Administration**
  - Adult dosing:
    - Loading dose: 372 mg (equivalent to 200 mg isavuconazole) either orally or as an intravenous infusion every 8 hours for 6 doses
    - Maintenance dose: 372 mg either PO or IV once daily. Maintenance doses should be started 12-24 hours after the last loading dose.
  - Treatment duration: variable (patients received up to 180 days of therapy in clinical trials)
  - Pediatric dosing: safety and efficacy in patients <18 years old have not been established.
  - Geriatric dosing: the pharmacokinetics of ISAV are comparable in young and patients > 65 years of age.
  - Renal and hepatic dosing: no dose adjustment is needed in patients with mild, moderate, or severe renal impairment, including those with ESRD. ISAV is not readily dialyzable. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A and B). ISAV has not been studied in patients with severe hepatic impairment and should be used in these patients only when the benefits outweigh the risks.
  - Preparation:
    - Reconstitute one vial of ISAV by adding **5 mL sterile water for injection, USP** to the vial and gently shake to dissolve.
    - Reconstituted solution should be further diluted in a **250 mL bag of 0.9% sodium chloride or 5% dextrose**
    - The resulting solution is clear and may show visible translucent to white particulates of ISAV (which will be removed by the in-line filtration). Gentle mixing or rolling the bag may minimize the formation of particulates.
    - Apply in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron and in-line filter reminder sticker to the infusion bag.
    - DO NOT use a pneumatic transport system
  - Administration:
    - Intravenous solution: administer over 1 hour as an IV infusion ONLY. Do not administer as an IV push or bolus and do not mix with other drugs when administering. The total time from reconstitution to administration should not exceed 6 hours at room temperature or 24 hours under refrigeration (2°C to 8°C).
    - Oral capsules: swallow whole. Do not crush, chew, dissolve, or open the capsules. May be administered with or without food.
    - Oral capsules and intravenous infusion formulations are bioequivalent. Dosage adjustment is not required when switching between formulations.
- **Hazardous Drug Information**:
  - **Genotoxicity**: no mutagenic or clastogenic effects were detected in the in vitro bacterial reverse mutation assay and the in vivo bone marrow micronucleus assay in rats
  - **Carcinogenicity**: two-year carcinogenicity studies of ISAV have not been performed. Hepatocellular adenomas and carcinomas have been reported in mice and rats for other drugs in the azole class at near human recommended doses.

- **Teratogenicity**: perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with ISAV at 90 mg/kg/day during pregnancy through the weaning period. Isavuconazonium chloride administration was associated with dose-related increases in the incidences of rudimentary cervical ribs in rats and rabbits.
- **Reproductive toxicity**: oral administration of ISAV did not affect the fertility in male or female rats treated at doses up to 90 mg/kg/day
- **Organ toxicity**: unknown
- **Similar to existing hazardous drug**: data are limited regarding similarities to hazardous drugs

- **Dose drug have to be prepared in a biologic safety cabinet (BSC)?**: No
- **Common Adverse Reactions**: the most common adverse reaction occurring in patients receiving ISAV in clinical trials were: nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated LFTs (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%)
- **Contraindications**:
  - ISAV is contraindicated in patients with known hypersensitivity to isavuconazole.
  - Coadministration of strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir is contraindicated because the concentration of ISAV can be significantly increased.
  - Coadministration of strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's Wort, or long-acting barbituates is contraindicated because the concentration of ISAV can be significantly decreased
  - ISAV shortened the QTc interval in a concentration-dependent manner and is contraindicated in patients with familial short QT syndrome
- **Precautions**:
  - *Hepatic adverse drug reactions*: hepatic adverse drug reactions have been reported in clinical trials. The elevations in liver-related laboratory tests were generally reversible and did not require discontinuation of ISAV. Cases of more severe hepatic adverse drug reactions (hepatitis, hepatic failure) have been reported in patients with serious underlying medical conditions during treatment with ISAV.
  - *Infusion-related reactions*: infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of ISAV. Discontinue the infusion if these reactions occur.
  - *Hypersensitivity reactions*: serious hypersensitivity and severe skin reactions, such as Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue ISAV if a patient develops a severe cutaneous adverse reaction. There is no information regarding cross-sensitivity between ISAV and other azole antifungals.
  - *Embryo-fetal toxicity*: ISAV may cause fetal harm when administered to a pregnant woman and should only be used during pregnancy when the benefits outweigh the risk.
- **Drug Interactions**: ISAV is a substrate of CYP3A4 and 3A5. In vitro, ISAV is an inhibitor of CYP3A4, 2C8, 2C9, 2C19, and 2D6. In vitro, ISAV is also an inducer of CYP3A4, 2B6, 2C8, and 2C9

Table 2. Pertinent Drugs Interactions

Medication	Recommendation	Comments
Ketoconazole	Contraindicate coadministration of all potent CYP3A4 inhibitors	There is more than a 5-fold increase in exposure of ISAV upon coadministration of ketoconazole
Lopinavir/ritonavir	Caution is advised when ISAV is coadministered with lopinavir/RTV	There is a 96% increase in exposure of ISAV when coadministered and a decreased exposure of lopinavir/RTV
Rifampin	Contraindicate coadministration of all potent CYP3A4 inducers	There is a 97% decrease in exposure of ISAV upon coadministration
Tacrolimus (FK-506)	Use with caution	Concomitant administration results in an increase

		in tacrolimus exposure. Monitor drug concentrations of FK-506.
Mycophenolate mofetil (MMF)	Use with caution	Increase MMF exposure. Patients should be monitored for MMF-related toxicities
Sirolimus	Use with caution	Increase in sirolimus exposure. Monitor sirolimus concentrations.
Bupropion	Use with caution	Decrease bupropion exposure. Dose increase of bupropion may be necessary

- **Pregnancy Category**: C; there are no well-controlled clinical studies of ISAV in pregnant women. ISAV should be used in pregnancy only if the potential benefit to the patient outweighs the risk to the fetus.
- **Lactation**: ISAV is excreted in the milk of lactating rats. Mothers should not breast feed while taking ISAV.

Summary data for non-FDA approved uses[2,3]:

- A phase II, randomized, double-blind, multi-center trial evaluated the safety and efficacy of three dosing regimens of ISAV compared to fluconazole (FLUC) in patients with uncomplicated esophageal candidiasis
    - A majority of subjects (n=146; 95.4%) in the per-protocol population had an endoscopically-confirmed clinical success at EOT
- A phase II dose-escalation study was conducted to study the safety and pharmacokinetics of ISAV as antifungal prophylaxis in acute myeloid leukemia patients with neutropenia.
    - 32 drug-related TEAEs occurred (11 low-dose vs 21 high-dose); the most common drug-related TEAEs were headache and rash (13% each)
    - 18/20 subjects (90%) who completed the study experienced treatment success in the low-dose cohort and 12 subjects in the high-dose cohort

Evaluation of Literature for FDA Approved Uses[4-6]:

Isavuconazole versus Voriconazole for Primary Treatment of Invasive Mold Disease Caused by *Aspergillus* and Other Filamentous Fungi (SECURE Trial)

- Study Design: phase III, international, multi-center, double-blind, non-inferiority, randomized controlled trial
- Study Objective: to compare the efficacy and safety of IV and oral ISAV formulations to the respective formulations of VORI in the primary treatment of invasive mold disease caused by *Aspergillus* sp or other filamentous fungi
- Inclusion Criteria:
    - Patients ≥ 18 years old
    - Proven/probable/possible invasive mold disease caused by Aspergillus sp or other filamentous fungi according to EORTC/MSG criteria
- Exclusion Criteria:
    - Hepatic dysfunction, moderate to severe renal dysfunction, chronic aspergillosis, aspergilloma, or allergic aspergillosis; >4 days of anti-mold treatment within 7 days of study start, advance HIV (CD4 <200) or AIDS-defining condition, unlikely to survive 30 days, mechanical ventilation
- Patient Number: 516 subjects included in the ITT population
- Interventions:
    - ISAV 200 mg 3 times daily IV for 2 days, followed by 200 mg once daily (IV or oral) from day 3 until EOT (max 84 days)
    - VORI 6 mg/kg IV twice daily on day 1, then 4 mg/kg IV twice daily on day 2, followed by 4 mg/kg IV or 200 mg PO twice daily from day 3 until EOT (max 84 days)
    - Therapeutic drug monitoring was not allowed
- Results:
    - Primary Outcome: all-cause mortality through day 42 in the ITT population with a 10% NI margin

- Secondary Outcomes: overall response at EOT in the mMITT population; all-cause mortality through day 84; overall clinical, mycological, and radiological responses on days 42 and 84

Table 3. Select baseline patient and disease characteristics for ITT analysis from SECURE trial

	ISAV (n=258)	VORI (n=258)
Age, yr, mean (SD)	51.1 ± 16.2	51.2 ± 15.9
Male sex, n (%)	145 (56.2%)	163 (63.2%)
Baseline Conditions, n (%)		
Hematologic malignancy	211 (81.8%)	222 (86.0%)
Allogenic BMT/HSCT	54 (20.9%)	51 (19.8%)
Active malignancy	173 (67.1%)	187 (72.5%)
Neutropenia	163 (63.2%)	175 (67.8%)
T-cell immunosuppressant use	111 (43.0%)	109 (42.2%)
Corticosteroid use	48 (18.6%)	39 (15.1%)
mITT infection-causing pathogens, n (%)	**ISAV (n=143)**	**VORI (n=129)**
Aspergillus species only	49 (34.3%)	39 (30.2%)
Aspergillus + other filamentous fungi	3 (2.1%)	1 (0.8%)
Non-Aspergillus species only	5 (3.5%)	6 (4.7%)
Filamentous fungi NOS	14 (9.8%)	15 (11.6%)

Table 4. Mortality and Overall Response Results

	ISAV	VORI	Treatment Difference % (95% CI)
ITT population	**n=258**	**n= 258**	
All-cause mortality (day 42)	48 (18.6%)	52 (20.2%)	-1.0 (-7.8 to 5.7)
Deaths	45 (17.4%)	50 (19.4%)	
All-cause mortality in the ITT population (day 84)	75 (29.1%)	80 (31.0%)	-1.4 (-9.2 to 6.3)
Deaths	72 (27.9%)	75 (29.1%)	
mITT population	**n=143**	**n=129**	
Overall response at EOT			
Success	50 (35.0%)	47 (36.4%)	1.6 (-9.3 to 12.6)
Complete	17 (11.9%)	13 (10.1%)	
Partial	33 (23.1%)	34 (26.4%)	
Clinical response at EOT	85/137 (62.0%)	73/121 (60.3%)	0.4 (-10.6 to 11.5)
Mycological response at EOT	54.143 (37.8%)	53/129 (31.1%)	3.8 (-7.4 to 15.1)
Radiological response at EOT	41/141 (29.1%)	42/127 (33.1%)	5.7 (-4.9 to 16.3)

- Safety: Treatment-emergent events were reported in 96.1% of subjects who received ISAV and 98.5% of subjects who received VORI. Treatment-emergent AEs thought to be related to the study drug were significantly more common among VORI subjects (59.8%) vs. ISAV subjects (42.4%, $p<0.001$). The most common adverse events were gastrointestinal disorders (ISAV 67.7%, VORI 69.5%)

- Conclusion: ISAV is noninferior to VORI for the primary treatment of suspected invasive mold disease with significantly fewer study drug-related adverse events.

Open-label Study of Isavuconazole in the Treatment of Patients With Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Cause by Rare Moulds, Yeasts, or Dimorphic Fungi (VITAL Trial)

- Study Design: phase III, multi-center, open-label, non-comparative study
- Inclusion Criteria:
  - Patients ≥ 18 years old

    - Proven/probable/possible invasive mucormycosis infection or proven/probable/possible invasive aspergillosis with renal impairment (CrCl < 50 mL/min or receipt of dialysis)
- Exclusion Criteria:
    - High risk for QT prolongation; protocol-defined hepatic dysfunction, chronic aspergillosis, aspergilloma, or allergic aspergillosis; >4 days of VORI, ITRA, or POSA within 7 days of study start, advance HIV (CD4 <50) or AIDS-defining condition, unlikely to survive 30 days
- Patient Number: 146 subjects included in the ITT population
- Interventions:
    - ISAV 200 mg 3 times daily IV for 2 days, followed by 200 mg once daily (IV or oral)
- Results:
    - Primary Outcome: All-cause mortality through day 42 in the mITT population
        - All-cause mortality through day 42 occurred in 37.8% of the mucormycosis mITT population
        - Three subjects in the mITT population with invasive aspergillosis and renal impairment died by day 42. All 4 subjects with invasive aspergillosis and normal renal function survived through day 42.
    - Secondary Outcome: overall response success rate at EOT
        - In the aspergillosis mITT population, overall response success at EOT occurred in 6 subjects (30%) with renal impairment and 2 of 3 evaluable subjects (66.7%) without renal impairment
        - Clinical, mycological, and radiological responses at EOT occurred in 56.5%, 39.1%, and 21.7%, respectively, of the overall aspergillosis mITT population
    - Safety: treatment-emergent adverse events occurred in 95.2% of the ITT population, with 41.1% of treatment-emergent events attributed to the study drug. The most common treatment-emergent adverse events were vomiting (24.7%) and nausea (23.3%).\
- Conclusion: ISAV was well-tolerated and effective for the treatment of invasive aspergillosis in subjects with renal impairment assessed by mortality and response outcomes

Pharmacogenomic Testing Recommended: No pharmacogenomics testing is required for use

Date: June 2015; **Prepared by:** Christina Sarubbi, PharmD

References:

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2. Viljoen J, Azie N, Schmitt-Hoffmann AH, Ghannoum M. A phase 2, randomized, double-blind, multicenter trial to evaluate the safety and efficacy of three dosing regimens of isavuconazole compared with fluconazole in patients with uncomplicated esophageal candidiasis. Antimicrob Agents Chemother 2015;59(3):1671-1679.
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5. Clinical Study Report 0103. Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi (VITAL). Astellas. Data on File. 2015.
6. Marty FM, Perfect JR, Cornely OA, et al. An open-label phase 3 study of isavuconazole (VITAL): focus on mucormycosis. Presented at Infectious Diseases Week (IDWeek) 2014 Annual Meeting, Philadelphia, October 8-12, 2014