Isavuconazonium sulfate (Cresemba®, Astellas Pharma US Inc.) **June 2017**
Non-Formulary

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

Criteria for Formulary Consideration of Isavuconazonium Sulfate

Efficacy
Isavuconazonium is approved by the FDA for treatment of invasive aspergillosis and invasive mucormycosis in adults.[1] The SECURE trial[3] was a phase III, double-blind, multicenter, international study that compared isavuconazonium to voriconazole for primary treatment of invasive aspergillosis. Day 42 all-cause mortality was 19% with isavuconazonium and 20% with voriconazole, with an adjusted treatment difference of -1.0% (95% CI -7.8 to 5.7). Because the upper bound of the 95% CI (5.7%) did not exceed 10%, non-inferiority was shown. For primary treatment of mucormycosis, isavuconazonium was evaluated in the VITAL study[4] which was a single-arm open label trial. Results were compared with amphotericin B treatment in a matched case-control analysis. Day 42 all-cause mortality with isavuconazonium was 7/21 (33%) compared to 13/39 (39%) in the amphotericin B-treated matched controls. Posaconazole is the other triazole that is used for Mucorales, but it has not been studied in primary treatment of invasive mucormycosis. Its role is currently limited to prophylaxis and step-down therapy.[13]

Safety
Potential serious adverse effects with isavuconazonium include hepatic adverse drug reactions (including hepatitis, cholestasis or hepatic failure including death), infusion reactions, and hypersensitivity reactions. The most common adverse effects are nausea, vomiting, diarrhea, hypokalemia, dyspnea, elevated liver enzymes, abdominal pain, headache, peripheral edema, constipation, fatigue and insomnia.[1,2] In the SECURE trial,[3] drug-related adverse events were reported in 109 (42%) patients receiving isavuconazonium and 155 (60%) receiving voriconazole (p<0·001). During treatment, isavuconazonium-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] vs 42 [16%]; p=0·016), eye disorders (39 [15%] vs 69 [27%]; p=0·002), and skin or subcutaneous tissue disorders (86 [33%] vs 110 [42%]; p=0·037). Additionally, isavuconazonium has been shown to shorten the QTc interval whereas all other triazoles are associated with prolonged QTc interval. The formulation of isavuconazonium as a water soluble prodrug facilitates IV administration without the need for the potentially nephrotoxic cyclodextrin excipient that is used with other triazoles.[3]

Uniqueness
Isavuconazonium does not require therapeutic drug monitoring (TDM) like some other triazoles because it demonstrates predictable and linear pharmacokinetics with low interpatient variability. It has good oral bioavailability and food does not significantly alter its absorption.[1] In contrast, TDM is recommended with voriconazole because of its narrow therapeutic window and interpatient variability due to genetic CYP2C19 polymorphisms and hepatic enzyme saturation. TDM is also recommended with the posaconazole solution due to its unpredictable and variable absorption.[5] Voriconazole and posaconazole are both strong inhibitors of CYP3A4 whereas isavuconazonium is a moderate inhibitor of that enzyme.[2,7,8]

Cost (AWP)
IV solution: 372mg $372/vial
PO capsules: 186mg $96 each

Recommendations
Add isavuconazonium to the formulary restricted to the infectious diseases service for treatment of invasive fungal infections in patients intolerant of first-line agents at therapeutic doses.

Based on a review of the current literature, the Antmicrobial Stewardship Program at Nebraska Medicine created the table below to guide clinicians when choosing therapy for invasive fungal infections. Therapeutic decisions should consider the specific organism, severity of infection, patient characteristics, potential medication interactions, and antifungal agent characteristics (bioavailability, tolerability, price, etc.).

Infection	**1st line Agents**	**2nd Line Agents**
Invasive Aspergillosis	Voriconazole	**Isavuconazonium**
Mucormycosis	Amphotericin B	**Isavuconazonium**
Histoplasmosis	Amphotericin B, Itraconazole or Voriconazole	Posaconazole or **Isavuconazonium**
High-risk fungal prophylaxis	Voriconazole	Posaconazole
Candidiasis	Micafungin or Fluconazole	Voriconazole

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Introduction
Invasive fungal infections are uncommon and occur primarily in immunocompromised patients, especially in patients with hematologic malignancies and those who have undergone solid organ or hematologic stem cell transplantation. *Aspergillus* and Mucorales are ubiquitous in nature and their spores can become airborne. These infections most commonly become localized in the lungs after inhalation of these spores. Invasive fungal infections are difficult to treat and are associated with significant morbidity, mortality and health care costs. Many of the available antifungals suffer from limited spectrum, adverse effects, significant drug-drug interactions and/or unpredictable pharmacokinetic profiles.[5]

Isavuconazonium has emerged as alternative treatment for these invasive fungal infections in patients who fail or are not able to tolerate the first line medications.[5,6] Trials evaluating the use of isavuconazonium for fungal prophylaxis in immunocompromised patients are currently ongoing.[9,10]

	1st line	2nd Line
Invasive Aspergillosis	Voriconazole	**Isavuconazonium**
Mucormycosis	Amphotericin B	**Isavuconazonium**
Histoplasmosis	Amphotericin B, Itraconazole or Voriconazole	Posaconazole or **Isavuconazonium**
High-risk fungal prophylaxis	Voriconazole	Posaconazole
Candidiasis	Micafungin or Fluconazole	Voriconazole

Pharmacokinetics
After IV administration of isavuconazonium, plasma concentrations of the prodrug and inactive cleavage product declined rapidly. The prodrug was below the level of detection by 1.25 hours after the start of a 1 hour infusion. Total exposure of the prodrug was less than 1% that of the active isavuconazole. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion. Total exposure to the inactive cleavage product was 1.3% that of isavuconazole. After oral administration, no significant concentrations of the prodrug or inactive cleavage product were seen in plasma. Oral administration of isavuconazonium with a high-fat meal resulted in an increase C_{max} by 9% and increased AUC by 9%. Isavuconazole is metabolized by CYP3A4/5 and UDP-glucuronosyltransferase (UGT). None of the metabolites has an AUC greater than 10% of isavuconazole.[1] The following table summarizes other important pharmacokinetic properties of isavuconazole.[2]

Half-life elimination (IV)	130 hours
Steady State Volume of Distribution	450 liters
Protein Binding (primarily to albumin)	>99%
Bioavailability	98%
Time to peak (oral)	2-3 hours
Excretion (oral)	46.1% feces, 45.5% urine
Excretion (IV)	95% urine

Pharmacology
Isavuconazonium sulfate is a prodrug that is rapidly hydrolyzed in the blood to active isavuconazole. Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function.[1,2]

FDA Approved Indications
- Treatment of invasive aspergillosis in adults (Approval date: March 6, 2015)[2]
- Treatment of invasive mucormycosis in adults (Approval date: March 6, 2015)[2]

Clinical Trials

SECURE Trial[3]

Study Design	Methods	Results	Conclusions/Comments

Maertens JA et al, 2016
 	
Trial design – Phase III, prospective, double-blind, randomized, international, multicenter, comparative-group study
 	
Number of patients in each group:
• ITT population: received any dose of the study drug
  ○ isavuconazonium n=258
  ○ voriconazole n=258
• mITT population: proven or probable invasive mold disease
  ○ isavuconazonium n=143
  ○ voriconazole n=129
• myITT population: proven or probable aspergillosis
  ○ isavuconazonium n=123
  ○ voriconazole n=108
 	
Intervention or treatment:
• Isavuconazonium 372 mg IV three times daily on days 1 and 2, then IV or PO once daily.
• Voriconazole 6mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then 4 mg/kg IV or 200 mg PO twice daily thereafter.
 	
Length of trial: 84 days
	Inclusion Criteria:
	• 18 years and older
	• Proven, probable or possible invasive mold disease caused by *aspergillus* or other filamentous fungi
	
	Exclusion Criteria:
	• Hepatic dysfunction (bilirubin ≥3x ULN, ALT or AST ≥5x ULN, cirrhosis or chronic hepatic failure)
	• Moderate-to-severe renal dysfunction (creatinine clearance <50 mL/min)
	• Concurrent treatment with strong inhibitors or inducers of CYP enzymes
	• Advanced HIV infection with CD4 count <200
	• Patients who had been administered more than four cumulative days of itraconazole, voriconazole, or posaconazole within the 7 days prior to the first dose of study drug
	• Body weight ≤40 kg
	• Female patients who were pregnant, breast-feeding or of childbearing potential and not using highly effective method of birth control
	
	Statistical analysis, power, etc:
	• The pre-specified non-inferiority margin for the primary end point is 10%
	• 255 patients per group provided 80% power for the primary endpoint
	• Stratified Cochran-Mantel-Haenszel method to calculate adjusted treatment difference.
	• Fisher's exact test for comparison of treatment-emergent adverse events between treatment groups
		Primary Efficacy Variable: Day 42 all-cause mortality in patients who received at least 1 dose of the study drug (ITT population)
		
		Secondary Efficacy Variables: Day 84 all-cause mortality; overall, clinical, mycological and radiological responses on day 42, day 84 and at end of treatment
		
		Results
		
		Isavuconazonium / Voriconazole / Adjusted Treatment Difference (95% CI)
		ITT - Day 42 all-cause mortality: 48 (19%) / 52 (20%) / -1% (-7.8 to 5.7)
		ITT - Day 84 all-cause mortality: 75 (29%) / 80 (31%) / -1.4 % (-9.2 to 6.3)
		mITT - Day 42 all-cause mortality: 28 (20%) / 30 (23%) / -2.6% (-12.2 to 6.9)
		mITT - Day 84 all-cause mortality: 43 (30%) / 48 (37%) / -5.5% (-16.1 to 5.1)
		myITT - Day 42 all-cause mortality: 15 (17%) / 24 (22%) / -2.7% (-12.9 to 7.5)
		myITT - Day 84 all-cause mortality: 24 (27%) / 39 (36%) / -5.7% (-17.1 to 5.6)
		Overall response at end of treatment: 50 (35%) / 47 (36%) / 1.6% (-9.3 to 12.6)
		Clinical response at end of treatment: 85/137 (62%) / 73/121 (60%) / 0.4% (-10.6 to 11.5)
		Mycological response at end of treatment: 54/143 (38%) / 53/129 (41%) / 3.8% (-7.4 to 15.1)
		Radiological response at end of treatment: 41/141 (29%) / 42/127 (33%) / 5.7% (-4.9 to 16.3)
		
		Adverse Events
		• Most common treatment-emergent adverse events: nausea, vomiting, diarrhea, pyrexia and hypokalemia.
		• Overall, fewer adverse events were considered drug-related (as determined by the investigator) for the isavuconazonium than voriconazole (109 [42%] vs 155 [60%], p<0.001)
		• Within system organ classes, rates of treatment-emergent adverse events were similar across most categories. The isavuconazonium group did have significantly lower frequency of hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders.
		
		Isavuconazonium (n=257) / Voriconazole (n=259) / p value
		Skin and subcutaneous tissue disorders: 86 (33%) / 110 (42%) / 0.037
		Eye disorders: 39 (15%) / 69 (27%) / 0.002
		Hepatobiliary disorders: 23 (9%) / 42 (16%) / 0.016
		
		(Skin and subcutaneous tissue disorders include rash, erythema, skin lesion and drug eruption. Eye disorders include visual impairment, photophobia, reduced visual acuity and retinal hemorrhage. Hepatobiliary disorders include hyperbilirubinemia, abnormal hepatic function, jaundice and cholestasis.)
			Author's Conclusion:
			Isavuconazonium was non-inferior to voriconazole for the primary treatment of suspected invasive mold disease. It was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. These results support the use of isavuconazonium for the primary treatment of patients with invasive mold disease.
			
			Comments:
			• The protocol did not allow therapeutic drug monitoring for voriconazole to maintain study blinding
			• Study funded by the drug manufacturer

VITAL Study[4]

Study Design

Marty FM et al, 2016

Trial design – single-arm open-label trial and case-control analysis

Number of patients in each group:

- 37 total patients with proven or probable mucormycosis received isavuconazonium
- 21 patients were given isavuconazonium as primary treatment
- 11 patients were given isavuconazonium for refractory disease
- 5 patients were given isavuconazonium because they were intolerant to other antifungals
- 33 patients from the FungiScope Registry who received primary amphotericin B-based treatment were matched to the 21 patients who received isavuconazonium as primary treatment

Intervention or treatment: Isavuconazonium 372 mg IV or PO three times daily for six doses followed by 372 mg once daily until disease resolution, failure or for 180 days or more.

Length of trial: Median isavuconazonium treatment was 84 days (IQR 19-179, range 2-882)

Methods

Inclusion Criteria:

- 18 years and older
- Proven or probable mucormycosis (documented by culture or histology/cytology)

Exclusion Criteria:

- Hepatic dysfunction (bilirubin ≥3x ULN, ALT or AST ≥5x ULN, cirrhosis or chronic hepatic failure)
- Concurrent treatment with strong inhibitors or inducers of CYP enzymes
- Advanced HIV infection (CD4 <50)
- Body weight ≤40 kg
- Female patients who were pregnant, breast-feeding or of childbearing potential and not using highly effective method of birth control

Statistical analysis, power, etc:

- Matching of controls based on severe disease (CNS or disseminated involvement), hematological malignancy and surgical treatment within 7 days of antifungal treatment initiation
- Hazard ratio and its 95% CI calculated from a Cox model without covariates.
- Patients with unknown survival status were regarded as deaths in the crude mortality calculations and were censored at the last known day alive for Kaplan-Meier analysis

Results

Primary Efficacy Variable: Day 42 all-cause mortality

Secondary Efficacy Variables: Overall, clinical radiological and mycological responses at day 42, day 84

Results

	Primary treatment (N=21)	Refractory (N=11)	Intolerant to other antifungals (N=5)	Total (N=37)
Clinical Response at EOT	10/18 (56%)	2/9 (22%)	2/4 (50%)	14/31 (45%)
Mycological response at EOT	6/19 (32%)	4/11 (36%)	2/5 (40%)	12/35 (34%)
Radiological Response at EOT	3/18 (17%)	2/10 (20%)	1/5 (20%)	6/33 (18%)
Day 42 all-cause mortality	7 (33%)	5 (45%)	2 (40%)	14 (38%)
Day 84 all-cause mortality	9 (43%)	5 (45%)	2 (40%)	16 (43%)

EOT=End of Treatment

Case-Control Analysis

	Isavuconazonium	Amphotericin B	p value
Crude all-cause mortality	7/21 (33%)	13/33 (39%)	0.775
Weighted all-cause mortality	33%	41%	0.595

Adverse Events

- Treatment-emergent adverse events occurred in 35 (95%) of patients. The most common adverse events were vomiting (32%), diarrhea (27%), nausea (27%), pyrexia (27%) and constipation (22%)
- 28 patients had serious adverse events.
- Pneumonia and septic shock occurred in 3 patients. No other serious adverse events occurred in more than 2 patients.
- 6 patients discontinued isavuconazonium treatment due to adverse events.
  - Relapse or progression of malignant disease (2 patients)
  - Acute liver injury (2 patients)
  - E. coli bacteremia (1 patient)
  - Nausea (1 patient)

Conclusions/Comments

Author's Conclusion: Isavuconazonium showed activity against mucormycosis with efficacy similar to amphotericin B. Isavuconazonium can be used for treatment of mucormycosis and is well tolerated.

Comments:

- Small sample size
- No blinding
- Study funded by the drug manufacturer

Warnings, Precautions, and Adverse Effects

Contraindications	• Known hypersensitivity to isavuconazonium • Familial short QT syndrome • Co-administration with strong CYP3A4 inhibitors or inducers[1]
Hepatic Adverse Drug Reactions	Elevations in liver enzymes have been reported in clinical trials. These elevations were generally reversible and did not require discontinuation of isavuconazonium. Cases of more severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including isavuconazonium. Monitor liver-related laboratory tests at baseline and throughout therapy. Discontinue isavuconazonium if clinical signs and symptoms consistent with liver disease develop that may be attributable to the medication.[1]
Infusion-Related Reactions	Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of isavuconazonium. In the SECURE trial,[3] potential anaphylaxis and severe cutaneous reactions were reported in 1.9% of patients. Discontinue the infusion if these reactions occur.[1]
Hypersensitivity Reactions	Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue isavuconazonium if a patient develops a severe cutaneous adverse reaction. There is no information regarding cross-sensitivity between isavuconazonium and other azole antifungal agents. Caution should be used when initiating isavuconazonium in patients with hypersensitivity to other azoles.[1]
Pediatrics	The safety and efficacy of isavuconazonium has not been studied in patients less than 18 years of age.[1]
Pregnancy	Pregnancy Category C. There are no adequate studies of isavuconazonium in pregnant women and the medication should only be used during pregnancy if the potential benefit to the patient outweighs the risk to the fetus. Based on animal data, isavuconazonium is predicted to have the potential to increase the risk of adverse developmental outcomes above background risk.[1]
Lactation	Animal studies found that isavuconazole was excreted in breast milk of rats. Breast feeding while taking isavuconazonium is not recommended.[1]

A total of 403 patients were exposed to isavuconazonium in two phase III clinical trials.[1] Serious adverse reactions occurred in 55% of patients and 14% of patients permanently discontinued treatment with isavuconazonium due to an adverse reaction. The adverse reactions which most often led to discontinuation of isavuconazonium were: confusion (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%). The following table includes treatment-emergent adverse reactions with rates of 5% or greater in patients who received isavuconazonium in the SECURE trial.[3]

	Isavuconazonium (N=257) n (%)	Voriconazole (N=259) n (%)
Nausea	71 (28)	78 (30)
Vomiting	64 (25)	73 (28)
Diarrhea	61 (24)	60 (23)
Hypokalemia	49 (19)	58 (22)
Dyspnea	44 (17)	35 (14)
Elevated liver laboratory tests[a]	44 (17)	63 (24)
Abdominal pain	43 (17)	59 (23)
Headache	43 (17)	38 (15)
Peripheral edema	39 (15)	46 (18)
Constipation	36 (14)	54 (21)
Fatigue	27 (11)	18 (7)
Insomnia	27 (11)	25 (10)
Back pain	26 (10)	19 (7)
Renal failure	26 (10)	21 (8)
Chest pain	23 (9)	16 (6)
Decreased appetite	22 (9)	28 (11)
Delirium[b]	22 (9)	30 (12)
Rash	22 (9)	36 (14)
Anxiety	21 (8)	18 (7)
Hypotension	21 (8)	28 (11)
Pruritus	21 (8)	15 (6)
Acute respiratory failure	19 (7)	22 (9)
Dyspepsia	16 (6)	14 (5)
Injection site reaction	16 (6)	4 (2)
Hypomagnesemia	14 (5)	27 (10)

[a] Elevated liver laboratory tests include reactions of increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood alkaline phosphatase, blood bilirubin, and gamma-glutamyltransferase.
[b] Delirium includes adverse reactions of agitation, confusion, delirium, disorientation, and mental status changes.

Interactions
Isavuconazonium is a substrate of CYP3A4. It inhibits CYP3A4 (moderate), CYP2C9 (weak), P-glycoprotein (P-gp) (mild) and Organic Cation Transporter 2 (OCT2) (mild). It induces CYP2B6 (weak) and CYP2C9 (weak/moderate).[2] Co-administration with CYP3A4 inhibitors or inducers can significantly alter the plasma concentrations of isavuconazonium and is contraindicated.[1] Moderate CYP3A4 inhibitors and inducers should be used with caution with isavuconazonium as they also have the potential to alter the plasma concentrations of isavuconazole. Drugs that are CYP3A4 substrates could have increased exposure when co-administered with isavuconazonium. Patients should be monitored for adverse reactions. Appropriate TDM and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when co-administered with isavuconazonium. Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when co-administered with isavuconazonium.[1]

Dosage and Administration
The loading dose is 372 mg IV or PO every 8 hours for 6 doses (48 hours). The maintenance dose of 372 mg IV or PO once daily should be started 12 to 24 hours after the last loading dose. It is not necessary to repeat the loading dose when switching between IV and oral formulations. There is no dose adjustment necessary in geriatric patients, patients with renal impairment and patients with mild or moderate hepatic impairment (Child-Pugh class A or B). For patients with severe hepatic impairment (Child-Pugh class C), no dose adjustment is provided, but isavuconazonium should be used with caution because it has not been studied in this population.[1,2]

Isavuconazonium for injection must be administered through an in-line filter (pore size 0.2 to 1.2 micron). Infuse over a minimum of 1 hour in 250 mL of 0.9% sodium chloride or 5% dextrose to reduce the risk of infusion related reactions. Do not infuse isavuconazonium with other intravenous medications. Flush intravenous lines with 0.9% sodium chloride or 5% dextrose prior to and after the infusion. Isavuconazonium capsules can be taken with or without food. Swallow capsules whole. Do not chew, crush, dissolve, or open the capsules.[1,2]

Monitoring Parameters
Monitor for hypersensitivity reactions with initial doses, liver function tests (e.g. AST, ALT, alkaline phosphatase, total bilirubin) at baseline and periodically during therapy, and infusion-related reactions (e.g. hypotension, dyspnea, chills, dizziness, paresthesias, hypoesthesia) during IV infusion.[2]

How Supplied
Isavuconazonium is available as 186 mg capsules (equivalent to 100 mg of isavuconazole). Store capsules at 20-25ºC in original blister packaging to protect from moisture. Excursions are permitted between 15-30ºC.[1,2]

The intravenous formulation is available in a single-dose vial as a sterile lyophilized powder containing 372 mg of isavuconazonium (equivalent to 200 mg of isavuconazole). Reconstitute 1 vial of isavuconazonium with 5 mL sterile water. Shake gently to dissolve. Remove 5 mL of the reconstituted solution from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride or 5% dextrose. The diluted solution may show visible translucent to white particulates of isavuconazonium (will be removed by in-line filtration). Use gentle mixing or roll bag to minimize the formation of particulates. Avoid unnecessary vibration or vigorous shaking of the solution and do not use a pneumatic transport system. Store intact vials at 2-8ºC. Reconstituted solution can be stored below 25ºC for a maximum of 1 hour prior to preparation of admixed solution. The admixed infusion solution can be stored at 20-25ºC for up to 6 hours or at 2-8ºC for up to 24 hours.[1,2]

Cost (AWP)
IV solution: 372mg $372/vial
PO capsules: 186mg $96 each

Pharmacoeconomic Analysis
An analysis[11] of hospital resource use during the SECURE trial did not find a statistically significant difference in overall median length of stay (LOS) between the isavuconazole (15 days) and voriconazole (16 days) arms. There was also no difference between readmission rates between treatment arms. It did find that median LOS was statistically significantly shorter for patients treated with isavuconazonium vs voriconazole among patients with moderate-to-severe renal impairment (9 days vs 19 days). Moderate-to-severe renal impairment was defined as eGFR-MDRD <60 mL/min/1.73 m^2. It should be noted that the SECURE trial did not enroll patients with CrCl <50 mL/min.[3]

	No or mild renal impairment		Moderate-to-severe renal impairment	
	Isavuconazonium (n=231)	Voriconazole (n=217)	Isavuconazonium (n=20)	Voriconazole (n=33)
Median eGFR-MDRD	104.2	109.4	52.0	47.6
Median LOS (days)			9.0	19.0

Utilization

	Jan-June 2016	July-Dec 2016	Jan-June 21, 2017
Unique Patients with Non-Formulary Orders for Isavuconazonium	1	5	3

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Reviewed by: Scott Bergman, Pharm.D., Trevor Van Schooneveld, MD
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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Isavuconazonium Sulfate (Cresemba®)
Drug manufacturer	Astellas Pharma US Inc.
Schedule of medication	N/A
Anticipated use per month, anticipated patient population	10-30 patients per year, immunocompromised patients including transplant and oncology.
Route of administration	IV and PO
Preparation	Reconstitute 1 vial of isavuconazonium with 5 mL sterile water. Shake gently to dissolve. Remove 5 mL of the reconstituted solution from the vial and add it to an infusion bag containing 250 mL of NS or D5W. The diluted solution may show visible translucent to white particulates of the drug (will be removed by in-line filtration). Use gentle mixing or roll bag to minimize the formation of particulates. Avoid unnecessary vibration or vigorous shaking of the solution.
Stability	0.9% sodium chloride and 5% dextrose are the only approved diluents for IV administration of isavuconazonium.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	• Store capsules at 20-25ºC in original blister packaging to protect from moisture. Excursions are permitted between 15-30ºC. • Store intact vials at 2-8ºC • Reconstituted solution can be stored below 25 ºC for a maximum of 1 hour prior to preparation of admixed solution. • Admixed infusion solution can be stored at 20-25ºC for up to 6 hours or at 2-8ºC for up to 24 hours
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☐ Yes ☒ N/A ☐
Can medication doses be sent to patient care units via pneumatic tube system? See IC24.	No ☒ Yes ☐ N/A ☐
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☐ Yes ☒ It has the potential to impact the DA function if the pharmaceutical subclass is active.
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any black box warning? For what?	No ☒ Yes ☐
Is this medication a hazardous agent?	No ☒ Yes ☐
Is the IV medication a vesicant or irritant?	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02.	No ☒ Yes ☐

Are there contraindications or significant warnings against medication use?	No ☐ Yes ☒
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Will the medication be restricted: MS68 Levels of Care • To a specific level of care (LOC)? • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	 No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☐ Yes ☒ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐