Rezafungin (REZZAYO™)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action[1,2]

- Rezafungin (RZF) is a novel semi-synthetic echinocandin with structural modifications to confer prolonged pharmacokinetic properties
- As with other echinocandins, RZF inhibits 1,3-β-D-glucan synthase enzyme complex present in fungal cell walls but not in mammalian cells. The enzyme inhibition prevents the formation of 1,3-β-D-glucan, an essential component of the cell wall of many fungi, including Candida species (spp.)

Indication(s) Under Review in This Document[1]

- RZF was approved by the FDA in March 2023 for patients ≥18 years of age who have limited or no alternative options for the treatment of candidemia and invasive candidiasis (IC)

Dosing & Dosage Form(s) Under Review[1]

- **Recommended dosing:** RZF is administered once weekly via intravenous infusion. Administer 400 mg as a loading dose, followed by a 200 mg weekly thereafter
  - RZF has not been studied beyond 4 weekly doses
- **Dosage form:** Available as RZF 200 mg solid powder in a single-dose vial for reconstitution

Clinical Evidence Summary

In-Vitro Considerations

- **Breakpoints**
  - The in-vitro activity of RZF against common *Candida* spp. is summarized in **Table 1**[3–5]
    - The MICs reported are considered tentative per Clinical Laboratory Standards Institute (CLSI) standards published in 2022[5]
    - Intermediate and resistant breakpoints will be reported once more data is available
  - Overall, the in vitro activity of RZF against *Candida* spp. was comparable to other approved echinocandins[4,5]

Table 1: CLSI breakpoints for RZF against *Candida* spp.[3–5]

Species	MIC Breakpoints/Interpretation, µg/mL		
	MIC_{50}	MIC_{90}	Susceptible (S)
C. albicans	0.03	0.06	≤ 0.25
*C. auris**	0.125	0.5	≤ 0.5
C. dubliniensis	0.06	0.12	≤ 0.12
C. glabrata	0.06	0.06	≤ 0.5
C. krusei	0.03	0.03	≤ 0.25
C. parapsilosis	1	2	≤ 2
C. tropicalis	0.03	0.06	≤ 0.25

- **Susceptibility Testing**
  - Susceptibility testing can be done via disk diffusion or Sensititre
- **Resistant *Candida* spp.**
  - Mutations in *fks* genes, which encode catalytic subunits of 1,3-β-D-glucan synthase, are known to confer echinocandin resistance in *Candida* spp. by altering cell-wall components.
  - In-vitro activities of the echinocandins were compared against *Candida* isolates with *fks* mutations[3,4,6]
    - Overall, RZF demonstrated similar in vitro activity to anidulafungin but better than caspofungin against isolates with *fks* mutations.

- The table below is adapted from a surveillance study by Pfaller and colleagues[7] and shows the percent resistance seen among these isolates and the echinocandins.

Table 2: Percent Resistance in Candida spp. with fks Alterations

	MICs above CLSI Breakpoint N, (%)			
Isolates with fks alterations	**Rezafungin**	**Anidulafungin**	**Caspofungin**	**Micafungin**
Candida tropicalis	5/7 (71%)	5/7 (71%)	5/7 (71%)	5/7 (71%)
Candida glabrata	18/25 (72%)	8/25 (32%)	14/25 (56%)	10/25 (40%)
Candida krusei	4/4 (100%)	4/4 (100%)	4/4 (100%)	4/4 (100%)

- The majority of tested candida isolates (within Table 2) that had fks mutations showed cross-resistance across all echinocandins.

- Activity of RZF against *Candida auris*
  - A study in 2020 by Helleberg and colleagues[8] evaluated the in vitro activity of RZF against a large sample of Candida isolates, including C. auris.
  - The in vitro activity of RZF against C. auris was similar to anidulafungin and micafungin and was more active than amphotericin B and fluconazole.
    - In vitro testing showed 111 of 122 (91%) clinical C. auris isolates were susceptible to RZF

Efficacy Considerations

- The STRIVE (phase 2) and ReSTORE (phase 3) trials were the major trials that demonstrated efficacy and safety of RZF for candidemia and/or IC.[9, 10]
  - Both studies were randomized, double-blind, active-controlled trials
  - Enrolled patients were assigned to either the RZF group or caspofungin (CAS) group
    - Patients in the CAS arm were eligible for fluconazole oral-stepdown after ≥3 days of IV CAS therapy. If switched, fluconazole was dosed as an 800 mg PO loading dose once, followed by 400 mg PO daily thereafter
    - Patients in the RZF arm who met qualifying criteria for oral step-down therapy after ≥ 3 days would receive oral placebo capsules in addition to the weekly RZF IV doses.
- The efficacy data from STRIVE and ReSTORE are summarized in **Table 3**

Table 3: Efficacy results for RZF from STRIVE and ReSTORE

Study	Design	Population	Results
ReSTORE[10] **Phase 3** (NCT03667690)	**Randomization stratified by** • Diagnosis (candidemia only or IC) • APACHE II score & ANC **Interventions** • RZF 400/200 mg QWk (2-4 doses total)* CAS (± PO fluconazole stepdown)† **Key Inclusion Criteria** Age ≥18 years with candidemia and/or IC **Key Exclusion Criteria** • Infection involving: ○ Septic arthritis in a prosthetic joint ○ Osteomyelitis ○ Endocarditis or myocarditis ○ CNS infection or endophthalmitis ○ Chronic disseminated candidiasis ○ Urinary tract candidiasis • Abnormal LFTs or severe hepatic impairment • History of severe ataxia, tremor, neuropathy, or multiple sclerosis	**Demographics (n=199)** • 62% male • Mean age, 61 years • 69% with candidemia only • 31% with IC • Mean APACHE II Score, 13 • 8% with ANC <500/µL ***Candida* spp.** • *C. albicans* (42%) • *C. glabrata* (26%) • *C. tropicalis* (20%) • *C. parapsilosis* (13%) **mITT§ (n=187)** • RZF (n=93) • CAS (n=94) • NI margin = 20%	*Outcomes listed as RZF vs. CAS* Primary outcomes: • **All-cause mortality at day 30** 24% vs. 21% (95% CI -9.7 to 14.4) • **Global cure‡ at day 14** 59% vs. 61% (95% CI -14.9 to 12.7)
STRIVE[9] **Phase 2** (NCT02734862)	**Randomization stratified by** • Diagnosis (candidemia only or IC) **Interventions** • RZF 400 mg QWk • RZF 400/200 mg QWk (2-4 doses total)* • CAS (± PO fluconazole stepdown)† **Key Inclusion Criteria** Age ≥18 years with candidemia and/or IC **Key Exclusion Criteria** • Infection involving: ○ Septic arthritis in a prosthetic joint ○ Osteomyelitis ○ Endocarditis or myocarditis ○ CNS infection or endophthalmitis • ANC ≤500/µL • Abnormal LFTs or severe hepatic impairment	**Demographics (n=207)** • 57% male • Mean age, 59 years • 79% with candidemia only • 21% with IC • Mean APACHE II Score, 14 ***Candida* spp.** • *C. albicans* (50%) • *C. glabrata* (20%) • *C. parapsilosis* (15%) • *C. tropicalis* (12%) **mITT§ (n=183)** • RZF 400 mg (n=76) • RZF 400/200 mg (n=46) • CAS (n=61)	Primary outcome: • **Overall cure** ** **at day 14** *RZF 400 mg* 61% *RZF 400/200 mg* 76% *CAS* 67% Secondary efficacy outcomes: • **Clinical response at day 14** *RZF 400 mg* 70% *RZF 400/200 mg* 80% *CAS* 71% • **All-cause mortality at day 30** *RZF 400 mg* 16% *RZF 400/200 mg* 4% *CAS* 13%

ANC absolute neutrophil count, ALT alanine aminotransferase, AST aspartate aminotransferase, *APACHE* modified Acute Physiology and Chronic Health Evaluation, *CAS* caspofungin, *CI* confidence interval, *CNS* central nervous system, *EOT* end of therapy, *IC* invasive candidiasis, *IV* intravenous, *LFT* liver function test, *mITT* modified intention to treat, *RZF* rezafungin, *QWk* once weekly

Efficacy Summary:

- The FDA Division of Anti-infectives recommended a 10% non-inferiority margin for 30-day all-cause mortality to obtain an indication for RZF without a limited use statement. A wider non-inferiority margin of 20% would be considered for a limited use indication[6]
- Currently, only one Phase 3 trial, ReSTORE, was conducted for RZF based on 20% non-inferiority margin[6,10]

* RZF was given as a single 400 mg IV loading dose, followed by 200 mg IV weekly, for a total of 2 to 4 doses

† CAS was given as a single 70 mg IV loading dose, followed by 50 mg IV daily treatment for a total of 2 to 4 weeks. For oral-stepdown therapy, fluconazole was given as a 800 mg PO loading dose once, followed by 400 mg PO daily thereafter

‡ Global cure was defined as clinical cure as assessed by the investigator, radiological cure for qualifying IC subjects at baseline, and mycological eradication

§ All patients who received ≥1 dose of RZF who had documented *Candida* infection at baseline

** Overall cure was defined as resolution of systemic signs attributable to candidemia and/or IC and mycological eradication

- The Phase 2 trial, STRIVE, was deemed inadequately controlled for its efficacy outcomes to be pooled with ReSTORE
- In ReSTORE, the all-cause mortality outcome resulted in an upper limit of the 95% CI of <20% but >10% which led to RZF approval with a limited use indication for candidiasis or IC

Safety Considerations

Safety Results from Clinical Trials:

Table 4: Pooled safety results from Phase 2 and 3 clinical trials

Study	Results	Comments
STRIVE & ReSTORE (ISS data)[1,6] **(Refer to Table 3 for information on study design)**	*Outcomes listed as RZF 400/200 mg (n=151) vs. CAS (n=166)* • **Any TEAE:** 91% vs. 83% **(95% CI 1 to 16)** • **RZA TEAE (≥5%) occurring at a greater rate than CAS**: Hypokalemia (15%), pyrexia (12%) • **Other Common RZA TEAE (≥5%)**: Diarrhea (11%), anemia (10%), vomiting (9%), nausea (9%), hypomagnesemia (8%), pneumonia (8%), hypophosphatemia (5%) • **Most reported TEAE with CAS (≥5%)** Hypokalemia (10%), hypophosphatemia (8%), pyrexia (7%) • **Serious TEAE:** 55% vs. 49% • **Serious TEAEs with fatal outcome:** 23% vs. 24% • **TEAE leading to drug discontinuation:** 9% vs. 9%	• Any TEAE was observed at slightly higher frequencies in the RZF group than CAS group **(RD 8%, 95% CI 1 to 16)** • Tremor occurred in four cases in the RZF group and none in the CAS group **(RD 2.6%, 95% CI 0.1% to 5%)** • Serious TEAE or TEAE leading to drug discontinuation was similar in RZF and CAS groups

CAS caspofungin, *CI* confidence interval, *GI* gastrointestinal, *ISS* Integrated Summary of Safety, *MAD* Multiple-ascending doses, *RD* risk difference, *RZA* rezafungin, *TEAE* treatment-emergent adverse events, *UTI* urinary tract infection, *QWk* weekly, *SAD* Single-ascending doses

- The pooled safety outcomes from STRIVE (Phase 2) and ReSTORE (Phase 3) were presented in the Integrated Summary of Safety (ISS) submitted to the FDA[6]
  - The pooled ISS population consisted of 151 subjects with candidiasis or IC who were exposed to therapeutic doses of RZF for 2 to 4 weeks[9, 10]
- Safety data were reported as treatment-emergent adverse events (TEAE)[9, 10]
  - TEAE was defined as an adverse event that occurred during or after study drug administration based on clinical chemistry, hematology and urine analysis laboratory test, vital sign, physical exams and electrocardiogram (ECG) abnormalities
- The safety data are summarized in **Table 4**
- **Other warnings / precautions**:[1]
  - **Infusion-related Reactions**
    - i.e., flushing, sensation of warmth, urticaria, nausea, or chest tightness
    - If reactions occur, slow or pause RZF infusion
  - **Photosensitivity**
    - Advise patients to use protection from sun exposure and other sources of UV radiation
      - Potential for phototoxicity were only reported in in-vitro and a rat study[6]
  - **Hepatic Adverse Reactions**
    - Monitor patients who develop abnormal liver tests and evaluate patients for their risk/benefit of continuing RZF therapy
- **Adverse reactions**[1]
  - **Less Common Adverse events (incidence <5%)**
    - **Neurotoxicity**[10]
      - **Tremors:**
        - Reported in 4/151 (2.6%) of RZF-treated patients and none of the CAS-treated patients from STRIVE and ReSTORE

        - All tremors developed in the second or third week after initiation of RZF treatment and resolved within a month of onset
    - Tremors were also observed in studies with non-human primates treated with RZF
- **Axonal degeneration:**
    - Axonal degeneration of nerves were reported in animal studies at doses ≥30 mg/kg in non-human primates that were dosed every 3 days for 3 months
    - Some of these effects were not reversible up to 13 weeks post-discontinuation of RZF

Other Considerations[8]

- **Pharmacokinetics**
    - Compared to other echinocandins, RZF has prolonged duration of activity[1,2]
    - Similar to other agents in its class, RZF has low risk for clinically significant drug interactions
    - The predicted pharmacokinetic properties of RZF are summarized in **Table 5**

Table 5: Pharmacokinetics of RZF 400 mg loading dose, followed by 200 mg weekly

Parameter	Value (mean ± SD)	
Exposure	**Day 1**	**Day 15**
C_{max} (mcg/mL)	19 ± 6	12 ± 4
$AUC_{0\text{-}168}$ (mcg*h/mL)	827 ± 252	667 ± 224
C_{min} (mcg/mL)	2 ± 1	2 ± 1
Distribution		
Protein binding	Mean 87% to 94% in patients; 96% to >98% in healthy adults	
Volume of distribution (Vd)	67 ± 28 L	
Metabolism	No clinically relevant hepatic metabolism (minimal metabolism via CYP450 pathways)	
Elimination		
Terminal half-life ($t_{1/2}$)†	**152 ± 29 hours**	
Excretion		
% feces	74% (major route), primarily as unchanged drug	
% urine	26%, primarily as inactive metabolites	

C_{max} maximum plasma concentration, C_{min} trough plasma concentration $AUC_{0\text{–}168h}$ area under the plasma concentration-time curve from time zero to 168 hours post dose
†Half-lives of other echinocandins: caspofungin (40-50 hours), micafungin (11-21 hours), anidulafungin (40-50 hours), ibrexafungerp (20 hours)

- **Special Populations**
    - **Pregnancy**
        - No clinical data on the use of RZF during pregnancy
        - In animal studies, no adverse embryofetal outcomes were observed in rats or rabbits
    - **Lactation**
        - No data on the presence of RZF or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production
        - In animal studies, RZF was present in rat milk
    - **Males of Reproductive Potential**
        - Based on rat studies, RZF could lead to decreased sperm motility, decreased sperm numbers, and increased incidence of sperm with abnormal morphology
    - **Geriatric Use**
        - From STRIVE and ReSTORE trials, 64 (42%) patients were ≥65 years of age and 26 (17%) were ≥75 years of age. These clinical trials did not include sufficient older adults to determine if they would respond to RZF differently compared to younger patients
- **Preparation**[1] *(refer to package insert for detailed preparation instructions)*
    - Dilute in 250 mL of 0.9% Sodium Chloride Injection, 0.45% Sodium Chloride Injection, or 5% Dextrose injection
        - Total infusion volume of 250 mL for either 400 mg or 200 mg doses

- **Storage**[1]
  - **Vials:** Store at controlled room temperature between 20°C and 25°C
  - **Intravenous infusion solution:** Stable for 48 hours when stored between 5°C and 25°C

Other Therapeutic Options

- Alternative treatments for candidiasis and/or invasive candidiasis are listed in **Table 6**

Table 6: Treatment Alternatives

Drug		Formulary Status[14]	Advantages	Disadvantages and Additional Considerations
Rezafungin		TBD	• FDA approved for candidiasis and/or IC who have limited or no alternative options [1] • Once-weekly dosing • Similar in-vitro data to other echinocandins • No dose adjustment required for renal or hepatic insufficiency • Low DDI risk potential	• Available IV only • Limited clinical efficacy and safety data • Patients with endocarditis or osteomyelitis were excluded from available studies • Has not been studied beyond 4 weekly doses • Poor penetration into CNS, eye, and urine
Caspofungin, Anidulafungin		NF	• Clinical activity against *Candida* isolates resistant to azole antifungals	• Once-daily dosing • Caspofungin requires dose adjustment for hepatic impairment • Higher doses may be required in patients with obesity • Caspofungin is a poor CYP450 substrate, predisposing it to more potential DDIs than rezafungin • Poor penetration into CNS, eye, and urine
Micafungin		F		
Fluconazole		F	• Available IV and PO • Can be used for stepdown PO therapy from echinocandins • Considered for patients who are hemodynamically stable, no recent azole exposure, and at not at high-risk for resistant *Candida* spp. • Once-daily dosing	• Drug-drug interactions • Risk of QT prolongation • High urinary concentrations unlike other antifungal alternatives
Voriconazole, Posaconazole		PA-F	• Available IV and PO • Can be used for stepdown PO therapy from echinocandins	• Twice-daily dosing • Drug-drug interactions • Risk of QT prolongation • Nonlinear pharmacokinetics with large interpatient variability • Affected by CYP2C19 polymorphism • Consider therapeutic drug monitoring
Itraconazole		F	• Available as oral capsule and solution	• Variable absorption and bioavailability • Capsules require food and an acidic gastric pH for solubilization • Oral solution should be taken on empty stomach
Isavuconazole		NF	• Available IV and PO • Favorable safety profile without risk of QT prolongation • Lower DDI potential than other azoles	
Amphotericin B and lipid formulations		F	• Less resistance development	• Available IV • Several formulations with varying dosing regimens • High rate of infusion-related reactions, requiring premedication and hydration • Higher risk of ADEs including nephrotoxicity and electrolyte abnormalities

ADR adverse drug reactions, *AKI* acute kidney injury, *CNS* central nervous system, *F* formulary *F-R* formulary restricted, *IC* invasive candidiasis, *IDSA* Infectious Diseases Society of America, *IV* intravenous, *NF* non-formulary, *PA-F* Local Prior Authorization Required, *PO* oral, *TBD* to-be-determined

Projected Place in Therapy

- RZF was approved for patients ≥18 years of age who have limited or no alternative options for the treatment of candidemia and invasive candidiasis (IC)
    - The limited use indication was supported by one Phase 3 trial, ReSTORE, which met the 20% non-inferiority margin when RZF was compared to CAS for 30-day all-cause mortality
    - RZF did not meet the 10% non-inferiority margin to be considered for approval without the limited use indication
- RZF is distinct from other approved echinocandins for its long duration of action which allows once-weekly dosing
- Compared to other echinocandins, RZF had:
    - Similar in-vitro activity against common *Candida* spp.
    - Similar cross-resistance for more resistant *Candida* spp., including *C. auris*
    - Similar efficacy outcomes for mortality, cure, and clinical response
    - Slightly higher incidence of TEAE than CAS group based on the Integrated Summary of Safety
    - A new adverse event of tremor reported, although appears to be uncommon
- RZF can be an option for patients who require prolonged outpatient treatment of candidemia/IC who are unable to be transitioned to oral azole stepdown therapy and who have challenges associated with OPAT (e.g., inability to place PICC line)
- Currently, the FDA has limited the indication to a maximum of 4 doses. Reasons for this include:
    - Limited efficacy data for complicated infections such as osteomyelitis or endocarditis
    - Small safety population with a signal towards tremor as an adverse event not seen with other echinocandins, supported by animal studies that identified tremor and axonal degeneration with prolonged use in primates. In some cases, this was not reversible.
    - The FDA is expected to get data on prolonged use from an ongoing study as prophylaxis for invasive fungal infections after hematopoietic stem cell transplant.
- Clinical studies evaluating the use of RZF for other indications are currently in progress, including:
    - Treatment of pneumocystis pneumonia in HIV adults
    - Prevention of invasive fungal diseases in adults undergoing allogeneic blood and marrow transplantation

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