CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217417Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217417
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Reviewer Name(s)	Celeste Karpow, PharmD, MPH
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Review Completion Date	March 21, 2023
Subject	Evaluation of Need for a REMS
Established Name	rezafungin
Trade Name	Rezzayo
Name of Applicant	Cidara Therapeutics, Inc
Therapeutic Class	echinocandin antifungal
Formulation(s)	(b) (4) cake or powder for reconstitution
Dosing Regimen	once weekly intravenous (IV) infusion, with an initial 400 mg loading dose, followed by a 200 mg dose once weekly thereafter

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rezzayo (rezafungin) is necessary to ensure the benefits outweigh its risks. Cidara Therapeutics, Inc submitted a New Drug Application (NDA) 217417 for rezafungin with the proposed indication for the treatment of candidemia and invasive candidiasis in adult patients. The risks associated with rezafungin include infusion-related reactions, photosensitivity, and hepatic adverse reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Anti-infectives (DAI) determined a REMS is not needed to ensure the benefits of rezafungin outweigh its risks. The efficacy of rezafungin was supported by the phase 3 noninferiority trial, in which the Day 30 All-Cause Mortality (ACM) rate was 23.7% in the rezafungin arm and 21.3% in the comparator arm.[1] The clinical reviewer concluded that the trial provided evidence to support an indication in patients 18 years of age or older who have limited options for the treatment of candidemia and invasive candidiasis with a limited use statement that rezafungin has not been studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida spp*.[2] The serious risks associated with rezafungin, infusion-related reactions, photosensitivity, and hepatic adverse reactions, will be addressed in the warnings and precautions section of the label.[2] Overall, while the size of the safety database is modest, the safety findings are consistent with the echinocandin class of drugs in this patient population.[1] The likely prescribers include infectious disease specialists, oncologists, or transplant specialists, who are expected to be familiar with the management of the risks observed with rezafungin.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the 505(b)(1), new molecular entity (NME) Rezzayo (rezafungin) is necessary to ensure the benefits outweigh its risks. Cidara Therapeutics, Inc submitted a New Drug Application (NDA) 217417 for rezafungin with the proposed indication for the treatment of candidemia and invasive candidiasis in adult patients. This application is under review in the Division of Anti-Infectives (DAI). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rezzayo (rezafungin), a 505(b)(1)[a], is a echinocandin antifungal proposed for treatment of candidemia and invasive candidiasis in adult patients.[2] Rezafungin is a semi-synthetic echinocandin which inhibits 1,3-β-D-glucan synthase enzyme complex present in fungal cell walls but not in mammalian cells.[2] This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall of

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

many fungi, including *Candida species* (*spp.*). Inhibition of 1,3-β-D-glucan synthesis results in concentration-dependent fungicidal activity against *Candida spp*.[2]

Rezafungin is proposed to be supplied as a 200 mg single-dose vial containing white to pale yellow (b) (4) cake or powder for dilution.[2] The proposed dosing regimen is once weekly by intravenous (IV) infusion over 1 hour, with an initial 400 mg loading dose, followed by a 200 mg dose once weekly thereafter for a maximum of 4 weekly doses.[b,2] The mean half-life of rezafungin is 127 hours following a 200 mg dose and 133 hours following a 400 mg dose which allows for once weekly dosing.[3] Rezafungin is not currently approved in any jurisdiction, and has been granted orphan drug and fast track designations.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217417 relevant to this review:

- 02/08/2016: Rezafungin was granted orphan drug designation for the treatment of candidemia and IC caused by susceptible *Candida spp.*[1,4]
- 06/27/2017: Fast track designation granted for IND 124401
- 07/22/2022: The Applicant submitted NDA 217417 proposed for treatment of candidemia and invasive candidiasis in adult patients
- 11/03/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. A REMS was not discussed.
- 01/24/2023: Antimicrobial Drugs Advisory Committee (AC) Meeting was convened to discuss the overall benefit-risk assessment for the use of rezafungin for treatment of candidemia/invasive candidiasis in adults with limited or no alternative treatment options. The AC voted 14 in favor and 1 against approval. A REMS proposal was not discussed.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Invasive candidiasis and candidemia are serious infections caused by *Candida spp* often affecting immunocompromised or critically ill patients. *Candida spp* is a fungus that is considered to be part of the normal microbiota of the gastrointestinal and genitourinary tracts of humans however it does have the propensity to invade and cause disease if there is an imbalance in the organisms that usually exist.[5] Candidemia is a *Candida spp* infection of the blood. Invasive candidiasis is caused by *Candida spp* species that colonize the gut and invade other parts of the body either through translocation or anastomotic leakage after laparotomy and cause either localized, deep-seated infection (e.g., peritonitis), or

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

candidemia.[6] Alternatively, *Candida spp* biofilms might form on catheters which can be subsequently released from the biofilm causing candidemia.[6] Once candidemia is formed, it may disseminate throughout the body to the heart, brain, lung, liver, spleen, kidneys, bone, or eye.[6] Candidemia may manifest from minimal fever to a sepsis syndrome resembling a severe bacterial infection.[c,7]

Invasive candidiasis is the 4th most common health care-associated infection and 2nd most common bloodstream infection in 2015.[8] Candidemia is among the most common bloodstream infections in the United States.[8] CDC's Emerging Infections Program estimated that there were 23,000 candidemia cases in the United States in 2017 based off the 1,226 candidemia cases identified in through candidemia surveillance in California, Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, Tennessee.[d,9] The incidence was 7/100,000 persons with greater rates in adults greater than or equal to 65 years (20.3/100,000), males (8.0/100,000), and people of Black race (12.6/100,000).[9] While candidemia is the most common form of invasive candidiasis, cases of invasive candidiasis might be twice as high as the estimates for candidemia.[10]

Invasive candidiasis and candidemia are associated with significant morbidity and mortality and often result in prolonged hospital stays.[4,10,11] CDC's Emerging Infections Program estimated that there were 3,000 deaths in the United States in 2017.[9] The mortality among patients with invasive candidiasis is reported as high as 40% even when treated with antifungal therapy.[e,6] Due to long hospital stays, invasive *Candida spp* infections are costly for patients and healthcare facilities.[10] CDC surveillance data indicate that in-hospital all-cause mortality (mortality) among people with candidemia is approximately 25%.[10]

3.2. Description of Current Treatment Options

There are four systemic antifungals that have demonstrated clinical effectiveness for the treatment of candidemia and invasive candidiasis.[4] These include the echinocandins, azoles, polyenes (amphotericin B formulations), and a single member of the antimetabolite class (flucytosine).[4] The Infectious Diseases Society of America recommends echinocandins as first-line therapy for the treatment of candidemia and invasive candidiasis except in instances involving the central nervous system, the eyes, or the urinary tract.[12,13] The echinocandins currently approved by the FDA include anidulafungin, caspofungin, and micafungin which are all only available as intravenous (IV) formulations.[14] Therefore, transition to oral azole antifungals is recommended in patients with azole-susceptible isolates once they are clinically stable.[4] Patients who are intolerant of azoles or otherwise are unable to take azoles due to drug

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): *The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug*.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved*.

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

interactions or resistance must continue daily IV antifungal therapy for at least two weeks after documented clearance of *Candida spp* from the blood in the case of candidemia or following adequate source control and clinical response in invasive candidiasis. Amphotericin B is considered a reasonable alternative for patients who have drug intolerances or are infected with drug-resistant pathogens, but its use as a first-line therapy is limited due to nephrotoxicity.[4,12,13] Flucytosine is usually only used in combination antifungal therapy due to a low barrier to resistance and may be a useful adjunctive therapy for refractory cases.[4,12,13]

The clinical safety profiles are similar among the FDA approved echinocandin antifungals.[4] They all include warnings for hypersensitivity reactions and hepatic adverse reactions in the Warnings and Precautions section of the labeling.[4] The micafungin labeling also includes warnings for hematologic effects, renal effects, and infusion and injection site reactions.[4] None of the echinocandin labeling include warnings related to neurotoxicity and the only nervous system adverse reaction reported in the clinical trials was headache.[4] Tremor was reported as an adverse reaction based on an open-label noncomparative clinical trial of anidulafungin in pediatric patients (n=68) and in the pooled safety experience from 34 studies of caspofungin in adult and pediatric patients or volunteers (n=1951) reported in the labeling.[4]

Products used to treat candidemia and invasive candidiasis are summarized in Table 2 in the Appendix.

4. Benefit Assessment

The phase 3 noninferiority trial, ReSTORE (NCT03667690) supporting this application consisted of a multicenter, randomized, double-blind study in which patients were randomized to receive either rezafungin or active control, caspofungin.[2] One hundred ninety nine patients were enrolled in which 100 patients were in the rezafungin arm and 99 patients were in the caspofungin arm.[4] One hundred eighty seven patients were included in the intent to treat population. Subjects in the rezafungin arm received a single 400 mg loading dose on Day 1 of Week 1, followed by 200 mg once weekly, for a total of two to four doses.[2] Patients in the caspofungin arm received treatment for a total of ≥14 days, beginning with a single 70 mg IV loading dose on Day 1 followed by caspofungin 50 mg IV once daily with the option to continue treatment for up to 28 days.[2] After ≥3 days (or the minimum duration of IV therapy according to the site's national/regional/local guidelines, whichever was greater) of caspofungin treatment, patients who met the stepdown therapy eligibility criteria could be switched to oral fluconazole at a dose of 6 mg/kg administered once daily (rounded to the nearest 200 mg increment) with a maximum daily dose of 800 mg.[2] The total IV plus oral treatment duration was 14 to 28 days.[4] To maintain the blind, subjects randomized to rezafungin received daily saline placebo to match for caspofungin IV, or received daily placebo for oral stepdown therapy.

The primary efficacy endpoint was ACM measured as survival status at Day 30 and assessed using a 20% noninferiority (NI) margin.[4] Rezafungin dosed weekly met the primary endpoint of demonstrating noninferiority to caspofungin on the primary endpoint.[3] The Day 30 ACM rate was 23.7% (22/93) in the rezafungin arm, while the caspofungin arm had an ACM rate of 21.3% (20/94); the difference (95% CI) was 2.4% (-9.7%, 14.4%).[3]

The clinical reviewer concluded rezafungin dosed weekly was noninferior to a regimen of daily caspofungin with optional stepdown to oral azole therapy within the prespecified 20% noninferiority margin for a Day 30 ACM endpoint.[3] In addition, the clinical reviewer concluded the trial provided evidence to support an indication in patients 18 years of age or older who have limited options for the treatment of candidemia and invasive candidiasis with a limited use statement that rezafungin has not been studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida*[2,3] In addition, the clinical reviewer concluded the trial provided evidence to support an indication in patients 18 years of age or older who have limited options for the treatment of candidemia and invasive candidiasis with a limited use statement that rezafungin has not been studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida spp*. The limited use statement was added since patients with endocarditis, osteomyelitis, and meningitis due to *Candida spp* were excluded from the clinical trials.[2]

Patients unable to be transitioned to oral azole stepdown therapy and those with contraindications to central line placement to complete therapy for candidemia or invasive candidiasis may be most likely to benefit from rezafungin due to the once weekly dosing regimen.[f,3]

5. Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for rezafungin. The safety of rezafungin was evaluated in 76 patients in the Phase 1 studies and 232 patients with candidemia and invasive candidiasis in Phase 2 and 3 clinical trials.[2] A total of 151 patients received an initial 400 mg loading dose followed by a 200 mg dose once weekly for a maximum duration of 4 weekly doses (including the loading dose) in Phase 2 and 3 clinical trials.[2]

The most common adverse reactions (incidence ≥ 5%) are diarrhea, vomiting, nausea, abdominal pain, constipation, hypokalemia, hypomagnesemia, hypophosphatemia, pyrexia, and anemia.[2] Adverse events were similar in the rezafungin arm compared to the caspofungin arm in the pooled safety analysis.[2]

Table 1: Summary of Adverse Events in the Pooled Safety Analysis[4]

	Rezafungin 400 mg/ 200 mg weekly n = 151 (%)	**Caspofungin 70 mg/ 50 mg IV daily n = 151 (%)**
Any adverse event (AE)	138 (91.4%)	138 (83.1%)
Serious adverse events (SAE)	83 (55%)	81 (48.8%)
SAEs with a fatal outcome	35 (23.2%)	40 (24.1%)
AE leading to permanent discontinuation	14 (9.3%)	15 (9%)

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): *The expected benefit of the drug with respect to such disease or condition*.

AE leading to dose modification of study drug	3 (2%)	4 (2.4%)
AE leading to interruption of study drug	3 (2%)	4 (2.4%)

A neurotoxicity safety signal (tremor and axonal degeneration) was identified in dosing studies of rezafungin in nonhuman primates (≥ 6-fold the clinical dose) and rats (2-4-fold the clinical dose). A higher incidence of tremors (4 in the rezafungin arm compared to 0 in the caspofungin arm) was observed in the phase 2 and 3 trials, but all episodes were mild and reversible. This will be described in the adverse reactions section of labeling.

Due to the indication and underlying severe illness in the study population, SAEs were common in the Phase 2 and 3 clinical trials. The most commonly reported SAEs in the rezafungin arm were septic shock, multiple organ dysfunction syndrome, sepsis, pneumonia, and bacteremia. There was no difference in mortality in the rezafungin arm compared to the caspofungin arm.[1] The most common etiology for death in the rezafungin arm was septic shock, multiple organ dysfunction syndrome, or sepsis.[1] In addition, no death could reasonably be attributed to rezafungin, in part due to the presence of significant comorbidities, coinfections, and palliative care in the study patient population.[1]

The adverse events of special interest include infusion reactions, photosensitivity, and hepatic adverse events. These adverse events will be described in the warnings and precautions and are summarized below.[1]

5.1. Infusion-Related Reactions

Infusion-related reactions occurred in <5% of patients receiving rezafungin.[2] Infusion-related reactions are known adverse reactions of the echinocandin drug class.[4] Recommendations in labeling for management of infusion-related reactions are to slow or pause the infusion.[2] If the infusion is paused due to infusion-related reactions, it may be restarted at a lower rate.[2]

5.2. Photosensitivity

Nonclinical and clinical studies indicate that rezafungin has mild phototoxic potential.[4] Recommendations in labeling for management of photosensitivity are to advise patients to use protection from sun exposure and other sources of UV radiation during treatment.[2]

5.3. Hepatic Adverse Reactions

Abnormalities in liver tests were observed in the clinical trial patients treated with rezafungin.[2] Clinically significant hepatic abnormalities occurred in some patients with serious underlying medical conditions who were receiving multiple concomitant medications with rezafungin.[2] Recommendations in labeling for management of hepatic adverse reactions are to monitor patients who develop abnormal liver tests during rezafungin therapy for evidence of worsening hepatic tests and evaluate patients for their risk/benefit of continuing rezafungin therapy.[2]

6. Expected Postmarket Use

If approved, rezafungin will primarily be prescribed by specialists, such as infectious disease specialists, oncologists, or transplant specialists, who are expected to be familiar with the management of antifungal toxicities such as infusion-related reactions, photosensitivity, and hepatic adverse reactions. Due to the IV route of administration of this drug, we expect this product will be administered in inpatient settings and outpatient settings such as infusion centers or under a specialized outpatient IV medication protocol.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for rezafungin beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of rezafungin on the basis of the efficacy and safety information currently available.

Both candidemia and invasive candidiasis are serious infections that can disseminate throughout the body and result in a sepsis syndrome.[6,7] Untreated, candidemia and invasive candidiasis result in prolonged hospital stays and are a particular risk to immunocompromised or critically ill patients.[10,11] The mortality among patients with invasive candidiasis is reported as high as 40% even when treated with antifungal therapy.[g,6] CDC's Emerging Infections Program estimated that there were 3,000 deaths in the United States in 2017.[9] While candidemia is the most common form of invasive candidiasis, cases of invasive candidiasis might be twice as high as the estimates for candidemia.[10]

Rezafungin is an echinocandin antifungal and provides a once weekly dosing option proposed for treatment of candidemia and invasive candidiasis in adult patients.[2] Rezafungin was developed under a flexible development program given the unmet needs for treatment of candidemia and invasive candidiasis. The efficacy of rezafungin was supported by the phase 3 noninferiority trial, ReSTORE in which the primary efficacy endpoint was Day 30 ACM assessed using a 20% noninferiority margin.[1] It has a similar spectrum of activity against the *Candida spp*. that are common causative pathogens of candidemia and invasive candidiasis. The clinical reviewer concluded that the phase 3 noninferiority trial provided evidence to support an indication in patients 18 years of age or older who have limited options for the treatment of candidemia and invasive candidiasis. The labeling will include a limited use statement that rezafungin has not been studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida spp*.[2] The limited use statement was added since patients with endocarditis, osteomyelitis, and meningitis due to *Candida spp.* were excluded from the clinical trials.[2]

[g] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

The serious risks associated with rezafungin include infusion-related reactions, photosensitivity, and hepatic adverse reactions.[2] These risks will be addressed in the warnings and precautions section of the label.[2] Overall, while the size of the safety database is modest, the safety findings are consistent with the echinocandin class in this patient population.[1] There are currently no boxed warnings for any risk in the prescribing information for rezafungin. The labeling will note that the safety of rezafungin has not been established beyond 4 weekly doses. The identified risks will be further evaluated in an ongoing clinical study assessing a longer duration of rezafungin dosing and through postmarketing pharmacovigilance. The likely prescribers include infectious disease specialists, oncologists, or transplant specialists, who are expected to be familiar with the management of the risks observed with rezafungin.

An Antimicrobial Drugs Advisory Committee (AC) Meeting was held on January 24, 2023 to discuss the overall benefit-risk assessment for the use of rezafungin for treatment of candidemia and invasive candidiasis in adults with limited or no alternative treatment options.[4] Specifically, FDA asked the AC to comment on the context of use for rezafungin, or the clinical scenario(s) in which rezafungin fulfills an unmet need. In addition, if the AC found overall benefit-risk assessment to not be favorable, then FDA asked the AC to comment on what additional information would be needed for the benefit-risk assessment to be favorable for the use of rezafungin.[4] The AC voted 14 in favor and 1 against approval of rezafungin in a limited use population. A REMS proposal was not discussed.

Based on the efficacy and risks associated with rezafungin for the treatment of candidemia and invasive candidiasis, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks; all risks can be adequately communicated with prescribing information.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable for the treatment of adult patients who have limited or no alternative options for the treatment of candidemia and invasive candidiasis. Therefore, a REMS is not necessary for rezafungin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. Table 2: Products used to treat candidemia and invasive candidiasis

Product Trade Name (Generic) Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Amphotericin B[15] 04/29/1992	Empirical therapy for presumed fungal infection in febrile, neutropenic patients; Treatment of Cryptococcal Meningitis in HIV infected patients; Treatment of patients with *Aspergillus species*, *Candida species* and/or *Cryptococcus species* infections (see above for the treatment of Cryptococcal Meningitis) refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate; Treatment of visceral leishmaniasis. In immunocompromised patients with visceral leishmaniasis treated with amphotericin B liposome for injection, relapse rates were high following initial clearance of parasites	0.5–0.7 mg/kg daily, but dosages as high as 1mg/kg daily should be considered for invasive *Candida spp* infections caused by less susceptible species, such as *C. glabrata* and *C. krusei*. The typical dosage for lipid formulation AmB is 3–5 mg/kg daily when used for invasive candidiasis.	Renal insufficiency	Boxed Warning, Warnings and Precautions

Eraxis (anidulafungin)[16] 02/17/2006	for the treatment of candidemia and the following *Candida* infections: intra-abdominal abscess and peritonitis in adults and pediatric patients 1 month of age and older	single 200 mg loading dose of ERAXIS on Day 1, followed by a 100 mg once daily maintenance dose thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.	Hepatic Adverse Reactions; Anaphylactic and Hypersensitivity Reactions; Risk of Neonatal Toxicity Associated with Polysorbates; Risk in Patients with Hereditary Fructose Intolerance (HFI)	Warnings and Precautions
Cancidas (caspofungin)[17] 01/26/2001	empirical therapy for presumed fungal infections in febrile, neutropenic adult and pediatric patients (3 months of age and older); for the treatment of candidemia and the following *Candida spp* infections: intra-abdominal abscesses, peritonitis, and pleural space infections in adult and pediatric patients (3 months of age and older); Caspofungin acetate for injection has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida spp*; for the treatment of esophageal candidiasis in adult and pediatric patients (3 months of age and older); for the treatment of invasive aspergillosis in adult and pediatric patients (3 months of age and older) who are refractory to or	Administer a single 70 mg loading dose on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be dictated by the patient's clinical and microbiological response. In general, continue antifungal therapy for at least 14 days after the last positive culture. Patients with neutropenia who remain persistently neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.	Hypersensitivity; Hepatic Effects; Elevated Liver Enzymes During Concomitant Use with Cyclosporine	Warnings and Precautions

	intolerant of other therapies .			
Mycamine (micafungin)[18] 03/16/2005	Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older; Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older; Prophylaxis of *Candida spp* Infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation	Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses: 100 mg once daily for a mean duration of 15 days; Treatment of Esophageal Candidiasis: 150 mg once daily for a mean duration of 15 days; Prophylaxis of *Candida spp* Infections in HSCT Recipients: 50 mg once daily for a mean duration of 19 days	Hypersensitivity Reactions; Hematological Effects; Hepatic Effects; Renal Effects; Infusion and Injection Site Reactions	Warnings and Precautions

Diflucan (fluconazole)[19] 01/29/1990	Vaginal candidiasis; Oropharyngeal and esophageal candidiasis; Cryptococcal meningitis; prophylaxis to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy	Average loading dose of 800 mg (12 mg/kg), followed by an average daily dose of 400 mg (6 mg/kg). Systemic *Candida spp* infections: optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used; Urinary tract infections and peritonitis: daily doses of 50 to 200 mg have been used in open, noncomparative studies of small numbers of patients; Cryptococcal meningitis: 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative	Hepatic injury; anaphylaxis, dermatologic, potential for fetal harm; Cytochrome P450 inhibitor	Warnings and Precautions

Vfend (voriconazole)[20] 05/24/2002	Invasive Aspergillosis; Candidemia in Non-neutropenic Patients and Other Deep Tissue *Candida spp* Infections; Esophageal Candidiasis; Scedosporiosis and Fusariosis.	Therapy must be initiated with the specified loading dose regimen of intravenous VFEND on Day 1 followed by the recommended maintenance dose (RMD) regimen. Intravenous treatment should be continued for at least 7 days. Once the patient has clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of VFEND may be utilized. The recommended oral maintenance dose of 200 mg achieves a voriconazole exposure similar to 3 mg/kg intravenously; a 300 mg oral dose achieves an exposure similar to 4 mg/kg intravenously. Loading dose: 6 mg/kg every 12 hours for the first 24 hours; Maintenance dose: 4 mg/kg every 12 hours which can be switched to 200 mg orally every 12 hours based on clinical response.	Hepatic Toxicity; Arrhythmias and QT Prolongation; Infusion Related Reactions; Visual Disturbances; Severe Cutaneous Adverse Reactions; Photosensitivity; Renal Toxicity; Adrenal Dysfunction; Embryo-Fetal Toxicity; Electrolyte disturbances; Pancreatitis; Skeletal Adverse Reactions; Clinically Significant Drug Interactions	Warnings and Precautions

Noxafil (posaconazole)[21] 09/15/2006	treatment of invasive aspergillosis in adults and pediatric patients 13 years of age and older; prophylaxis of invasive Aspergillus and *Candida spp* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy; treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older	Dosing depends on formulation. Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day, starting on the second day.	Calcineurin-Inhibitor Toxicity; Arrhythmias and QT Prolongation; Electrolyte Disturbances; Hepatic Toxicity; Renal Impairment; Midazolam Toxicity; Vincristine Toxicity; Risk in Patients with Hereditary Fructose Intolerance (HFI); Breakthrough Fungal Infections; Venetoclax Toxicity	Warnings and Precautions
Sporanox (itraconazole)[22] 09/11/1992	for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: Blastomycosis, pulmonary and extrapulmonary; Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are	200 mg (20 mL) once or twice daily by mouth for 1 to 2 weeks	Congestive Heart Failure, Cardiac Effects and Drug Interactions; Hepatic Effects; Cardiac Dysrhythmias; Cardiac Disease; Interaction potential	Boxed Warning, Warnings and Precautions

	refractory to amphotericin B therapy.			
Cresemba (Isavuconazonium sulfate)[23] 03/06/2015	Invasive Aspergillosis; Invasive mucormycosis	Loading dose: 372 mg every 8 hours for 6 doses for 48 hours. Maintenance dose: 372 mg once daily.	Hepatic Adverse Drug Reactions; Infusion-Related Reactions; Hypersensitivity Reactions; Embryo-Fetal Toxicity; Drug Interactions; Drug Particulates	Warnings and Precautions
Ancobon (flucytosine)[24] 11/26/1971	treatment of serious infections caused by susceptible strains of *Candida spp* and/or *Cryptococcus*. *Candida spp*: Septicemia, endocarditis and urinary system infections have been effectively treated with flucytosine. Limited trials in pulmonary infections justify the use of flucytosine. *Cryptococcus*: Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses have been reported. Flucytosine capsules should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine.	50 to 150 mg/kg/day administered in divided doses at 6-hour intervals.	Caution in patients with impaired renal function and bone marrow depression; Drug toxicity with dihydropyrimidine dehydrogenase.	Boxed Warning, Warnings and Precautions

10.2. References

1. FDA Presentations for Rezafugin.
2. Draft prescribing information for rezafungin as currently edited by FDA. 2023.
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