

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: December 5, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

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Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of CRESEMBA (isavuconazonium sulfate) outweigh the risks

Drug Name: CRESEMBA (isavuconazonium sulfate) for Injection and as an Oral Capsule

Therapeutic Class: Triazole Anti-fungal

Form and Dosage: Lyophilized powder containing (b) (4) 372.6 mg isavuconazonium sulfate (equivalent to 200 mg (b) (4)) for intravenous infusion (u) (4)

Office of New Drugs: Division of Anti-Infective Products

Application Type/Number: NDA 207-500 Cresemba (b) (4) Oral Capsule and NDA 207-501 Cresemba (b) (4) IV Injection, both received on July 8, 2014.

Applicant: Astellas Pharma Global Development, Inc. on behalf of Astellas Pharma US, Inc. (Astellas)

OSE RCM #: 2014-1361 Master Record

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for isavuconazonium sulfate (Cresemba) proposed as an intravenous (IV) solution and as a hard capsule for oral administration for the treatment of life-threatening invasive fungal infections, *Aspergillosis* and invasive mucormycosis in adult patients. New drug applications (NDA), 207-500 (oral capsule formulation) and NDA 207-501 (IV formulation), were submitted to the Division of Anti-Infective Drugs on July 8, 2014 in support of the proposed indications.

A risk management plan (RMP) was submitted to both NDAs without a proposed REMS program for isavuconazonium (ISA). The RMP submitted to the FDA is identical to the RMP submitted to the European Union (EU) for the same oral and IV formulations and the same proposed indications for the treatment of invasive *Aspergillosis* and invasive mucormycosis. Safety issues of hepatotoxicity and infusion-related reactions, among other serious risks (exfoliative cutaneous reactions, QT prolongation/shortening) reported with use of ISA will be discussed at an Anti-infective Drugs Advisory Committee Meeting on January 22, 2015.

At this time, the DRISK and the DAIP concur that ISA will not require a REMS to ensure that the benefits of ISA outweigh the reported risks of elevated liver transaminases and infusion-related reactions. Isavuconazonium will be the fourth-in class (triazole anti-fungal product), if approved, and the target providers for this proposed patient population are familiar with the serious risks associated with use of triazole anti-fungal products. In the pivotal study, the active comparator to ISA, voriconazole (VRC), was first approved in 2002 and is associated with many serious risks, including the two major safety risks of hepatotoxicity and infusion-related reactions associated with ISA. Due to the three triazole anti-fungal products currently marketed and the well characterized safety profile of this class, the DAIP and the DRISK do not currently recommend a REMS program for risk management of ISA, if approved.

1 INTRODUCTION

The NDA 207-501 contains drug product information [Common Technical Document (CTD) Module 3.2 Product] for the IV formulation of ISA and incorporates all remaining CTD Modules via cross reference to NDA 207-500. The NDA 207-500 contains drug product information for the hard oral capsules of ISA and all other data to support both NDAs. The Late Cycle Meeting with the applicant is scheduled on January 9, 2015.

Anti-Infective Drugs Advisory Committee Meeting on Isavuconazonium

An Anti-infective Drugs Advisory Committee (AIDAC) Meeting will be convened on January 22, 2015 to discuss the totality of the efficacy and safety data for ISA (NDA 207-500/oral formulation and NDA 207-501/IV formulation) proposed for two indications primarily supported by the results from a global, multicenter, randomized, controlled Phase 3 trial in which ISA was compared to VRC for the treatment of invasive aspergillosis and the results from an open-label, multicenter, single-arm study of ISA for the treatment of invasive mucormycosis, and other rare molds, yeasts, or dimorphic fungi. The DAIP would like the AIDAC to discuss whether these data are adequate to support

safety and efficacy of ISA for the treatment of invasive aspergillosis and invasive mucormycosis.

The Prescription Drug User Fee Act (PDUFA) due date for both of these NDAs is March 8, 2015.

2 BACKGROUND

Proposed Product

Isavuconazonium (isavuconazole, abbreviated ISA), the active moiety of ISA sulfate, is a new molecular entity (NME) and a proposed fourth-in-class, triazole antifungal product. Isavuconazonium is a water-soluble pro-drug containing the active moiety, isavuconazole, that claims antifungal activity against pathogenic fungi.¹ Isavuconazonium 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-demethylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakening the membrane structure and function (see proposed labeling, *Section 12.4 Microbiology*).

Isavuconazonium has *in vitro* antifungal activity against *Aspergillosis*, *A. fumigatus*, rare moulds, Mucorales including *Rhizomucor*, *Absidia*, *Mucor*, and *Cunnonhamella*, as well as against *Candida* including many fluconazole-resistant strains.¹ Per the applicant, ISA was developed to facilitate IV administration, without the need for nephrotoxic excipients such as cyclodextrin and with an almost complete bioavailability after oral administration.¹

The use of ISA as the active moiety establishes ISA as a member of the azole class of antifungals. The applicant claims that ISA has *in vitro* broad spectrum activity against *Aspergillosis*, several species of Mucorales, and *Candida* species. Administration of ISA in animal models of fungal infection showed *in vivo* efficacy against these same pathogens. These data suggest that ISA may have therapeutic benefit for the treatment of patients with invasive fungal infections.¹

Non-clinical studies reported that ISA is associated with potential embryo-fetal toxicity based on findings skeletal abnormalities in rats and rabbits. These findings are consistent with previously reported non-clinical studies for other azole anti-fungal products.² No pregnant women have been exposed to ISA. Clinical experience with ISA in pregnant women was strictly avoided per protocol and has not occurred per the applicant.²

Proposed Formulation, Strength, Dosage and Administration

The two proposed to-be-marketed formulations and strengths for isavuconazole are:

- As a sterile lyophilized powder (containing 372.6 mg isavuconazonium sulfate, equivalent to 200 mg (b) (4) for intravenous infusion or as an oral capsule (containing 186.3 mg of isavuconazonium sulfate equivalent to 100 mg

¹ NDA 207-500 Isavuconazonium, Global Submit (GS), Module 2.5 Clinical Overview, page 9 of 76

² NDA 207-500 ISA, GS, Module 1.16 RMP, Section VII.3.2.3 Embryo-fetal Toxicity, page 105 of 379

(b) (4), recommended as a loading dose of 200 mg every 8 hours, for 48 hours (6 doses), via *oral* or *IV* administration.

- The maintenance dose is recommended as 200 mg once per day via *oral* or *IV* administration starting 12 to 24 hours after the last loading dose. The *oral capsule* can be taken with or without food. The administration of the *IV dose* is via an infusion set with an in-line filter over a minimum of 1 hour.
- Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in Cresemba or in the materials specified for reconstitution.
- Proposed labeling includes a detailed *Section 2, DOSAGE AND ADMINISTRATION; Section 2.1 Instructions for Use in Patients; and Section 2.2 Intravenous Administration.*

2.1 ASPERGILLOSIS

Aspergillosis is the collective term used to describe all disease entities caused by any one of the approximately 35 pathogenic and allergenic species of *Aspergillosis*. Only those species that grow at 37° Centigrade can cause invasive infection, although some species without this capability can cause allergic symptoms. The *A. fumigatus* is responsible for most of the cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. The *A. flavus* is more prevalent in some hospitals and causes a higher proportion of cases of sinus and cutaneous infections and keratitis than *A. fumigatus*.³

The primary risk factors for invasive aspergillosis are profound neutropenia and glucocorticoid use; risk increases with longer duration of these conditions. Higher doses of glucocorticoids increase the risk of both acquisition or invasive aspergillosis and death from infection. Neutrophil and/or phagocyte dysfunction is also an important risk factor, as evidenced by aspergillosis in chronic granulomatous disease, advanced Human Immunodeficiency Virus (HIV) syndrome, and relapsed leukemia. An increasing incidence of invasive aspergillosis in medical intensive care units suggests that, in patients who are not immunocompromised, temporary abrogation of protective responses as a result of glucocorticoid use or a general anti-inflammatory state is a significant risk factor. Many patients have some evidence of prior pulmonary disease, typically a history of pneumonia or chronic obstructive pulmonary disease.³

Patients with chronic pulmonary *Aspergillosis* have a wide spectrum of underlying pulmonary disease, often tuberculosis or sarcoidosis. Patients are immunocompetent except for some cytokine regulation defects, most of which are consistent with an inability to mount an inflammatory immune response.³

Both the frequency of invasive disease and the pace of its progression increase with greater degrees of immunocompromise. Invasive *Aspergillosis* is arbitrarily divided into acute and sub-acute forms that have courses of ≤ 1 month and 1 to 3 months,

³ Chapter 204, *Aspergillosis* by DW Denning, 18th Edition, Harrison's Principles of Internal Medicine, Vol 1, DL Longo, AS Fauci, DL Kasper, SL Hauser, JL Jameson, J Loscalzo, p 1655

respectively. More than 80% of cases of invasive aspergillosis involve the lungs. The most common clinical features are no symptoms at all, fever, cough (sometimes productive), nondescript chest discomfort, trivial hemoptysis, and shortness of breath. The disease progresses despite the fever responding to glucocorticoids.⁴

Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The mortality rate for invasive aspergillosis is ~50% if the infection is treated, but it is 100% if the diagnosis is missed. Cerebral *Aspergillosis*, *Aspergillosis* endocarditis, and bilateral extensive invasive pulmonary aspergillosis have very poor outcomes, as do invasive infection in persons with late-stage acquired immunodeficiency syndrome (AIDS), relapsed uncontrolled leukemia, and in recipients of allogenic hematopoietic stem cell transplants.³

2.2 ARMAMENTARIUM OF THERAPY FOR INVASIVE ASPERGILLOSIS

Antifungal drugs active against *Aspergillosis* include voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and amphotericin B. Initial IV administration is preferred for acute invasive aspergillosis and oral administration for all other disease that requires antifungal therapy.³

Currently, voriconazole is the preferred agent for invasive aspergillosis. Caspofungin, posaconazole and lipid-associated amphotericin B are second-line agents. Amphotericin is not active against *Aspergillosis terreus* or *Aspergillosis nidulans*.³ Currently, there is no FDA-approved drug for treatment of invasive mucormycosis based on a clinical trial.

An infectious disease consultation is usually involved in the care of patients with invasive disease, given the complexity of the clinical management. It is not clear whether combination therapy for acute invasive aspergillosis is beneficial, but it is widely used for extremely ill patients and for those with a poor prognosis.³ See the **Appendix**, to this review, **Table 1**, Anti-Infective Options for Treatment of Invasive Aspergillosis.

2.3 GENERIC PRODUCTS FOR THE TREATMENT OF INVASIVE ASPERGILLOSIS

The FDA is aware of one abbreviated NDA (ANDA) submission (posaconazole) for the treatment of invasive aspergillosis. The FDA is not aware of any patent challenges, though a patent challenge may occur at any time for a FDA approved drug product.

2.1 Regulatory History

The regulatory history specific to the two NDAs, 207-500 (oral capsule) and 207-501 (IV), for isavuconazole follows:

- May 6, 2013: The FDA granted Orphan Drug Designation for isavuconazonium for the treatment of invasive *Aspergillosis*.
- October 25, 2013: The FDA granted Orphan Drug Designation for the treatment of Zygomycosis.

⁴ Chapter 204, Aspergillosis by DW Denning, 18th Edition, Harrison's Principles of Internal Medicine, Vol 1, DL Longo, AS Fauci, DL Kasper, SL Hauser, JL Jameson, J Loscalzo. page 1656

- November 5, 2013: Pre-NDA Meeting with the FDA (multi-discipline). There was no discussion on consideration of a REMS for isavuconazonium.
- November 8, 2013: Isavuconazonium designated as a Qualified Infectious Disease Product (QIDP) for the indication of treatment of invasive aspergillosis
- February 14, 2014: Isavuconazonium designated as a QIDP for the indication of treatment of invasive mucormycosis.

(b) (4)

- July 8, 2014: The applicant submitted two Original NDAs, 207-500 and 207-501, for the proposed indications of treatment of adult patients with life-threatening invasive *Aspergillosis* and invasive mucormycosis.
- August 22, 2014: The Division of Medication Error and Prevention and Analysis (DMEPA) approved the proposed Trade Name, Cresemba™, for isavuconazole (oral capsule (100 mg) and for IV injection (200 mg per vial).

2.2 Materials Reviewed

- July 8, 2014: Original NDA 207-500 (Oral capsule) and NDA 207-501 (IV Injection) Cresemba (isavuconazonium) proposed for the treatment of adult patients with invasive Aspergillosis and invasive mucormycosis. Both NDAs include the same RMP in Module 1.16 Risk Management Plan.
- September 29, 2014: Interdisciplinary Review Team for thorough QT Studies Consultation: through QT Study Review by Huifang Chen, Ph. D.; Qianyu Dang, Ph.D.; Jee E. Lee, Ph.D.; Jiang Liu, Ph.D.; Michael Y. Li, Ph.D.
- October 3, 2014: NDAs 207-500 AND 207-501 (isavuconazonium), Mid-Cycle Meeting slide presentation by Edward Weinstein, M. D., Clinical Reviewer, DAIP.
- November 20, 2014: Office of Prescription and Drug Promotion (OPDP) Review on the proposed labeling for CRESEMBA capsules and injection written by Christine Corser, Pharm.D.
- November 18, 2014: NDAs 207-500 and 207-501 (isavuconazonium), 120-Day Safety Update Report (SUR)
- December 2, 2014: The most recent revisions, per DAIP, to proposed labeling.
- *Pending December 5, 2014: Clinical Review by Ed Weinstein, M,D., DAIP*

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The safety and efficacy of isavuconazole (ISA) is based on two Phase (P) 3 studies and two P 2 studies for the proposed indications of treatment of adult patients with invasive aspergillosis (IA) and for the treatment of adult patients with mucormycosis. Voriconazole (VRC) was selected as the comparator because it is approved for the

treatment of invasive aspergillosis and is the first-line agent recommended by the IDSA Guidelines.⁵

- **Study 9766-CL-0104/WSA-CS-004**, a **P3**, double-blind (DB), randomized (R), non-inferiority, active-controlled (AC) study to evaluate efficacy and safety of ISA vs VRC for the primary treatment of invasive fungal disease (IFD) caused by Aspergillosis species (spp.) or other filamentous fungi. There were 102 sites in this study.
 - *Treatment Groups*: ISA 258 patients (pts); safety analysis set (SAF) 257 pts; VRC 258 pts; SAF 259 pts.
 - *Loading Dose*: ISA 200 mg every 8 hours (q8h) IV for 2 days vs VRC 6 mg/kg q12h IV for 1 day.
 - *Maintenance Dose*: ISA 200 mg once per day IV or oral.
 - *Primary Efficacy Endpoint*: Crude rate of all-cause mortality through day 42.
- **Study 9766-CL-0103/WSA-CS-003** was a **P3**, open-label (OL) non-comparative study to evaluate the safety and efficacy of ISA for the treatment of IA in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi. There were 34 sites in this study. For the proposed invasive mucormycosis indication, a subgroup of 37 mITT-Mucorales patients was identified with the clinical trials 9766-CL-0103.
 - *Treatment groups*: ISA 146 pts; Renally impaired (RI) 59 pts.; Non-renally impaired (NRI) 87 pts
 - *Loading Dose*: ISA 200 mg q8h IV or oral on days 1 and 2.
 - *Maintenance Dose*: ISA 200 mg q24h IV or oral from day 3 to end of treatment (EOT)
 - *Primary Efficacy Endpoint*: Data Review Committee (DRC)-assessed overall response at ay 42.
- **Study 9766-CL-0101/WSA-CS-001** was a **P2**, R, DB, parallel group (PG), non-inferiority study to compare the efficacy and safety of 3 oral dosing regimens of ISA to a standard oral fluconazole (FLU) regimen for the treatment of patients with uncomplicated esophageal candidiasis. There were 8 sites in this study.
 - *Treatment Groups*: ISA-A 40 pts; ISA-B 40 pts; ISA-C 41 pts; FLU-D 38 pts.
 - **Loading Dose**: ISA-A 200 mg day 1; ISA-B 400 mg day 1; ISA-C 400 mg day 1; FLU-D 200 mg day 1.
 - *Maintenance Dose*: ISA-A 50 mg/day; ISA-B 400 mg/week; ISA-C 100 mg/day; FLU-D 100 mg/day.

⁵ Walsh TJ, TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Disease Society of America. Clin Inf Dis. 2008;46:327-60.

- *Primary Efficacy Endpoint*: Endoscopically confirmed clinical response at EOT
- **Study 9766-CL-0102/WSA-CS-002** was a P2, OL, multicenter study of safety and efficacy of escalating IV and oral ISA in the prophylaxis of patients undergoing chemotherapy for acute myeloid leukemia (AML). There were 3 sites in this study.
 - *Treatment Dose*: Safety Population - Group 1, 11 pts; Group 2, 12 pts.
 - *Loading Dose*: Group 1 - 400/200/200 mg day 1, 200/200 mg Day 2; Group 2 – 800/400/400 mg day1, 400/400 mg day 2.
 - *Maintenance Dose*: Group 1, 200/day; Group 2, 400 mg/day
 - *Primary Efficacy Endpoint*: Rate of microbiological success (absence of breakthrough fungal infections and lack of need for other systemic acute fungal therapy (AFT)).

Demographics

In P3 study CL-0104, the majority of patients were White (78%), male (60%) and had mean age of 51 years of age. A total of 48% were from regions other than North America (11%) and Western Europe, Australia, and New Zealand (41%). A total of 10.6% of patients were renally impaired (GFR < 60 mL/min/1.73 m²). There were no important differences between ISA and VRC treatment groups in regards to baseline characteristics.

Over 84% of patients had a hematologic malignancy, 20% of patients had a prior allogenic bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) and 66% had neutropenia (absolute neutrophil count < 0.5 x 10⁹/L or < 500/mm³).

The majority of patients who had a proven or probable IFD (by the DRC) had an IFD in the lower respiratory tract only.⁶ Per the applicant, the DRC reported that no pathogen was identified in approximately half of the population (51.5%). *Aspergillus species* (spp.) was the only identified causal organism in 32% of patients. The most common pathogen in both treatment arms was *Aspergillus fumigatus*.

In the P2 and other P3 population, the mean age was 48.1 years, a total of 66% of patients were male, and 63% were white. See the Clinical Review by Edward Weinstein, M. D., DAIP, for additional details on demographics in each clinical trial.

Disposition

Per the Clinical Reviewer, 527 patients were randomized into a clinical trial: 263 to ISA and 264 to VRC. There were 11 patients who were randomized but did not receive any dose of study treatment. Therefore, the intent-to-treat population (ITT) consisted of 516 patients (258 in each treatment group).

Out of the 516 patients in the ITT population, 244 patients were excluded from the modified ITT (mITT) population because the DRC assessed the patient as having either possible or no IFD at baseline. The Clinical Reviewer explains that there is only a net difference of 3 patients between the mITT and the mITT-FDA populations, the m-ITT-FDA population includes 20 patient show were considered probable based on a BAL GM

⁶ NDA 207-500, ISA, GS, Module 2.5, Clinical Overview, page 33 of 118

≥ 1.0; but, excludes 17 patients who were considered probable in the mITT population based on a single serum GM between 0.7 and 1.0. See the Clinical Review by Ed Weinstein, M. D.

3.1 EFFICACY RESULTS

3.1.1 Invasive Aspergillosis

The primary efficacy analysis was all-cause mortality through Day 42. All-cause mortality was assessed as a secondary endpoint. In the absence of historical placebo-controlled (PBO) trials, an estimation of the all-cause mortality rate through day 42 in untreated patients was 84.8% with a 95% Confidence Interval (CI) of (75.1%, 94.5%), based on a meta-analysis of the historical literature. A 10% non-inferiority margin provided statistical evidence that ISA is superior to PBO, preserves at least 80% of the estimated VRC treatment effect, and is clinically meaningful.⁷

In pivotal study 9766-CL-0104, the median duration of study drug therapy was 45 days with the median duration of IV therapy 5 days in both treatment groups. In the DB study, all-cause mortality through Day 42 in the ITT population was 18.6% and 20.2% in the ISA and VRC treatment groups, respectively. This study met the primary objective of demonstrating non-inferiority of ISA relative to VRC since the upper bound of the 95% CI (5.683%) around the adjusted treatment difference (ISA-VRC: -1.0%) was lower than the prespecified non-inferiority margin of 10%. See **Table 2** which shows the primary outcome, all-cause mortality.

Table 2. Primary Outcome: All-cause Mortality

	Isavuconazonium		Voriconazole		Diff. (%) ^a	95% CI [#]
	N	n (%)	N	n (%)		
ACM thru Day 42						
ITT**	258	48 (18.6)	258	52 (20.2)	-1.0	(-7.8; 5.7)
mITT	143	28 (19.6)	129	30 (23.3)	-2.6	(-12.2; 6.9)
Mycological ITT	123	23 (18.7)	108	24 (22.2)	-2.7	(-12.9; 7.5)
ACM thru Day 84						
ITT	258	75 (29.1)	108	24 (22.2)	-2.7	(-12.9; 7.5)
Unknown survival status treated as death in the analyses. ACM-All-cause mortality; Diff-difference; N-number ITT-intent-to-treat; mITT- modified intent-to-treat;						
[#] 95% CI for treatment difference based on a normal approximation.						
** Primary efficacy endpoint; non-inferiority margin - = 10%						
Table from Mid-Cycle slides by Ed Weinstein, M. D., Clinical Reviewer, DAIP						

⁷ NDA 207-500, ISA, GS, Module 2.5, Clinical Overview, p 36 of 118

The DRC-assessed overall response at the end of treatment (EOT) was a key secondary endpoint. Per the Clinical Reviewer, for the mITT population, the DRC-assessed overall response rates at EOT were similar between treatment groups (35% for ISA and 36.4% for VRC). The lower bound of the 95% CI about the adjusted treatment difference is -12.8%. Complete response was observed in 11.9% ISA patients and 10.1% VRC patients. Partial response was observed in 23.1% ISA patients and 27.8% of VRC patients. The results of the mITT-FDA population are similar to that of the mITT population. See the Clinical Review by Ed Weinstein, M. D., for details on subgroup analyses that support the primary outcome.

3.1.2 Invasive Mucormycosis

In study 9766-CL-0103, the mITT-Mucorales patients and primary therapy patients, respectively, the median duration of study drug therapy was 84 days and 102 days, with the median duration of IV treatment being 10 and 9.5 days. The population considered for the proposed indication consists of 37 mITT-Mucorales patients from the ITT population whom the DRC classified as having Mucorales only.

All-cause mortality through day 42 and day 84 in the mITT-Mucorales population occurred in 14 patients (37.8%) and in 16 patients (43.2%), respectively. All-cause mortality through Day 42 and day 84 in patients who received ISA as primary therapy occurred in 7 patients (33.3%) and 9 patients (42.9%), respectively. See **Table 3** that demonstrates all-cause mortality through Day 42 and Day 84 (mITT-Mucorales)

Table 3. All-Cause Mortality through Day 42 and Day 84 (mITT-Mucorales)

	Primary Therapy N = 21	Refractory N = 11	Intolerant N = 5	Total N = 37
All-cause mortality thru day 42	7 (33.3%)	5 (45.5%)	2 (40%)	14 (37.8%)
All-cause mortality thru day 84	9 (42.9%)	5 (45.5%)	2 (40%)	16 (43.2%)

NDA 207-500, ISA, GS, Module 2.5, Clinical Overview, Table 4, page 44 of 118. A patient with the last known survival status before day 42 or before day 84 or missing and the last assessment day was before day 42 or day 84 was counted as death.

The success rate for the DRC-assessed overall response at EOT in the mITT-Mucorales population was 31.4%, with 14.3% of patients considered to have complete success and 17.1% to have partial success. Of the patients in the mITT-Mucorales population who were treated with ISA as the primary therapy, 15.8% of patients were considered to have complete success, 15.8% to have partial success and 31.6% were considered to have stable disease.

3.2 CLINICAL SAFETY

Safety Population and Exposure

A total of 547 patients received at least one dose of ISA in the P2 and P3 studies:

- 144 patients in the P2 studies
- 403 patients (with invasive *Aspergillois* and other filamentous fungi, or rare moulds, yeast and dimorphic fungi) in the P3 studies.

A total of 309 of 547 patients (57%) received ISA for at least 21 days, 276 of 547 patients (51%) received ISA for at least 28 days, 144 of 547 patients (26%) received ISA for at least 84 days, and 52 of 547 patients (10%) received ISA for at least 180 days. Over 400 patients received a loading dose of IV ISA 200 mg q8h for 2 days followed by a 200 mg daily maintenance dose, the dose proposed for clinical use.

The safety population employed by the Clinical Reviewer for DAIP is based on 516 patients: 257 patients treated with ISA and 259 patients treated with VRC. Adverse events (AEs) are coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1. The data cutoff was March 31, 2014 for ISA studies.

3.2.1 Deaths

Per the Clinical Reviewer, ISA demonstrated a favorable safety profile with similar rates of mortality as the comparator, VRC. Per the Clinical Reviewer for DAIP, there were a total of 62 deaths (24.1%) in ISA-treated patients and 72 deaths (27.8%) in VRC-treated patients (deaths within 28 days after the EOT), consider treatment-emergent adverse events (TEAEs). See **Table 4A** for a summary of the TEAEs causally attributed to each death, listed by the System Organ Class (SOC). See **Table 4B** for deaths that occurred beyond 28 days of exposure to ISA and VRC.

Table 4A. TEAEs leading to Death in the P3, Controlled Population (within 28 days)

System Organ Class (SOC)	Isavuconazonium n = 257 pts	Voriconazole n = 259 pts
Total	62 (24.1%)	72 (27.8%)
Blood and lymphatic system disorders	2 (0.8%)	1 (0.4%)
Cardiac disorders	4 (1.6%)	5 (1.9%)
Gastrointestinal disorders	0	1 (0.4%)
General disorders and administration site conditions	2 (0.8%)	8 (3.1%)
Hepatobiliary disorders	1 (0.4%)	0
Immune system disorders	1 (0.4%)	0
Infections and infestations	28 (10.9%)	18 (6.9%)
Metabolism and nutrition disorders	0	2 (0.8%)
Neoplasms benign, malignant and unspecified	10 (3.9%)	21 (8.1%)
Nervous system disorders	3 (1.2%)	7 (2.7%)
Renal and urinary disorders	1 (0.4%)	0

Respiratory, thoracic and mediastinal disorders	14 (5.4%)	12 (4.6%)
Vascular disorders	2 (0.8%)	1 (0.4%)
Table and data from Clinical Review (Table 7.3.2) by Ed Weinstein, MD, DAIP.		

Table 4B. Deaths Occurring within the P3 Controlled Population > 28 Days

Category	ISA (n=257)	VRC (n=259)
Deaths w/in 28 days after EOT, TEAE reported	61	69
Deaths w/in 28 days after EOT, AE reported (AE onset prior to treatment)	1	1
Deaths > 28 days after EOT, TEAE reported	1	3
Deaths > 28 days after the EOT, AE reported	13	11
Deaths > 28 days after the EOT, no AE reported	5	3
Total of all known deaths following drug exposure	81	87
Ref for Table: <i>Draft</i> ADIAC Background Package for Isavuconazonium		

See the Clinical Review by Ed Weinstein, M. D., Table 7.3.3 that shows, by preferred term (PT), all TEAEs resulting in death in the P3, controlled population.

3.2.2 Discontinuations

The adverse events (AEs) leading to discontinuation of study drug were experienced in 37 patients (14.4%) treated with ISA and 59 patients (22.8%) treated with VRC. The Clinical Reviewer attributed the AEs associated with discontinuation to ISA in 21 patients (8.2%) and to VRC in 35 patients (13.5%). The AEs of hepatotoxicity and/or hepatobiliary disorders and infections were the events that prompted the majority of study discontinuations. See the Clinical Review by Ed Weinstein for details on AEs that led to discontinuation of study drug.

3.2.3 Non-Fatal Serious Adverse Events

Non-fatal serious TEAEs were reported in 99 patients (38.5%) treated with ISA and 121 patients (46.7%) treated with VRC. See **Table 5** that shows the SOC associated with the non-fatal TEAEs.

Table 5. Non-Fatal TEAEs

System Organ Class (SOC)	Isavuconazonium n = 257 pts (%)	Voriconazole n = 259 pts (%)
Total	99 (38.5%)	121 (46.7%)
Blood and lymphatic system disorders	27 (10.5%)	17 (6.6%)
Respiratory, thoracic and mediastinal disorders	27 (10.5%)	33 (12.7%)
Infections and infestations	26 (10.1%)	46 (17.8%)
Nervous system disorders	14 (5.5%)	10 (5.9%)
General disorders and administration site conditions	10 (3.9%)	12 (4.6%)
Gastrointestinal disorders	9 (3.5%)	1 (4.3%)
Neoplasms benign, malignant and unspecified	9 (3.5%)	9 (3.5%)
Renal and urinary disorders	9 (3.5%)	10 (3.9%)
Cardiac disorders	7 (2.7%)	7 (2.7%)
Immune system disorders	3 (1.2%)	6 (2.3%)
Injury, poisoning and procedural complications	3 (1.2%)	3 (1.2%)
Investigations	3 (1.2%)	6 (2.3%)
Musculoskeletal and connective tissue disorders	3 (1.2%)	0
Skin and subcutaneous tissue disorders	3 (1.2%)	2 (0.8%)
Eye disorders	2 (0.8%)	1 (0.4%)
Hepatobiliary disorders	2 (0.8%)	6 (2.3%)
Metabolism and nutrition disorders	2 (0.8%)	6 (2.3%)
Vascular disorders	2 (0.8%)	5 (1.9%)
Psychiatric disorders	1 (0.4%)	6 (2.3%)
These data are from the Clinical Review (Table 7.3.7) by Ed Weinstein, M. D., DAIP.		

Arrhythmia and QT Prolongation

QT prolongation is a known class effect of azole anti-fungal products. One (1) patient (0.4%) is reported to have experienced QT shortening among the ISA-treated patients compared to zero patients treated with VRC.

Non-fatal arrhythmias and QTc shortening were observed with ISA exposure and confirmed to be proportional to dose and serum concentration. Patients with familial short QT are at increased risk for arrhythmia with exposure to ISA. The applicant

completed two TQT studies and neither showed QT prolongation, and both showed QT shortening (9766-CL-0004; 9766-CL-0017). A slight decrease of QTcI after exposure to ISA exposure (repeat doses up to 150 mg) was noted (difference for ISA minus PBO of < 12 msec).⁸

In the P3 studies, 11 ISA-treated patients (2.8%) experienced post-baseline QTcF < 330 msec. in 10 of 11 of these patients (91%), QTcF, 330 msec was a single, transient finding. In the remaining patient 1 patient (1/11, 9%), baseline QTcF was < 330 msec and remained < 330 msec throughout the study. None were associated with ventricular arrhythmias or adverse events.⁷

The QT-IRT Review was completed on September 29, 2014 and concluded that no significant QTc prolongation effect of ISA (200 mg and 600 mg) was detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ISA (200 mg and 600 mg) and the PBO were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. See the QT-IRT Review in DARRTS.

Serious Hepatotoxicity and Elevated Liver Test Results

Serious hepatotoxicity events were observed with exposure to ISA. Hepatic reactions including elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin have been reported in ISA clinical trials. The elevations in liver tests were generally reversible and did not require discontinuation of ISA. Cases of more severe hepatic 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 products including ISA. See the **Appendix**, to this review, **Table 1** with risks associated with the approved azole anti-fungal products.

Among 516 patients in the P3 study, 104 with IFD caused by *Aspergillus* species or other filamentous fungi, elevated transaminases (ALT or AST) > 3 x upper limit of normal (ULN) were reported in 4.4% of patients treated with ISA and 10.6% of patients treated with VRC. Elevations of liver enzymes > 10 x ULN were reported in 1.2% of patients treated with ISA and 2.4% of patients treated with VRC. Proposed labeling recommends monitoring hepatic enzymes prior to exposure to isavuconazonium, if it should be approved. Per the Clinical Reviewer, Hy's Law (combined ALT or AST > 3 x upper limit of normal (ULN) and alkaline phosphatase (ALP) < 2 x ULN and total bilirubin > 2 x ULN) was confirmed in 3 cases of patients treated with ISA and 7 patients treated with VRC. See the Clinical Review by Ed Weinstein for these data and timelines of these 14 cases of confirmed Hy's Law. Exposure to VRC is known to be associated with elevated transaminases and the potential of elevated serum total bilirubin.

Cholecystitis and cholelithiasis were experienced in 8 patients, each, in both treatment groups, (1.5%) and (2%), ISA and VRC, respectively. Cholestasis and jaundice were reported in 10 patients, each, in both treatment groups, (1.8%) and (2.5%), ISA and VRC, respectively. Hepatic and hepatobiliary disorders were reported in 4 patients, each, in both treatment groups, (0.7%) and (1.0%), ISA and VRC, respectively. One death (0.4%)

⁸ NDA 207-500, ISA, GS, Module 1.16, RMP, Table 33, page 95 of 379

in a patient treated with ISA is causally attributed hepatotoxicity. ISA has not been studied in patients with severe hepatic impairment.

Infusion Reactions

Infusion reactions are considered important based on the known risk of infusion reactions with other products in the class of azole anti-fungal products.

Infusion reactions reported to have occurred during the IV administration of ISA or during the two (2) days after IV ISA dosing included hypotension, dyspnea, chills, dizziness, paresthesia and hypoesthesia. The frequency of infusion-related serious reactions occurring within 2 days after IV infusion in the P3 controlled study (CL-0104) was reported in 26 patients (10.1%) treated with ISA compared to 18 patients (6.9%) treated with VRC. It is notable that study discontinuation occurring within 2 days after IV infusion in the P3 controlled study was 3.1% in ISA-treated patients compared to 2.3% in the VRC-treated patients. Respiratory failure was experienced by 10 patients (3.9%) treated with ISA and by 9 patients (3.5%) treated with VRC. See the Clinical Review by Ed Weinstein, M. D., for additional details, including the P2 studies with infusion reactions. Proposed labeling includes recommendation that ISA should be discontinued should any of these events occur.

Hypersensitivity Reactions

Hypersensitivity reactions including anaphylaxis and severe skin reactions were reported with ISA treatment. The frequency of severe cutaneous adverse reactions in the P3 controlled studies was 1.2% in ISA-treated patients compared to 0.8% in VRC-treated patients.

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, were reported with ISA treatment. Severe cutaneous adverse reactions in the P3 studies were: 3 patients (1.2%) treated with ISA and 2 patients (0.8%) treated with VRC. Dermatitis exfoliative was reported in 1 patient in each treatment arm, (0.4%) and 0.4%), ISA compared to VRC, respectively. Erythema multiforme was reported in 2 patients (0.8%) with ISA treatment and no patients (0) with VRC treatment. Toxic skin eruption was reported in 1 patient treated with VRC and no patients treated with ISA.

Severe cutaneous adverse reactions are a known serious risk with other azole antifungal therapies (see the **Appendix**, to this review, **Table 1**, which shows the serious risks with azole anti-fungal products).

3.2.4 Common Adverse Events

The most frequent adverse reactions ($\geq 10\%$) reported with ISA treatment were: nausea 71 patients (26%), vomiting in 64 patients (25%), diarrhea in 61 patients (22%), pyrexia in 57 patients (22.2%), hypokalemia in 45 patients (17.5%), headache in 41 patients (17%), constipation in 36 patients (14%), dyspnea in 34 patients (13.2%), cough in 33 patients (12.8%), febrile neutropenia in 32 patients (12.5%), chills in 27 patients (10.5%), fatigue in 27 patients (10.5%), edema peripheral in 26 patients (10.1%), back pain in 26 patients (10.1%), abdominal pain in 25 patients (9.7%), hypertension in 25 patients (9.7%),

Other important common AEs reported in < 10 % of patients treated with ISA were: pruritus in 19 patients (6.6%), rash in 17 patients (6.6%), elevated gamma-glutamyltransferase in 16 patients (6.2%), septic shock in 15 patients (5.8%), hypomagnesaemia in 14 patients (5.4%), respiratory failure in 14 patients (5.4%), ALT increased in 13 patients (5.1%), thrombocytopenia in 11 patients (4.3%), AST increased in 11 patients (4.3%), and hyperglycemia in 10 patients (3.9%).

See the Clinical Review by Ed Weinstein, M. D., specifically Table 7.4.3 which reports AEs across both ISA and VRC treatment groups.

3.2.5 Adverse Events and/or Potential Risks of Special Interest

- Visual Adverse Events

Under the SOC Eye disorders, visual impairment was reported in 4 patients (1.6%) treated with ISA vs 19 patients (7.3%) treated with VRC; photophobia in 2 patients (0.8%) treated with ISA vs 6 patients (2.3%) treated with VRC; visual acuity reduced 1 patient (0.4%) treated with ISA vs 6 patients (2.3%) treated with VRC; and retinal hemorrhage no patients treated with ISA vs 5 patients treated with VRC.

- Psychiatric disorders

Psychiatric adverse events were reported as hallucination in 6 patients (2.3%) treated with ISA vs 11 patients (4.2%) treated with VRC; and agitation in 2 patients (0.8%) vs 7 patients (2.7%) treated with VRC.

- Drug Interactions

Isavuconazonium is a sensitive substrate of CYP3A4/5. The CYP3A4/5 inhibitors or inducers may alter plasma concentrations of ISA. The applicant completed drug interaction studies to investigate the effect of co-administration on pharmacokinetics (PK) of ISA and the effect of ISA on the PK of co-administered drugs. Ketoconazole, Lopinavir/ritonavir, and Rifampin are contraindicated as co-administration with ISA.

Lopinavir/ritonavir, Atorvastatin, Cyclosporine, Sirolimus, Midazolam, Tacrolimus, Bupropion, Mycophenolate Mofetil, and Digoxin are recommended to be used with caution with ISA. For additional information, see the proposed ISA labeling (Section 7, Drug Interactions, and Section 12, Clinical Pharmacology).

- Development of Resistant Strains

ISA clinical trials did not identify any strains of filamentous fungi in which resistance emerged during therapy. Per the applicant, in the United States, species resistant to VRC and Posaconazole remain rare, < 1%.⁹ According to the applicant, acquired ISA resistance may be reduced by discontinuing ISA treatment when clinical parameters or laboratory tests indicate that active fungal infection has subsided.¹⁰ (b) (4)

⁹ Mayr A, Lass-Flörl C. Epidemiology and anti-fungal resistance in invasive Aspergillosis according to the primary disease: Review of Literature. Eur J Med Res. 2011;16(4):153-7.

¹⁰ NDA 207-500 ISA, GS, Module 1.16 RMP, Table 38, page 111 of 379

3.2.6 120-Day Safety Update Report

The 120-Day Safety Update Report (SUR) does not include any significant changes or addenda. See the Clinical Review by Ed Weinstein, M.D., for details on the 120-Day SUR.

4 DISCUSSION

Triazole anti-fungal agents are the recommended treatment of choice for adult patients with invasive fungal infections such as *Aspergillosis*, *Candidiasis* including esophageal *Candidiasis*, *Blastomycosis*, and/or *Histoplasmosis*. The FDA-approved triazole antifungal products are voriconazole, itraconazole, and posaconazole. The proposed indication for ISA is for the treatment of adult patients with invasive *Aspergillosis* and invasive mucormycosis in adult patients. Currently, there is no FDA-approved product for treatment of invasive mucormycosis based on a clinical trial. Isavuconazonium, if it should be approved by the FDA, will be the fourth-in-class, triazole antifungal agent.

The primary efficacy endpoint was all-cause mortality through Day 42. In the ITT population, the all-cause mortality rate through Day 42 was 18.6% for ISA and 20.2% for VRC. The adjusted difference between treatment groups was -1.0% with a corresponding 95% confidence interval of (-8.0, 5.9). Based on the upper bound of the 95% CI in less than 10%, non-inferiority of ISA compared to VRC was demonstrated with respect to all-cause mortality through Day 42. Per the Clinical Reviewer, the results are robust across the various populations and are similar, regardless of whether the protocol-defined or FDA-defined criteria are employed for defining the mITT population.

The safety profile of ISA is consistent with the class of triazole anti-fungal agents and is most similar to the serious risks associated with use of VRC, the comparator product employed in P3 study 9766-CL-0104/WSA-CS-004. The serious adverse events reported with ISA are hepatotoxicity, including 3 cases fulfilling Hy's Law; infusion-related reactions including hypersensitivity reaction and anaphylactic shock; exfoliative cutaneous reactions; QT abnormalities. Embryo-fetal harm is included in proposed labeling for ISA based on animal studies and the finding of skeletal abnormalities in offspring. At this time, ISA is proposed as pregnancy category C.

Severe cutaneous adverse events, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are known azole class effects. The exact mechanism of azole associated severe cutaneous adverse reactions is unknown.

Voriconazole and the proposed ISA labeling include the following common serious risks in Section 5, *Warnings and Precautions*: hepatotoxicity, infusion-related reactions, exfoliative cutaneous reactions, arrhythmias and QT prolongation; drug-drug interactions; and fetal harm (based on animal studies).

The risk management strategy for the class of triazole anti-fungal agents includes labeling with recommendations for monitoring patients during infusion and monitoring laboratory tests aligned with specific known risks (e. g., liver enzyme test results). None of the

approved triazole anti-fungal products has a Medication Guide and none have been required to have a REMS based on post-marketing safety (all three azole anti-fungal products were approved prior to the Food and Drug Administration Amendments Act (FDAAA) which includes the determination to require a REMS program for a product to ensure that the benefits outweigh the risks.

The target providers for ISA are the same target providers for the three FDA-approved and marketed triazole anti-fungal products. These target providers, should ISA be approved, are familiar with the safety profile of the class of triazole anti-fungal agents and the management of these serious events.

The proposed RMP for ISA includes a routine pharmacovigilance plan without a proposed REMS. At this time, the DAIP and the DRISK concur that a REMS program is not needed to ensure that the benefits of ISA, outweigh the risks. If approved, ISA will be the fourth-in-class azole anti-fungal product. Currently, the DAIP and the DRISK agree that labeling will be adequate to communicate the reported serious risks with the use of ISA.

The patient population most likely affected by invasive aspergillosis and/or invasive mucormycosis are severely immunocompromised patients, such as hematopoietic stem cell transplant recipients with graft versus host disease, hematologic malignancies with prolonged neutropenia from chemotherapy and/or transplant therapies. Oncology and/or transplant prescribers and related support healthcare providers monitor these patients very closely. The DAIP and the DRISK concurred, at this time, that labeling with patient information will be used to communicate the serious risks associated with ISA, if approved.

The DAIP proposes to keep the labeling for ISA, if approved, similar to the approved labeling for the class of triazole antifungal agents. As of this review the DAIP does not plan to require a Medication Guide for ISA, if approved. The AIDAC will be convened on January 22, 2015 for discussion of the totality of clinical efficacy and safety data with ISA compared to VRC for invasive Aspergillosis, and with ISA for invasive mucormycosis. At this time, there are no planned questions on a potential REMS program for ISA. The DRISK will attend the AIDAC as panel members may discuss risk management concerns for ISA.

The DAIP is considering a postmarketing commitment (PMC) from the Division of Microbiology concerning the development of antifungal resistance to ISA. The applicant may need to conduct surveillance studies for 5 years from the date of marketing Cresemba, if approved, [REDACTED] (b) (4) [REDACTED] in organisms relevant to the indication in the package insert for invasive aspergillosis and invasive mucormycosis.

5 CONCLUSION

The DRISK and the DAIP concur, at this time, that a REMS program is not required for ISA, if approved, to ensure that the benefits of ISA outweigh the risks associated with its use. The proposed indication for ISA is for treatment of adult patients with invasive *Aspergillosis* and invasive mucormycosis. An AIDAC will be held on January 22, 2015. The DAIP and the DRISK will weigh discussion and feedback from the Committee on

the serious risks associated with use of ISA and proposed risk management. The DAIP should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for ISA, with the formulation for injection as IV administration or with the hard oral capsule.

APPENDIX: See the next page for **Table 1**.

Table 1. Anti-Infective Treatment Options for Invasive Aspergillosis (version 04Dec2014)

Trade Name	CRESEMBA	VFEND	SPORANOX	NOXAFIL
Established Nm	Isavuconazonium (ISA) IV/O	Voriconazole (VRC) IV/O	Itraconazole IV/O	Posaconazole IV/O
NDA	207-501	021-267	020-966	205-596; 022-003
NME	Yes	No	None Known	
Approval Date	Pre-approval	Initial 2002; Feb-2014	30-Mar-99	
Class	Triazole Antifungal	Triazole Antifungal	Triazole Antifungal	
Indications	Proposed for the treatment of: 1.1 Invasive aspergillosis, 1.2 Invasive mucormycosis.	1.1 Invasive aspergillosis; 1.2 Candidaemia (non-neutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, wounds. 1.3 Esophageal candidiasis; 1.4 Serious infections (see label).	Fungal infections in immuno-compromised pts: 1.1 Blastomycosis (pul, extra-pul) 1.2 Histoplasmosis (chronic cavitory pul, disseminated non-meningitis. 1.3 Aspergillosis (pul, extra-pul)	1.1 Prophylaxis of IA and Candida infections 1.2 Tx of oropharyngeal Candidiasis including oropharyngeal Candidiasis refractory to itraconazole and or fluconazole.
Boxed Warning	Not proposed	None	Yes: Risks: CHF, Drug Interactions	None
Contraindications	Hypersensitivity to ISA (b) (4) Coadministration w/strong CYP-3A4 inhibitors, ie, ketoconazole, or high-dose ritonavir. Co-administration w/strong CYP-3A4 inducers, ie, rifampin, carbamazepine, St. John's Wort, long-acting barbituates. Use in pts w/ Familial Short QT syndr.	Efavirenz 400 mg q ≥ 24 hrs;	Drug Interactions (CYP3A4) Hypersensitivity to itraconazole; IV Sodium Chloride; Severe renal impairment;	Known hypersensitivity to posaconazole/other azole antifungal. Do not administer w/ the following: Sirolimus, CYP3A4 substrates, HMG-CoA Reductase Inhibitors, Ergot alkaloids.
Warnings & Precautions	(b) (4)	5.1 Clinically Significant Drug Interactions	5.1 Hepatic; 5.2 Cardiac Dysrhythmias;	5.1 Calcineurin Inhibitor Toxicity 5.2 Arrhythmias & QTc prolong.

	5.3 Infusion Related Reactions (b) (4) 5.5 Embryo-Fetal toxicity 5.6 Drug Interactions	5.2 Hepatic Toxicity 5.3 Visual Disturbances 5.4 Embryo-Fetal Toxicity 5.5 Pts w/Hereditary Galactose Intolerance Lapp Lactase Def. or Glucone-Galactose Malabsorpt. 5.6 Arrhythmias and QT Prolong. 5.7 Infusion Reactions 5.8 Laboratory Tests 5.9 Pts w/Hepatic Impairment 5.10 Pts w/Renal Impairment 5.11 Monitoring Renal Funct. 5.12 Monitoring Pancreatic Funct. 5.13 Dermatology Reactions 5.14 Skeletal Adverse Reactions	5.3 Cardiac Disease. Precautions: Hepatotoxicity Neuropathy Hearing Loss	5.3 Hepatic Toxicity 5.4 Renal Impairment: Avoid in pts w/moderate to severe renal impairment (CrCl < 50 mL/min). Midazolam - Noxafil can prolong effects of Noxafil. 5.5 Use w/ Midazolam
Med. Guide	No MG proposed	No MG		
REMS	None proposed	No		
(b) (4) ANDA 200-833 Caspofungin IV-Not Marketed/Tentative Approval/No RLD; NA-Not applicable; Pts-Patients; w-with;				

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/s/

CAROLYN L YANCEY

12/05/2014

REMS Review for CRESEMBA (isavunconazonium), oral and IV formulations

CYNTHIA L LACIVITA

12/07/2014

Concur