CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s000 / 207501Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley MD MPH
Subject	Deputy Office Director Decisional Memo
NDA #s	207500 and 207501
Applicant Name	Astellas Pharma US, Inc.
Date of Submission	July 08, 2014
PDUFA Goal Date	March 08, 2015
Proprietary Name / Established (USAN) Name	CRESEMBA / Isavuconazonium sulfate
Dosage Forms / Strength	Capsules, 186 mg isavuconazonium sulfate Powder for Injection, 372 mg isavuconazonium sulfate/vial
Proposed Indication	1. Invasive aspergillosis 2. Invasive mucormycosis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Edward Weinstein MD PhD
Statistical Review	Cheryl Dixon PhD
Pharmacology Toxicology Review	Owen McMaster PhD
CMC/Pharmaceutical Quality Reviews	Nina Ni PhD, Yichun Sun PhD, Gene Holbert PhD Vinayak Pawar, PhD, Banu Zolnik, PhD
Microbiology Review	Shukal Bala PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Office of Scientific Investigations	Antoine El-Hage PhD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D Shawna Hutchins MPH BSN RN
CDTL Review	John Alexander MD MPH
Division Director Review	Sumathi Nambiar MD MPH

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1. Introduction

Astellas Pharma US, Inc. (the Applicant) has submitted NDAs 207500 and 207501 for CRESEMBA (isavuconazonium sulfate) Capsules and Powder for Injection, respectively. Isavuconazonium sulfate is a prodrug of isavuconazole and is a member of the azole class of antifungal drugs. Following administration, isavuconazonium sulfate is rapidly hydrolyzed to isavuconazole by esterases.

The mechanism of action of isavuconazole is similar to other drugs of the azole class and involves the inhibition of the cytochrome P450 sterol 14 α-demethylase enzyme, which has a role in the synthesis of ergosterol, a component of the fungal cell membrane. Depletion of ergosterol is known to disrupt the structure and function of the fungal cell membrane, including accumulation of toxic sterol intermediates, leading to inhibition of fungal growth.

The proposed indication is treatment of invasive aspergillosis and treatment of invasive mucormycosis. The currently approved therapies for invasive aspergillosis include different formulations of amphotericin B, itraconazole, voriconazole, and caspofungin. The only drug approved for the treatment of invasive mucormycosis is amphotericin B. Both of these serious fungal diseases are rare and generally occur in immune suppressed patients in the U.S. A prospective surveillance study conducted at 23 transplant centers in the U.S. between 2001 and 2006 prospectively enrolled and followed 16,200 patients receiving a hematopoietic stem cell transplant. The 12 month cumulative incidence for invasive aspergillosis was 1.6% and approximately 0.3% for invasive mucormycosis.[1] The incidence for both diseases is somewhat lower in solid organ transplant patients.[2] Isavuconazonium sulfate received orphan drug designation for both proposed indications.

Each CRESEMBA capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). CRESEMBA powder for injection is supplied in a single-dose vial containing 372 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole).

The proposed dosing regimen is:
Loading Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours) via oral (2 capsules) or intravenous administration (1 reconstituted vial).
Maintenance Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily via oral (2 capsules) or intravenous administration (1 reconstituted vial) starting 12 to 24 hours after the last loading dose.

The efficacy review for this NDA relies upon the results of two Phase 3 studies, a randomized trial comparing isavuconazonium sulfate to voriconazole for the treatment of patients with invasive aspergillosis (trial 9766-CL-0104), and a single arm trial in patients with invasive fungal disease including invasive mucormycosis (trial 9766-CL-0103).

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[1] Kontoyiannis DP, Marr KA, Park BJ et al. Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Inf Dis* 2010;50: 1091-1100.

[2] Park BJ, Pappas PG, Wannemuehler KA et al. Invasive Non-*Aspergillus* Mold Infections in Transplant Recipients, United States, 2001–2006. *Emerg Infect Dis* 2011;10:1855-64.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of isavuconazonium sulfate for the indications proposed. For a detailed discussion of NDAs 207500 and 207501, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background/Regulatory

Isavuconazonium sulfate was developed under IND 72593 for the powder for injection dosage form. The IND was originally owned by Basilea Pharmaceuticals and subsequently by Astellas Pharma US, Inc. IND 119307 was also in effect for the capsule dosage form. A series of meetings were held between the Applicant and the Agency regarding the development of isavuvonazonium sulfate. The design of trial 9766-CL-0104 was discussed extensively, and the Applicant and Agency agreed on the design in 2006. In addition to orphan drug designation noted above, the products received qualified infectious disease product (QIDP) designation for the treatment of invasive aspergillosis and for the treatment of invasive mucormycosis. As isavuconazonium sulfate has QIDP designation for the submitted indications, these NDAs received a priority review.

This would be the first marketing approval world-wide for isavuconazonium sulfate.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

For the capsule dosage form, the reviewers concluded that the Applicant had provided sufficient information to assure the identity, purity, strength, and quality of the drug product, and the stability data provided supports the proposed expiration dating period of 30 months. The Biopharmaceutics reviewer concluded that the dissolution method and acceptance criterion for isavuconazonium sulfate capsules were acceptable for batch release and stability testing and recommended approval.

For the powder for injection dosage form, the reviewers concluded that the Applicant had provided sufficient information to assure the identity, purity, strength, and quality of the drug product. The powder for injection is a sterile lyophilized product in a vial containing a single dose of isavuconazonium sulfate 372 mg. The reviewers concluded that the stability data support the proposed shelf life of 24 months for the drug product when stored in a refrigerator. The Product Quality Microbiology reviewer found the sterility controls acceptable and recommended approval. The powder for injection is to be administered by intravenous infusion after reconstitution with 5 mL of water for injection and further dilution with 0.9% saline or 5% dextrose solution. The reconstituted solution may be stored for up to 1 hour prior to preparation of the infusion solution. The prepared (diluted) solution should be kept not more than 6 hours at room temperature or 24 hours stored at 2°-8° C.

A safety issue discussed in the course of the review was that a white precipitate was observed to form during preparation of the solution for intravenous administration when the reconstituted solution was mixed with either 0.9% saline or 5% dextrose solution. The precipitate was conclusively identified as isavuconazole. The reviewer noted that isavuconazole levels in the drug substance and drug product cannot be lowered any further due to the poor solubility of isavuconazole in aqueous media. The reviewer also noted that neither the precipitate nor the removal of the precipitate with an inline filter will affect the efficacy of the drug product based on data obtained at maximum in-use storage times and after filtration. The Applicant provided data to demonstrate that there was (b) (4) with filters of two sizes (0.2 µm and 1.2

µm). Compatibility was also demonstrated between the drug product and two different types of in-line filters. During clinical trials, the product was administered through an in-line filter. The Dosage and Administration section (2.0) of the prescribing information includes a statement that the product should be administered using an inline filter. The Warnings and Precautions section of the prescribing information includes a warning regarding particulates and states that the product is to be administered through an in-line filter. I conclude that this safety concern can be adequately mitigated with labeling and use of an in-line filter.

Manufacturing site inspections were completed and all manufacturing sites were deemed acceptable.

(b) (4)

Following discussions with the review team, the Applicant, and senior leadership of the Office of Pharmaceutical Quality and the Office of New Drugs, it was agreed to use isavuconazonium sulfate as the established name with the strength of isavuconazonium sulfate expressed (b) (4) A statement with the isavuconazole equivalent strength would be prominently included in the carton and container labeling as well as the prescribing information. I conclude that this decision is consistent with statute and is most likely to reduce the risk of medication error. The review team and senior leadership agreed that this exception to the USP Salt Policy is justified to reduce the risk of medication error.

In summary, the particulate risk for the intravenous dosage form can be mitigated through use of an in-line filter and labeling, the decision regarding the established name and strength labeling is appropriate to reduce the risk of medication error, and there are no outstanding CMC/pharmaceutical quality issues precluding approval.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology-Toxicology reviewer stated that the nonclinical toxicology program was adequate to support marketing, and there are no nonclinical pharmacology or toxicology data that preclude approval.

[3] See: 21 U.S.C. §352(e)(1)(A)(ii)

In repeat dose toxicology studies, drug administration was associated with reversible increases in liver weights and/or hepatocellular hypertrophy in mice and rats. The reviewer assessed this as an adaptive response to induction of CYP3A and CYP2B enzymes as there was no evidence of hepatocellular damage. The prescribing information advises monitoring of liver tests during therapy.

When administered to pregnant animals during early embryo-fetal development, the drug induced skeletal abnormalities and/or variations in the rat and rabbit at doses as low as one tenth of the systemic exposure of the maintenance human dose. In dams dosed orally during pregnancy and throughout the weaning period, there was increased perinatal mortality among rat pups. Isavuconazole was detected in the milk of lactating dams at levels up to 17 times higher than plasma levels. The prescribing information describes the non-clinical findings and indicates that Cresemba may cause fetal harm when administered to a pregnant woman. The prescribing information states, (b) (4)

The Applicant did not conduct carcinogenicity studies. Because of the expected duration of treatment, particularly for patients with mucormycosis who may require a course of treatment close to or exceeding six months, the reviewer recommended that the Applicant conduct a minimum of a single 2 year carcinogenicity study in rats and one other abbreviated carcinogenicity evaluation as a Post-Marketing Requirement (PMR). I agree with this recommendation.

In summary, there are no non-clinical pharmacology toxicology issues precluding approval. The Applicant has agreed to conduct two-year mouse and rat carcinogenicity studies as PMRs.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer concluded that the Clinical Pharmacology information provided by the Applicant was acceptable and supports the use of the proposed dosage regimen for the indications proposed.

In vitro, it was demonstrated that isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases, predominantly butyrlcholinesterase. The pharmacokinetics (PK) is dose proportional in the dose range of 100-600 mg. The absorption median T_{MAX} is 2-3 hours and there is no food effect. The drug is >99% protein bound. The elimination half-life ($T_{1/2\ term}$) is approximately 5 days. The drug is a substrate of CYP3A4 and CYP3A5. It is equally excreted in feces and urine.

In the analyses of trial 9766-CL-0104, it was observed that the subgroup of patients categorized as "Asian" (based on race or country of origin) had higher mortality than non-Asians in the isavuconazonium sulfate arm and this difference was not noted in the comparator arm. In a sensitivity analysis, it was clear that sites located in South Korea were driving this mortality imbalance. Thus, the imbalance was not attributable to race or region. The reason for the higher mortality at South Korean sites is not clear.

It was observed that Asians had approximately 50% higher exposure compared to non-Asians for the same dosing regimen. Dose adjustment was not deemed necessary as the overall exposure-response relationship for efficacy and safety was flat within the concentration range achieved in trial 9766-CL-0104.

Due to the potential for drug interactions, co-administration of strong CYP3A4 inhibitors (such as ketoconazole or high-dose ritonavir) or strong CYP3A4 inducers (such as rifampin, carbamazepine, St. John's Wort, or long-acting barbiturates) are contraindicated. Recommendations for dose adjustment or monitoring for other potential drug interactions is included in the prescribing information.

(b) (4)

I conclude that the labeling is appropriate to mitigate risks related to Clinical Pharmacology considerations, and there are no Clinical Pharmacology issues precluding approval.

6. Clinical Microbiology

The Clinical Microbiology reviewer found the NDAs approvable and recommended changes to the proposed labeling and a post-marketing study which were agreed to by the Applicant.

The activity of isavuconazole was measured in vitro against different species of *Aspergillus* and Mucorales. Among the *Aspergillus* species, isavuconazole MIC_{90} values were lower against *A. fumigatus, A. flavus, A. nidulans, and A. terreus* compared to *A. niger*. In vitro activity against isolates of various Mucorales species was variable. Overall, MIC_{90} values were lower against *Aspergillus* species (range 1-4 µg-mL) compared to Mucorales (range 1-32 µg-mL).

In animal models, the activity of isavuconazole was reported in mice with disseminated aspergillosis (*A. flavus, A. fumigatus, and A. terreus)*, and immunocompromised mice, guinea pigs, and rabbits with pulmonary aspergillosis. In each animal model except for the guinea pig pulmonary aspergillosis model, isavuconazole improved survival and/or reduced fungal burden in animals infected with *A. flavus,* or *A. fumigatus*. In *A. terreus* infected mice, isavuconazole was not effective under the experimental conditions tested.

The activity of isavuconazole was less clear in the animal models of Murcormycosis presented. In neutropenic mice infected by the inhalational route with a strain of *Rhizopus oryzae*, isavuconazole at the highest dose tested was effective in improving survival. A similar experiment in DKA mice infected by the inhalational route with the same inoculum size failed to demonstrate a survival benefit. When a lower inoculum was used to challenge DKA mice by the inhalational route, a trend toward increased survival was observed. Isavuconazole was not effective in improving survival in hematogenously disseminated DKA and neutropenic mouse models. Models using Mucorales other than *R. oryzae* were not presented.

The reviewer noted that there is a potential for development of resistance to isavuconazole, likely due to multiple mechanisms including substitution in the target gene, alterations in sterol profile, and efflux pump activity. (b) (4)

(b) (4)

I conclude that there are no Clinical Microbiology issues precluding approval. The reviewer recommended that the Applicant conduct a surveillance study for five years post-marketing, collecting MIC data for clinical isolates of *Aspergillus* and Mucorales species. This will be helpful in determining (b) (4) The Applicant has agreed to conduct this study as a PMR.

7. Clinical/Statistical Efficacy

Invasive Aspergillosis

The Statistical reviewer, Clinical reviewer, CDTL, and Division Director all concluded that substantial evidence of efficacy for the treatment of invasive aspergillosis had been provided.

For this indication, the primary evidence of efficacy is based on a single Phase 3 trial. Trial 9766-CL-0104 was a randomized, double-blind, non-inferiority, comparative group study which evaluated the efficacy and safety of isavuconazonium sulfate compared to voriconazole. The primary objective of the trial was to assess non-inferiority of isavuconazonium sulfate compared to voriconazole for all-cause mortality through Day 42. The ITT population was the protocol-defined primary analysis population for the primary endpoint of all-cause mortality through Day 42. The pre-specified non-inferiority margin of 10% was adequately justified. The justification is detailed in the Statistical Review for these NDAs.

The Intent-to-Treat (ITT) population consisted of 516 patients (258 in each treatment group). The modified ITT (mITT) population, which included ITT patients who had proven or probable invasive fungal disease (IFD) as assessed by the Data Review Committee (DRC), consisted of 143 isavuconazonium sulfate patients and 129 voriconazole patients. Of these, 123 isavuconazonium sulfate patients and 108 voriconazole patients had proven or probable invasive aspergillosis and were included in the mycological ITT (myITT) population (culture, cytology, histology, or galactomannan evidence of infection). All-cause mortality through Day 42 in the ITT population was 18.6% for isavuconazonium sulfate and 20.0% for voriconazole. The adjusted difference between treatment groups was -1.0% with a corresponding 95% confidence interval (CI) of (-8.0%, 5.9%). Non-inferiority of isavuconazonium sulfate compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42 since the upper bound of the 95% CI is less than 10%. The results are robust and similar across the mITT (using both protocol-defined and recently FDA-recommended galactomannan criteria[4]) and myITT populations. The key secondary endpoint of DRC-assessed overall response at EOT was similar between treatment groups (35.0% for isavuconazole and 36.4% for voriconazole, mITT population).

Supportive data for the invasive aspergillosis indication comes from trial 9766-CL-0103. Trial 9766-CL-0103 was an open-label, Phase 3 trial conducted to evaluate the safety and efficacy of

[4] Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis, Available at: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf

isavuconazonium sulfate for the primary treatment of invasive fungal disease caused by *Aspergillus* species in patients with renal impairment, or caused by rare filamentous fungi. The trial enrolled a total of 149 patients, with 24 patients assessed by the DRC as having only an *Aspergillus* infection. Twenty of these 24 patients were renally impaired. The all-cause mortality rate through Day 42 was 12.5% for all patients with invasive aspergillosis and 15% for those with invasive aspergillosis who were renally impaired. Although the number of patients is small, the results including those of renally impaired patients are similar to those observed in trial 9766-CL-0104.

Invasive aspergillosis is an orphan disease. The conduct of a randomized active comparator trial such as trial 9766-CL-0104 is challenging, and acceptance of a single trial with supportive evidence seems appropriate in this case. I conclude that the robust results of trial 9766-CL-0104 supported by the efficacy results for the *Aspergillus* infection subgroup of trial 9766-CL-0103 provide substantial evidence of efficacy for the treatment of invasive aspergillosis.

Invasive Mucormycosis

The Statistical reviewer, Clinical reviewer, CDTL, and Division Director all concluded that there is adequate evidence of efficacy for the treatment of invasive mucormycosis.

The primary evidence to support efficacy for the treatment of invasive mucormycosis was based on the single arm open-label trial 9766-CL-0103. As described above, the study enrolled a total of 149 patients, and 46 of these had invasive mucormycosis. Of these 46 patients with mucormycosis, 37 were assessed by the DRC as having proven or probable invasive mucormycosis infection only and constitute the mITT-Mucorales subgroup, the subgroup which is the focus of the mucormycosis efficacy review. Of these 37 patients in the mITT-Mucorales subgroup, 21 received isavuconazonium sulfate as primary therapy. An additional 16 patients received isavuconazonium sulfate as second line or salvage therapy after progression of disease on initial therapy (11 "refractory") or after failing to achieve therapeutic drug levels or experiencing an adverse drug reaction on initial therapy (5 "intolerant"). DRC-assessed overall response was specified as the primary endpoint in the protocol. However, both the Applicant and the Agency agreed that day 42 mortality was the most relevant primary endpoint because it was consistent with trials of other antifungal drugs and allowed for comparison with historical controls.

For the mITT-Mucorales subgroup, the all-cause mortality rate through Day 42 was 37.8% with an exact 95% CI of (22.5%, 55.2%). The Day 84 all-cause mortality rate was 43.2% (95% CI 27.1, 60.5). The DRC assessed overall response at EOT was 31.4% with an exact 95% CI of (16.9%, 49.3%).

The review team sought to identify an appropriate historic control group for the mITT-Mucorales subgroup of trial 9766-CL-0103. In a published case series of 929 cases of invasive mucormycosis diagnosed during the years 1940-2003, Roden and colleagues noted a mortality rate of 97% (233/241) in those who received no treatment.[5] However, 92% of the cases were diagnosed with invasive mucormycosis post-mortem. Skiada and colleagues published a case series of 230 cases of invasive mucormycosis diagnosed during the years 2005-2007 in Europe,

[5] Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41(5):634-53.

with 4% of cases diagnosed post-mortem.[6] They reported that 21/22 (95%) untreated patients did not survive. While the high proportion of autopsy diagnoses in the Roden case series is a significant limitation, the mITT-Mucorales subgroup of trial 9766-CL-0103 had more patients with malignancy and/or bone marrow transplant than the Roden or Skiada case series which may increase the mortality risk for the trial 9766-CL-0103 patients. (see Table 1).

Table 1: Comparative Underlying Patient Diagnoses in Mucormycosis Populations
Source Table 29, Clinical Review, NDA 207500 and 207501

	Trial 9766-CL-0103 mITT Mucorales Subgroup	Skiada et al. Case Series	Roden et al. Case Series
Hematologic Malignancy	22/37 (59%)	102/230 (44%)	154/929 (17%)*
Neutropenia at baseline	10/37 (43%)	N/D	N/D
BMT	13/37 (35%)	21/230 (9%)	44/929 (5%)
Diabetes mellitus	4/37 (11%)	39/230 (17%)	337/929 (36%)
Solid Organ Transplant	3/37 (8%)	10/230 (4%)	61/929 (7%)
Solid Organ Malignancy	2/37 (5%)	11/230 (5%)	N/D*
Other	3/37 (8%)		
Aplastic Anemia	1/37 (3%)	4/230 (2%)	N/D
No Underlying Disease	1/37 (3%)	0/230 (0%)	176/929 (19%)
Burn/Trauma	0/37 (0%)	46/230 (20%)	43/176 (24%)

*Malignancy not differentiated between solid organ and hematologic in the Roden et al case series

The Applicant also provided analyses based on the Fungiscope Registry, a global web-based database, coordinated by the Clinical Trials Centre at the University of Cologne, Germany. The database includes more than 150 cases of invasive mucormycosis diagnosed and treated between 2003 and 2013. There were 29 patients in the database with invasive mucormycosis who did not receive appropriate therapy and all died by day 42. The autopsy diagnosis rate was not reported.

An additional contemporary case series was published by Chamilos et al.[7] The authors reviewed the medical records of consecutive patients at the MD Anderson Cancer Center with hematologic malignancies, including hematopoietic stem cell transplant recipients, who had proven or probable invasive mucormycosis during the period 1989-2006. All patients were alive at the time of diagnosis. Seventy patients who had received initial amphotericin based treatment were included in the case series. Six days after the onset of symptoms to the initiation of amphotericin based treatment was identified as the mortality breakpoint between early treatment and delayed treatment, with 35 patients in each group. The delayed treatment group had a 2-fold increase in mortality rate at 12 weeks after diagnosis (82.9%), compared with early treatment (48.6%).

[6] Skiada A, Pagano L, Groll A, et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. *Clin Microbiol Infect* 2011; 17(12):1859-67.
[7] Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clin Infect Dis* 2008;47:503-9.

The mortality rate in the delayed treatment group in the Chamilos et al. case series could be considered a conservative estimate of the untreated control mortality rate. For the mITT-Mucorales subgroup of trial 9766-CL-0103 receiving primary therapy with isavuconazonium sulfate, the upper limit of the 95% CI for day 84 all-cause mortality is below the lower bound of the 95% CI for the mortality 12 weeks after diagnosis for the 6-day delayed treatment group in the Chamilos et al. case series. (see Table 2) While all the patients in Chamilos et al. case series had hematologic malignancy, the day 84 all-cause mortality rate for the patients with hematologic malignancy in the mITT-Mucorales subgroup of trial 9766-CL-0103 of 41% (9/22) [95% CI 20.4, 61.5] was similar to the mortality rate for the primary therapy patients in this trial, and the upper bound of the 95% CI is also below the lower bound of the 95% CI for the 6-day delayed treatment group in the Chamilos et al. case series.

Table 2: Cross-Study Comparison of Mortality Rates
Source Table 40 Clinical Review, NDA 207500 and 207501

	Trial 9766-CL-0103 mITT Mucorales Subgroup	Trial 9766-CL-0103 mITT Mucorales Subgroup (primary therapy)	Chamilos et al. Case Series Delayed Therapy Subgroup (mortality at 12 weeks after diagnosis)
Day 42*	14/37 (37.8%) [95% CI 22.5, 55.2]	7/21 (33.3%) [95% CI 14.6, 57.0]	82.9% [95% CI **68.9**, 96.8]
Day 84	16/37 (43.2%) [95% CI 27.1, 60.5]	9/21 (42.9%) [95% CI 21.8, **66.0**]	

*One patient with unknown survival status at day 42 was presumed dead
All confidence intervals were calculated using exact binomial method.

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Invasive mucormycosis is a very rare orphan disease. The conduct of a randomized control trial would not be feasible. I conclude that the case series from the published literature discussed above provide an adequate historical control estimate for the mortality rate associated with no treatment. While there are limitations with respect to differences in patient characteristics between groups, the mortality rate associated with no treatment is high and predictable. The data strongly supports the conclusion that the treatment effect of isavuconazonium sulfate is superior to no treatment. Therefore, acceptance of a historic control is appropriate in this circumstance, and trial 9766-CL-0103 is an adequate and well-controlled trial meeting the provisions of 21CFR§314.126(b)(2)(v). I find that the robust results of the randomized control trial 9766-CL-0104 provide important supportive evidence by demonstrating the efficacy of isavuconazonium sulfate in the treatment of another invasive fungal disease. In summary, substantial evidence of efficacy for isavuconazonium sulfate for the treatment of invasive mucormycosis has been provided.

A limitation of trial 9766-CL-0103 is that a number of species in the order Mucorales are known to cause invasive mucormycosis, and some were not isolated from patients enrolled in the trial. A limitation of trial 9766-CL-0104 is that patients with infections caused by non-fumigatus *Aspergillus* species were few. The Applicant has agreed to a Post-Marketing Commitment (PMC) to establish a registry to collect and analyze clinical efficacy-related outcome data for patients treated with isavuconazonium sulfate who have invasive mucormycosis or infection with non-fumigatus *Aspergillus* species.

8. Safety

The Clinical reviewer, CDTL, and Division Director all concluded that there were no safety issues precluding approval.

The safety database of 1,692 subjects exposed to isavuconazonium sulfate includes 1,145 healthy volunteers from 40 Phase 1 studies, 144 patients in the Phase 2 trials, and 403 patients in the Phase 3 trials. The mean duration of exposure was 59.9 days.

In trial 9766-CL-0104, there were no imbalances between isavuconazonium sulfate and voriconazole in mortality or overall SAEs.

Hepatic TEAEs were reported in 23/257 (8.9%) isavuconazonium sulfate treated patients compared to 42/259 (16.2%) voriconazole-treated patients. The three hepatic SAEs reported in the isavuconazonium sulfate arm were hepatitis, acute hepatitis, and cholecystitis, and one of these had no apparent risk factor other than isavuconazonium sulfate exposure. In the combined Phase 2 and Phase 3 safety population, 5/535 (0.9%) isavuconazonium sulfate treated patients satisfied the laboratory criteria for Hy's Law. All cases had alternative etiologies such as concurrent sepsis, multi-organ failure, and concurrent use of other hepatotoxic drugs.

In trial 9766-CL-0104, potential anaphylaxis and severe cutaneous reactions were reported in 1.9% of patients in both treatment arms. In Trial 9766-CL-0104, potential infusion-related serious TEAEs were reported in 10.1% of patients in the isavuconazonium sulfate arm compared to 6.9% in the voriconazole arm.

Twenty-one patients in trial 9766-CL-0104 and six patients in trial 9766-CL-0103 were inadvertently administered intravenous isavuconazonium sulfate without an in-line filter. No embolic or thromboembolic AEs were reported in these patients.

Hepatic adverse drug reactions, infusion-related reactions, hypersensitivity reactions, and the need to administer isavuconazonium sulfate through an in-line filter are included as warnings in the Warnings and Precautions section of the prescribing information.

A randomized, double-blind, placebo and active-controlled thorough QT (TQT) study was performed. The study enrolled 160 subjects who received oral isavuconazonium sulfate (equivalent to 200 mg and 600 mg of isavuconazole), placebo, and a single oral dose of moxifloxacin 400 mg. No clinically relevant prolongation of the QT interval was observed, however a dose-and-concentration related shortening of the QTc interval was observed. The Contraindications section (4) of the prescribing information includes a statement about QTc interval shortening and use of isavuconazonium sulfate is contraindicated in patients with Familial Short QT syndrome.

I conclude that risks can be adequately mitigated through labeling, and there are no safety concerns that preclude approval.

9. Advisory Committee Meeting

These NDAs were discussed by the Anti-Infective Drugs Advisory Committee on January 22, 2015.

The committee discussed and voted on the question of whether the Applicant demonstrated substantial evidence of safety and efficacy of isavuconazonium for the proposed indication of treatment of invasive aspergillosis. The vote was 11 Yes, 0 No, 0 Abstain.

The committee discussed and voted on the question of whether the Applicant demonstrated substantial evidence of safety and efficacy of isavuconazonium for the proposed indication of treatment of invasive mucormycosis. The vote was 8 Yes, 2 No, 1 Abstain. Rationales stated by panel members are discussed in the CDTL Review.

10. Pediatrics

As both products have orphan drug designation for both indications, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

11. Other Relevant Regulatory Issues

Six clinical investigator sites were inspected. There were some GCP deficiencies observed at 4 sites, with these 4 ultimately adjudicated as VAI. The OSI reviewer concluded that the clinical data for these sites was acceptable in support of the NDA.

There are no other unresolved relevant regulatory issues.

12. Labeling

As discussed in Section 3 of this memo, the major labeling issues discussed in the course of the review concerned the established name and strength. Following the discussions summarized in Section 3, the Applicant resubmitted proprietary name requests as:

> Cresemba (Isavuconazonium Sulfate) capsules, 186 mg
> Cresemba (Isavuconazonium Sulfate) for injection, 372 mg

The DMEPA reviewer concluded that the proprietary names were acceptable.

As discussed in Section 3, the labeling will include information on the strength of isavuconazonium sulfate and the equivalent amount of isavuconazole (b) (4) For example, the Dosage Forms and Strengths section of the prescribing information states:

(b) (4)

The DMEPA reviewer found the carton and container labeling acceptable, given the decision to include the equivalency statement. The reviewer expressed concern regarding the extensive use of the isavuconazole equivalency statement in the Dosage and Administration section of the prescribing information. In addition, the reviewer expressed concern regarding the emphasis on dosing by number of vials or capsules instead of milligrams in the dosing table in Section 2.2 of the prescribing information. I acknowledge these concerns, but it is my conclusion that the labeling to be approved represents our best approach to reduce the risk of medication error in this

challenging situation. I agree with the perspective of the Division Director who states, "The circumstances surrounding this product pose unique challenges, based on information already available in the medical literature and the fact that the drug is an azole antifungal drug. Hence, it is important to include information about the equivalent amounts of isavuconazole in relevant sections of labeling. The reason for greater emphasis on dosing based on the reconstituted vial was to obviate any potential for administering a fraction of the vial based on isavuconazole doses and to emphasize that the entire contents of the single-dose vial should be administered." Post-marketing, we will monitor the FAERS system and other sources for reports of medication error and work with the sponsor to modify labeling if warranted.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

Risk Benefit Assessment:

Isavuconazonium sulfate is a new azole antifungal drug available in both oral and intravenous formulations. Adverse drug reactions observed in clinical trials included serious hepatic adverse drug reactions similar to other drugs in this class, infusion-related and hypersensitivity reactions, and drug interactions related to CYP3A4 metabolism. Embryo-fetal toxicity was observed in animals. The intravenous formulation may form insoluble particulates following reconstitution; the intravenous formulation must be administered through an in-line filter.

Invasive aspergillosis is a life-threatening infection. Isavuconazonium sulfate provides an additional treatment option for this infection with both intravenous and oral formulations, and the adverse drug reaction risks are reasonable in light of the seriousness of the disease. The evidence of efficacy is based primarily on robust results of a randomized controlled non-inferiority trial described in Section 7 of this Memo. The benefit risk is favorable for the approval of isavuconazonium sulfate for the treatment of invasive aspergillosis.

Invasive mucormycosis is a rare life-threatening infection which requires a prolonged course of treatment, particularly for immune suppressed patients. The only approved treatment is intravenous amphotericin B, which has common and serious associated adverse drug reactions, including renal toxicity. Based on clinical trial data which did not provide for a direct comparison with amphotericin B, isavunconazonium sulfate likely will be associated with less common and less severe adverse drug reactions. In addition, the oral formulation will provide a useful option for physicians and patients when prolonged treatment is required. The evidence of efficacy is based primarily on the results of a small historically controlled single-arm trial. The rationale for my conclusion that there is substantial evidence of efficacy is detailed in Section 7 of this Memo. I conclude that the benefit risk favors the approval of isavuconazonium sulfate for the treatment of invasive mucormycosis, and that this approval is consistent with regulations regarding drugs to treat life-threatening and severely debilitating illnesses at 21CFR§312.84.

Post-marketing Risk Evaluation and Mitigation Strategies:
None

Postmarketing Requirements and Commitments:

The Applicant has agreed to the following PMRs:

Conduct a prospective study over a five-year period to determine if decreased susceptibility to Cresemba (isavuconazonium sulfate) is occurring in the target population of organisms that are in the approved Cresemba (isavuconazonium sulfate) label.

Conduct a two-year mouse carcinogenicity study.

Conduct a two-year rat carcinogenicity study.

The Applicant has agreed to the following PMC:

Establish a registry to collect and analyze clinical efficacy-related outcome data on patients treated with isavuconazonium sulfate who have invasive mucormycosis or infection with non-fumigatus *Aspergillus* species.

Exclusivity:
Isavuconazonium sulfate has been granted QIDP designation. Isavuconazonium sulfate will be approved for the treatment of invasive aspergillosis and invasive mucormycosis, the same indications identified in the QIDP designation letters of November 8, 2013 and February 7, 2014 respectively. Isavuconazonium sulfate has not previously received a 5-year GAIN exclusivity extension. Therefore, the criteria for the 5-year GAIN exclusivity extension under section 505E(a) of the Act are met.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
03/06/2015