

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207500Orig1s000 / 207501Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	{See Electronic Stamp Date}
<b>From</b>	John Alexander, MD, MPH
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA#</b>	207,500 and 207,501
<b>Applicant</b>	Astellas Pharma US, Inc.
<b>Date of Submission</b>	July 8, 2014
<b>PDUFA Goal Date</b>	March 8, 2015
<b>Proprietary Name / Established (USAN) names</b>	Cresemba (b) (4)
<b>Dosage forms / Strength</b>	Capsules (b) (4) equivalent to 100 mg of isavuconazole) For Injection (b) (4) equivalent to 200 mg of isavuconazole)
<b>Proposed Indication(s)</b>	1. Invasive Aspergillosis 2. Invasive Mucormycosis
<b>Recommended:</b>	Approval for both NDA applications and both indications

## 1. Introduction

Astellas Pharma US, Inc. (the applicant) has submitted NDA 207, 500 and 207,501 for Cresemba (Isavuconazonium) Capsules and Powder for Injection, respectively. The applicant is seeking approval of these dosage forms of isavuconazonium for the treatment of patients with aspergillosis or mucormycosis. To support the aspergillosis indication, the applicant has submitted the results of a randomized, double-blind, noninferiority trial comparing isavuconazonium with voriconazole. To support the mucormycosis claim, the applicant has submitted data on patients with mucormycosis from a prospective, open-label, non-comparative trial. The safety and efficacy findings of the various review disciplines for the isavuconazonium NDA are the main topic of this CDTL review.

## 2. Background

Isavuconazonium is a pro-drug of the active agent, isavuconazole, a triazole antifungal drug. Isavuconazonium was the subject of IND 72593, sponsored by Basilea Pharmaceuticals, which became active in June 2005. An end-of-phase 2 meeting was held in December 2005. At that meeting, much of the discussion was related to controlled studies for (b) (4). However, the IND sponsor (b) (4).

The review division recommended a controlled clinical trial for evaluation of efficacy in *Aspergillus* infection, stating that a (b) (4)

(b) (4) The sponsor was advised that “An adequate and well-controlled study demonstrating efficacy in the primary treatment of invasive aspergillosis could be supportive of efficacy in zygomycosis, [...] and in other infections due to rare pathogens.”

The IND sponsor (b) (4) but subsequent communication in November 2006 documents agreements with a revised version of this protocol. Review of the non-comparative protocol for patients with invasive aspergillosis and renal impairment or invasive fungal infections due to rare moulds was conducted in 2007.

In 2010, the IND sponsorship was changed to Astellas, and the comparative trial was revised to specify 42-day mortality as the primary endpoint. The communication with the sponsor regarding the justification of the non-inferiority margin and use of the Intent-to Treat (ITT) as the primary analysis population extended over several meeting into 2011. There were also subsequent communications about the cut-off values of galactomannan from serum and broncho-alveolar lavage (BAL) specimens for diagnosis of *Aspergillus* infection. A separate IND for the oral capsule formulation (IND 119,307) was submitted in August 2013.

Isavuconazonium received orphan drug designation for both of the proposed indications in 2013. Isavuconazonium was also designated as a qualified infectious disease product in 2013 for both of the proposed indications.

A pre-NDA meeting was held with the IND sponsor in October 2013 to discuss CMC issues for the NDA. A separate pre-NDA meeting was held in November 2013 to discuss the content and format of the NDA submission for other disciplines.

### 3. CMC

The CMC review of NDA 207,500 for isavuconazonium capsules was conducted by Drs. Gene Holbert and Yichun Sun. The CMC review of NDA 207,501 for isavuconazonium for injection was conducted by Dr. Nina Ni. The CMC reviewers provided similar recommendations for both applications. The reviewers indicated that the applicant had provided sufficient information to assure the identity, purity, strength, and quality of the drug products. However, the office of compliance had not made an overall acceptable recommendation for the involved facilities of the drug products. The CMC reviewers also noted remaining issues regarding labeling of the drug products. Therefore, the CMC reviews state that the applications are not ready for approval until these issues have been resolved. There was also an ONDQA Biopharmaceutics review of the dissolution methods for the isavuconazonium capsules by Dr. Banu Zolnik. The ONDQA Biopharmaceutics review indicated that the capsule application could be approved from their perspective.

- General product quality considerations

Briefly, the information regarding drug substance was provided in the application for isavuconazonium capsules (NDA 207,500). NDA 207,501 references the capsule NDA for drug substance information. The drug substance is a sulfate salt of isavuconazonium, which is a pro-drug. The drug substance is a white to yellowish white powder. Isavuconazonium is hydrolyzed to form isavuconazole (BAL4815) the active moiety, and a cleavage product (BAL8728). The drug substance is manufactured in a (b) (4). Drug substance stability studies were adequate to support stability through 24 months. The reader is referred to the CMC review for NDA 207,500 for detailed information about the drug substance.

The drug product for NDA 207,500 is hard (b) (4) capsules, containing 186.3 mg of isavuconazonium sulfate (approximately (b) (4)). The capsules have a Swedish orange body imprinted with the Astellas logo, and a white cap imprinted with "ISA". The manufacture of the isavuconazonium capsules involves (b) (4). The capsules are packaged in aluminum blisters (one capsule per blister) and connected to a separate cavity with a desiccant strip. The stability studies of the capsules were considered sufficient to support the proposed 30-month expiration dating period.

The drug product for NDA 207,501 is a sterile lyophilized powder containing 372.6 mg of isavuconazonium sulfate (approximately (b) (4)) per vial. The inactive ingredients are mannitol as a bulking agent and sulfuric acid for pH adjustment. (b) (4). The vials are composed of Type I glass, with a (b) (4) rubber stopper and an aluminum flip-off cap. The steps in the commercial manufacturing process are: (b) (4). The stability data support the proposed shelf life of 24 months when the product is stored in a refrigerator.

- Facilities review/inspection

As of the end of January, the recommendations of the office of compliance were still pending. The office of compliance was awaiting district recommendations after recent inspection of the drug substance manufacturing site.

- Other notable issues

The main labeling issue for CMC relates to the appropriate labeling of the (b) (4).

Another notable issue with the injection product is particulate formation, occurring when the reconstituted solution of isavuconazonium is further diluted in D5W or normal saline for intravenous infusion. After addition to the diluent, a white precipitate forms. Because of the white precipitate, the diluted solution fails USP <788> limits for particulates. The precipitate was identified as isavuconazole (BAL 4815) which forms from the pro-drug during the manufacturing process. The applicant was unable to remove the residual amounts of isavuconazole from the drug product. During clinical trials, the product was administered through an in-line filter, and the applicant has provided labeling to require use of an in-line filter with the marketed product. The applicant has performed testing to show that administration through the filter does not significantly alter the delivery of the pro-drug, but does remove the particulates. Testing was performed with 0.2 and 1.2 micron filters. Labeling instructions describe preparation of the diluted solution and use of the in-line filter to reduce risk from the particulates. (b) (4)

## 4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Dr. Owen McMaster. He concluded that the nonclinical data would not preclude approval of the NDA applications for isavuconazonium.

- General nonclinical pharmacology/toxicology considerations

The nonclinical studies included oral administration of isavuconazonium for up to 39 weeks in monkeys, 26 weeks in rats, and 13 weeks in mice. Isavuconazonium was administered intravenously for up to 6 weeks in rats and monkeys. The nonclinical findings include reversible increases in liver weights and/or hepatocellular hypertrophy in rats and mice with oral administration. Labeling includes information about clinical findings of liver toxicity, consistent with the nonclinical data.

Increases in adrenal weights and hypertrophy/vacuolization were noted with repeated administration of isavuconazonium in monkeys. The changes were reversible and there were no atrophic/necrotic lesions seen, so the clinical significance of the adrenal findings is unclear. Increased thyroid weights and follicular cell hypertrophy/hyperplasia were seen in rats, but these were not observed in monkeys. Because of differences between rats and humans, these rat findings are likely not predictive of human risk.

Intravenous administration of isavuconazonium was associated with hemorrhage, vasculitis/perivasculitis, necrosis and/or thrombosis at the injection site, but no other new toxicities compared with oral administration. While adverse effects were related to dose in animal studies, there were no new toxicities associated with longer duration of treatment.

The nonclinical review also noted effects of isavuconazonium on cardiomyocyte membrane ion channels. Other drugs in the azole class have been associated with QT prolongation. Isavuconazonium was noted to have a strong inhibitory effect on L-type calcium channels as

well as inhibition of rapid delayed rectifier potassium channels ( $I_{Kr}$ ). The  $I_{CaL}$  and  $I_{Kr}$  channels have opposite effects on QT length. The effect on  $I_{CaL}$  channel may be the basis for QT shortening effects of isavuconazonium.

- Carcinogenicity

Carcinogenicity studies have not been conducted for isavuconazonium, and the applicant did not propose conducting such studies. The applicant also noted findings of hepatocellular adenomas and carcinomas in carcinogenicity studies in rats and mice using other azoles. Based on the duration of treatment seen in human clinical trials, the reviewer recommended that carcinogenicity studies of isavuconazonium be performed as post-marketing requirements. This recommendation was conveyed to the applicant at the late-cycle meeting, where a 2-year carcinogenicity study in rats and 6-month study in transgenic mice were suggested. The applicant will provide their proposal for the carcinogenicity studies in mid-February. It is expected that the carcinogenicity studies will be included as post-marketing requirements, if the application is approved.

- Reproductive toxicology

Reproductive toxicology studies of isavuconazonium were conducted. Isavuconazonium induced skeletal abnormalities and/or variations in rats and rabbits at doses as low as one-tenth of systemic exposure (based on AUC comparison) at the clinical maintenance dose of 200 mg once daily. Increased mortality in rat pups was noted when dams were dosed orally during pregnancy and through the weaning period. Isavuconazole was detected in the milk of lactating dams at up to 17 times the concentration in plasma. Bone abnormalities have also been associated with administration of other azoles. The reproductive toxicology findings for isavuconazonium have been included in the proposed labeling.

- Other notable issues

None

## 5. Clinical Pharmacology/Biopharmaceutics

The review by the clinical pharmacology team recommended approval of the NDA applications and the proposed dose regimen. Salient findings from the review are described below.

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Both IV and oral administration of isavuconazonium were evaluated. The absolute bioavailability of isavuconazonium was 98%. Maximum plasma concentrations of isavuconazole, the active cleavage product, were achieved 2-3 hours after oral administration. No significant concentrations of the pro-drug or inactive cleavage product were detected in

plasma after oral administration. There was no significant effect of food on isavuconazole exposure.

The pro-drug and the inactive cleavage product were detected during IV infusion (given over one hour). The pro-drug fell below the level of detection within 15 minutes after the end of IV infusion, though the inactive cleavage product could be detected up to 8 hours after the start of the infusion. Isavuconazonium is rapidly hydrolyzed in blood to isavuconazole by esterases. Exposure to isavuconazonium (based on AUC) was less than 1% that of isavuconazole.

The PK of isavuconazole is dose proportional for doses up to 600 mg per day of isavuconazonium. The mean half-life of isavuconazole was 130 hours, and the mean volume of distribution was approximately 450 L. Isavuconazole is highly protein bound (>99%), mainly to albumin.

- Drug-drug interactions

The active moiety, isavuconazole, is a substrate of CYP3A4 and 3A5. In vitro, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, P-gp, BCRP, and OCT2-mediated drug transporters. In vitro, isavuconazole is also an inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9.

Co-administration with ketoconazole resulted in an increase in isavuconazole AUC by 422%; use of isavuconazonium with strong CYP3A4 inhibitors is not recommended. Lopinavir /ritonavir increased AUC (by 96%) of isavuconazole, while lopinavir and ritonavir AUC decreased by 27% and 31%, respectively. Multiple doses of isavuconazonium increased the AUC of midazolam by 103% and increased the AUC of sirolimus by 84%. Monitoring of immunosuppressant concentrations (tacrolimus, sirolimus, and cyclosporine) is recommended when co-administered with isavuconazonium.

- Pathway of elimination

Following oral administration of radio-labeled isavuconazonium in healthy volunteers, 46.1% of the radioactive dose was recovered in feces, and 45.5% was recovered in urine. Less than 1% of the total amount was recovered in urine as intact isavuconazole. After IV administration of radio-labeled cleavage product, 95% of the total dose was recovered in the urine.

- Briefly comment on each of the critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment.

No dose adjustment is recommended based on age or gender. Isavuconazole exposure was evaluated in individuals with mild and moderate hepatic insufficiency (Child-Pugh Classes A and B). No dosage adjustment was recommended for mild to moderate hepatic insufficiency, but no data were available for severe hepatic insufficiency. No dosage adjustment is recommended for renal impairment, including patients with end-stage renal disease. Isavuconazole is not dialyzable. Isavuconazole AUC and C<sub>max</sub> were not significantly affected in patients with varying degrees of renal impairment relative to healthy controls.

- Demographic interactions/special populations

A population PK model was used to assess pharmacokinetics of isavuconazole in Chinese compared to western subjects. Chinese subjects were found to have 40% lower clearance, and approximately 50% higher AUC compared to western subjects. Body mass index did not have a role in these differences. No dose adjustment is recommended for Chinese subjects. Isavuconazole has not been evaluated in pediatric patients.

- Thorough QT study or other QT assessment

Thorough QT studies conducted by the applicant were reviewed by the QT Interdisciplinary Review Team. The TQT studies showed a concentration-dependent decrease in the QT interval. The product is contraindicated in patients with familial short QT syndrome.

- Other notable issues

In the controlled trial of invasive aspergillosis, there was no exposure-response (ER) relationship established for the adverse events evaluated (anxiety, nausea, headache, pruritus, fatigue or ALT elevation). There was an exposure-response trend for the mortality endpoint with higher mortality in the highest exposure quartile compared to the lower quartiles. Because of higher exposure in Asian vs. non-Asian patients, the clinical pharmacology team noted what appeared to be a relationship between Asian race, higher exposure and higher mortality. However, this relationship was confounded by higher mortality in cases from sites in South Korea. In sensitivity analyses, removal of the South Korean site eliminated the ER relationship. Therefore, the clinical pharmacology team did not recommend any dose adjustment based on higher exposure for the Asian population.

The clinical pharmacology review also included evaluation of (b) (4)

(b) (4)

The evaluation of (b) (4) is discussed further in the next section of this memo.

## 6. Clinical Microbiology

The clinical microbiology review was conducted by Dr. Shukal Bala. The reader is referred to the clinical microbiology review for detailed information about the microbiological findings.

- General considerations

Isavuconazonium is a pro-drug, hydrolyzed in vivo to release the active moiety, isavuconazole. Isavuconazole is a triazole antifungal drug with a mechanism of action similar to other azole antifungal drugs. Isavuconazole inhibits ergosterol synthesis, leading to disruption of fungal cell membranes and inhibition of fungal growth.

The in vitro activity of isavuconazole was assessed using standardized methods for evaluating the minimum inhibitory concentrations of isavuconazole. Table 1 in the clinical microbiology review summarizes the in vitro activity of isavuconazole against various *Aspergillus* and Mucorales species. Overall the MIC<sub>90</sub> values for *Aspergillus* species ranged from 1-4 mcg/mL, and were generally lower than the MIC<sub>90</sub> values for Mucorales (range 1-32 mcg/mL). There is the potential for resistance to isavuconazonium to develop. Increased MIC values for isavuconazole involved multiple mechanisms (mutations in the target gene, altered sterol profile, or efflux). Cross-resistance with other azoles was suggested based on higher MIC for isavuconazole seen in isolates with reduced susceptibility for other azoles.

Animal models were used to evaluate the activity of isavuconazole in *Aspergillus* infections. Neutropenic and non-neutropenic mice were used for models of disseminated aspergillosis with *A. flavus*, *A. fumigatus*, and *A. terreus*. In the model of *A. terreus* infection, isavuconazole did not appear effective in reducing the kidney fungal burden. Neutropenic mice, guinea pigs, and rabbits were used in models of pulmonary infection with *A. fumigatus*. Except for the guinea pig model, isavuconazole appeared to improve survival or reduce fungal burden. In the guinea pig model, oral isavuconazonium did not appear effective in improving survival or reducing pulmonary fungal burden.

For mucormycosis, neutropenic and diabetic ketoacidotic (DKA) mice were studied in both pulmonary and disseminated infection with *Rhizopus oryzae*. In vivo activity was not assessed in other Mucorales species. In the pulmonary model, the high dose of isavuconazonium improved survival of neutropenic mice, but not DKA mice. In another study involving a lower fungal burden and lower dose of isavuconazonium, a trend toward improved survival was seen in DKA mice. In the disseminated infection model, there was no difference in survival between the different dose groups and placebo.

The reviewer evaluated the relationship of in vitro MIC and outcome of isavuconazonium treatment from the efficacy trials conducted by the applicant. Overall, there were few isolates from the clinical trials, with *A. fumigatus* and *A. flavus* as the most common *Aspergillus* isolates. *R. oryzae* was the most common isolate other than unspciated *Mucormycetes* among the patients with mucormycosis. There was no correlation between MIC of the baseline pathogen and clinical or microbiological outcome.

- Discussion of primary and secondary reviewers' comments and conclusions

The reviewer considered the applications for isavuconazonium approvable, pending agreement on labeling. The primary reviewer and team leader were in agreement regarding these recommendations.

- Notable issues

The applicant proposed [REDACTED] (b) (4)

The applicant did not propose [REDACTED] (b) (4) for other *Aspergillus* species or for Mucorales infections, because of the limited data available. For the target attainment analysis

using *A. fumigatus* in animal models, different target exposures were identified, varying by the model and outcome used. The murine model may also have been limited by shorter half-life of isavuconazole in mice. It was unclear which target would be most clinically relevant. Similarly, the analysis from clinical trial data comparing outcome (mortality and DRC-adjudicated clinical and microbiological success) with baseline MIC did not show any correlation. These analyses were limited by the small number of patients with fungal isolates at baseline, even for the most common pathogen isolated (*A. fumigatus*).

(b) (4)

The reviewer also recommended that the applicant should conduct a postmarketing surveillance study. The study would evaluate changes in minimum inhibitory concentrations (b) (4) for fungi relevant to the indications over a period of five years from the marketing of isavuconazonium. The applicant has agreed to conduct the postmarketing surveillance study as a postmarketing requirement.

## 7. Clinical/Statistical- Efficacy

The clinical review was conducted by Dr. Edward Weinstein, the primary reviewer, with secondary review conducted by Dr. Elizabeth O'Shaughnessy. The statistical review was conducted by Dr. Cheryl Dixon. The reader is referred to these reviews for detailed information about the efficacy findings for the NDA applications.

The statistical reviewer concluded that there was adequate evidence of efficacy to support the indication of the treatment of invasive aspergillosis (IA). For the mucormycosis claim, she noted that inferential testing to compare isavuconazonium treatment with no treatment or an active control is not possible. She still recommended that the results be considered adequate evidence of efficacy to support the invasive mucormycosis (IM) indication, though she deferred to the medical division for the final decision.

The clinical reviewers recommended approval of isavuconazonium for both of the proposed indications. For the IA indication, the reviewers concluded that non-inferiority of isavuconazonium to voriconazole had been demonstrated in trial 9766-CL-0104. For the IM indication, the medical officer considered the available evidence adequate to support efficacy of isavuconazonium. The results of clinical trials supporting each indication are summarized below.

For the invasive aspergillosis claim, a randomized, double-blind, non-inferiority trial (9766-CL-0104) comparing isavuconazonium with voriconazole provide the main evidence of efficacy. Additional supportive evidence for invasive aspergillosis comes from the open-label, non-comparative trial (9766-CL-0103) of patients with aspergillosis and renal impairment or patients with invasive fungal disease caused by rare moulds, yeasts, or dimorphic fungi.

The randomized double-blind trial of IA had a primary objective of comparing all-cause mortality through day 42 in patients receiving isavuconazonium or voriconazole for primary treatment of invasive fungal disease due to *Aspergillus* or other filamentous fungi. The trial included 527 randomized patients. There were 516 patients (258 per treatment arm) in the ITT population, defined as patients who received at least one dose of study medication. Patients were eligible for enrollment if they had proven, probable or possible invasive fungal disease by European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria. Patients with renal impairment were excluded from this trial because of restrictions for the use of voriconazole in such patients; they were instead eligible for the open-label, non-comparative trial of isavuconazonium treatment. The modified ITT (mITT) population consisted of patients with proven or probable invasive fungal disease by EORTC/MSG criteria. There were 143 mITT patients in the isavuconazonium arm, and 129 mITT patients in the voriconazole arm. The mycological ITT (myITT) population included mITT patients with *Aspergillus* confirmed by culture, histology or galactomannan assay. The myITT population consisted of 123 patients in the isavuconazonium arm and 108 patients in the voriconazole arm. In addition to mortality as an outcome, a data review committee assessed clinical, radiological, mycological, and overall response.

In the ITT population, the mortality rate at day 42 was 18.6% in the isavuconazonium group and 20.2% in the voriconazole group. The adjusted treatment difference was -1.0%, and the 95% confidence interval was (-8.0, 5.9). The upper bound of this confidence interval was lower than the pre-specified non-inferiority margin of 10%. The statistical review provides a discussion of the basis for the non-inferiority margin in section 5.1 of the review, but this margin is well supported based on a prior clinical trial showing superiority of the comparator, voriconazole, to amphotericin B and estimates of the effect of both drugs over placebo from historical literature.

The results of other analyses in this trial are consistent with the primary endpoint for the mITT population, myITT population and a mITT-FDA population based on FDA guidance describing diagnostic criteria for the galactomannan assay. In these populations, the treatment differences for mortality ranged from -2.1 to -2.7 with the difference favoring isavuconazonium. The upper bound of the 95% CI ranged from 7.3 to 8.2 in these analyses, all below the 10% pre-specified NI margin for the primary analysis. The analyses of mortality at day 84 were consistent with the 42-day mortality results. The DRC-assessed overall response at end of treatment was a key secondary endpoint. The overall response in the mITT population was 35% in the isavuconazonium group and 36.4% in the voriconazole group. Success in this analysis was based on complete or partial response as assessed by the DRC. The adjusted treatment difference in the overall response analysis was -1.6, and the 95% CI was (-12.8, 9.6).

Supportive evidence for the IA claim was provided by the open-label, non-comparative trial which enrolled 24 patients with invasive fungal infections due to *Aspergillus* only. These included 20 patients with renal impairment. In these patients, the all-cause mortality rate through day 42 was 3/24 (12.5%) for IA patients and 3/20 (15%) for IA patients with renal impairment, consistent with the results from the blinded trial.

Overall, there is conclusive evidence of treatment benefit of isavuconazonium for the treatment of invasive aspergillosis from the comparative clinical trial. In addition, the supportive evidence suggests that isavuconazonium could be an important treatment option for patients with invasive fungal infections and renal impairment, since available treatment options are limited in these patients. I concur with the recommendations of the clinical and statistical reviews for approval of isavuconazonium for the treatment of invasive aspergillosis.

For the mucormycosis claim, the main evidence of efficacy comes from comparison outcomes for 37 patients with mucormycosis from the open-label trial with a historical control. The clinical review describes the overall trial and the basis for selection of 37 patients with fungal disease due to Mucorales pathogens only from the non-comparative trial. In this group, there were 32 patients with proven infection and 5 with probable infection. Most patients (n=21) received isavuconazonium as primary treatment, while 11 patients had refractory infection, and 5 were intolerant of other treatment options. Through day 42, the all-cause mortality rate in these patients was 14/37 (37.8%), including one refractory patient whose survival status was unknown. The 95% confidence interval around this mortality rate was (22.5, 55.2). For the primary treatment group, the all-cause mortality rate through day 42 was 7/21 (33%), with a 95% CI of (14.6, 57.0). The all-cause mortality rate through day 84 was 16/37 (43.2%) for the entire Mucorales group and 9/21 (42.9%) for those receiving primary treatment. The DRC-assessed overall response at end of treatment was available for 35 of the Mucorales patients, and 19 patients receiving primary treatment. Two of the primary treatment patients were continuing isavuconazonium treatment at the point of database closure. Success (complete or partial overall response) was reported in 11/35 (31.4%) Mucorales patients, and 6/19 (31.6%) patients receiving primary treatment. The applicant provided an analysis of mortality through day 42 for matched controls from the Fungiscope registry. All of the matched controls received amphotericin B treatment, and some were switched to posaconazole as treatment for refractory infection. In comparison to the 42-day mortality rate of 7/21 (33.3%) for primary isavuconazonium treatment, the matched controls were reported with a 42-day mortality rate of 13/33 (39.4%) with a 95% CI of (22.9, 57.9) for this control mortality rate. The mortality rates appear comparable, but this analysis is limited by the small numbers of patients in both groups, and the lack of agreement on what would constitute evidence of a treatment effect for isavuconazonium in this analysis. In the clinical review, table 40 provides the primary reviewers analysis of mortality rates for isavuconazonium-treated patients with invasive mucormycosis and historical data for mortality in untreated patients from a meta-analysis of untreated patients. (The reader is referred to the clinical review for detailed information about the meta-analysis and demographic comparisons of isavuconazonium treatment and the historical controls.) Table 40 also provides an estimate of the effect of a 6-day delay of treatment derived from a literature report (Chamilos et al, Clinical Infectious Diseases 2008; 47(4):503-9). These analyses suggest that mortality outcomes with isavuconazonium treatment of invasive mucormycosis are significantly better than the historical mortality of untreated

mucormycosis, and reduced mortality relative to that seen in patients with delayed treatment. The comparison with untreated mortality from the literature is limited by the inclusion of patients with post-mortem diagnosis of mucormycosis, since such patients may be substantially different from patients with pre-mortem diagnosis who are identified early enough to begin anti-fungal treatment.

The evidence of efficacy for invasive mucormycosis is limited, as would be expected for a disease as rare as mucormycosis. However, despite these limitations, I concur with the recommendations of the reviewers to approve isavuconazonium for the treatment of invasive mucormycosis. This recommendation is made after due consideration of the limitations of mortality comparisons from a non-comparative trial to historical data, the difficulty of conducting a trial in a disease with an estimated incidence of 1.7 per million population, the similar mortality with matched control patients receiving amphotericin B treatment, the supportive evidence provided by the comparative data in the related indication of invasive aspergillosis, and the potential for offering an added treatment option for patients with renal impairment.

## 8. Safety

The clinical review by Dr. Edward Weinstein provides a thorough review of safety findings with isavuconazonium treatment. The reader is referred to the clinical review for detailed information. A REMS review was conducted by Dr. Carolyn Yancey of the Division of Risk Management. The REMS review documents concurrence of DAIP and DRISK that A REMS program is not required for approval of isavuconazonium, based on the available information.

The clinical development program included a total of 1692 individuals who received at least one dose of isavuconazonium, though most of these individuals were healthy subjects in phase 1 studies. There were 403 isavuconazonium patients and 259 comparator patients enrolled in the two efficacy trials. This provides a reasonable population size for evaluation of safety with prolonged treatment, given that both indications studied are rare conditions. The double-blind, comparative trial of patients with IA (257 isavuconazonium patients and 259 comparator patients) provided the main source of comparative safety data. The efficacy trials also provide the main data for safety with prolonged treatment, since the longest duration of treatment in phase 2 trials was 28 days. The mean and median durations of isavuconazonium treatment in the efficacy trials were 76.1 days, and 57 days, respectively. Roughly 25% of patients in these trial received treatment for 84 days or longer.

Specific safety findings related to isavuconazonium included hepatotoxicity associated with azole anti-fungal drugs. There were 24 hepatobiliary adverse events reported in the isavuconazonium arm and 44 such events in the voriconazole group in the controlled efficacy trial. Some of the hepatic reactions were significant, including one patient where isavuconazonium was discontinued in a case of fatal hepatitis. There were 3 isavuconazonium patients and 7 voriconazole patients meeting Hy's Law laboratory criteria, though the patient population is at risk for hepatotoxicity from underlying disease.

Another safety concern related to isavuconazonium treatment is based on the findings treatment-related QTc shortening in the thorough QT studies. In the comparative efficacy trial there was one patient reported with an AE of QT shortening (QTcF = 378 msec) with no apparent clinical consequence, though the patient withdrew consent for further treatment. There were no such patients in the voriconazole group. No events of ventricular tachycardia or ventricular fibrillation were reported in the trial. This effect of QT shortening may represent a risk for some patients with familial short QT syndrome, but the clinical significance of the QT shortening effect of isavuconazonium for the general population appears to be low.

Another safety issue investigated in the clinical review is any risk associated with the formation of drug particulates in the intravenous formulation. Because of formation of particulates, IV isavuconazonium was administered through an in-line filter in the clinical trials. There were 27 reported instances of isavuconazonium administration without an in-line filter, with no reported clinical consequence. However, this group is too small to provide assurance of safety; the product labeling will recommend administration of isavuconazonium through an in-line filter, as was done for most patients in the clinical trials.

Overall evaluation of safety in the controlled trial showed similar safety profile to the comparator voriconazole, though rates of treatment emergent adverse events related to skin and eye system organ classes were lower for isavuconazonium. This reflects certain adverse reactions (visual disturbances, photosensitivity and exfoliative rashes) associated with voriconazole treatment. Deaths and non-fatal adverse reactions were reported at roughly similar rates in the two treatment groups. Serious adverse events were reported in fewer isavuconazonium patients, 134/257 (52.1%), compared to the voriconazole arm, 149/259 (57.5%). There were also fewer adverse events leading to discontinuations in the isavuconazonium arm, 37/257 (14.4%), compared to the voriconazole arm, 59/259 (22.8%). The clinical review summary did note specific adverse reactions associated with the azole antifungal drugs, hypersensitivity and infusion-related reactions, reported with isavuconazonium treatment. Product labeling will also address risks of embryo-fetal toxicity based on animal studies showing skeletal anomalies in rats and rabbits, and the similarity to fetal toxicities in animal studies of other azole antifungal agents.

I concur with the conclusion of the medical officer that the applicant has demonstrated an acceptable safety profile for isavuconazonium.

## **9. Advisory Committee Meeting**

An advisory committee meeting was held on January 22, 2015. The applicant and FDA presentations focused on the efficacy results from the two pivotal trials submitted by the applicant, and the overall safety findings for isavuconazonium. The committee was asked whether substantial evidence had been demonstrated for each of the two proposed indications.

For invasive aspergillosis, the committee voted yes unanimously on the question: “Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the treatment of invasive aspergillosis?” The committee made some recommendations for product

labeling related to the instructions for preparation of the intravenous solution, and labeling regarding various adverse reactions.

For invasive mucormycosis, the committee voted 8 yes, 2 no, and 1 abstention on the question: “Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the treatment of invasive mucormycosis?” Among those voting yes, there was a great deal of hesitation described by the committee members, based on the concerns about reliance on a noncomparative trial with a historical control. The members generally recommended collection of additional data on treatment of patients with mucormycosis. There were two members who voted no, Dr. Follman and Dr. Bennett. Dr. Follman stated he would have preferred for FDA to evaluate the efficacy of isavuconazonium in comparison to amphotericin B. He recommended a more sophisticated analysis of the benefit of isavuconazonium relative to the delayed treatment trial from the published literature. Dr. Bennett stated his concern was about “setting the bar low” for the approval of additional products. Dr. Bennett was not convinced of the activity of isavuconazonium for this indication. Dr. Sheetz abstained; explaining that his vote reflected the concerns raised by both yes and no voters for this question.

## 10. Pediatrics

The trials conducted by the applicant included adult patients. The safety and effectiveness of isavuconazonium in pediatric patients has not been evaluated. Since the applicant was granted orphan drug designation for isavuconazonium for both of the proposed indications, the pediatric requirements under the Pediatric Research Equity Act do not apply to the NDA applications for isavuconazonium. At the late cycle meeting with the applicant, (b) (4)



## 11. Other Relevant Regulatory Issues

Inspections of six clinical investigator sites in the two efficacy trials are described in the clinical inspection summary for these NDA applications. There were regulatory violations noted for four inspection sites (preliminary classification: voluntary action indicated). The two other sites had a preliminary classification of no action indicated. Overall, the inspection summary concluded that the noted regulatory violations are unlikely to affect data acceptability. In consultation with the review team, the inspection summary concluded that the data submitted from these six sites are acceptable and may be used in support of the NDA applications.

The applicant provided financial disclosure information, described in the appendix (section 9.7) of the clinical review. There was one investigator who reported significant payments by the applicant. However, the limited number of patients enrolled by this investigator would not have had a significant effect on the trial outcome if they were excluded.

No other pertinent regulatory issues were noted for these applications.

## 12. Labeling

Regarding labeling of the proposed product, many of the issues regarding for the package insert have been resolved. The applicant has agreed to specific changes in the proposed labeling including revisions to the clinical studies section describing the data supporting the mucormycosis claim, (b) (4) and the contraindications and warnings for the product. The recommendations for the package insert from the office of prescription drug promotion were addressed during the labeling review. The patient package insert has also been reviewed, and revisions to provide information consistent with the recommendations of the patient labeling review have been conveyed to the applicant.

There is an unresolved issue regarding the representation of the (b) (4) for the NDA applications. The original proposal by the applicant provided (b) (4) At this time, the issue of how to best describe the (b) (4) information for the product are being resolved.

The proposed proprietary name, Cresemba, was considered conditionally acceptable, though DMEPA may need to re-evaluate the (b) (4) It is unlikely that the second evaluation would change the acceptability of the proposed proprietary name.

The recommendations for carton and container labeling from the DMEPA review are being conveyed to the applicant. The acceptability of the carton and container labeling is also affected by the decision regarding the representation of the established name and dose strength.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of both new drug applications for isavuconazonium for both of the proposed indications.

- Risk Benefit Assessment

Based on the available evidence, the applicant has shown that isavuconazonium is non-inferior to voriconazole in the treatment of patients with invasive aspergillosis. The primary outcome evaluated in this trial is the effect on all-cause mortality through day 42, and isavuconazonium would be expected to reduce the risk of mortality, relative to no treatment for invasive aspergillosis. Overall, the safety profile of isavuconazonium was acceptable from the safety

findings of the comparative trial. Though specific risks for hepatotoxicity, hypersensitivity reactions, infusion reactions, and QT shortening were noted, the risks appear reasonable relative to the mortality benefit.

For the invasive mucormycosis claim, the analyses suggest that treatment with isavuconazonium would reduce the risk of mortality relative to no treatment, though the limitations of the analyses (specifically the comparison of non-comparative trial results to a historical control from the literature) have been described. Despite these limitations, the risks of isavuconazonium treatment are reasonable relative to the expected benefit of treatment of invasive mucormycosis. Since the only approved product for mucormycosis is amphotericin B, which has known adverse renal effects, isavuconazonium may provide an important treatment option for treatment of patients with renal impairment in this indication.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS program is not considered necessary for approval of these NDA applications.

- Recommendation for other Postmarketing Requirements and Commitments

The applicant has agreed in principle to two postmarketing requirements (PMR):

- 1) [REDACTED] (b) (4)  
The PMR would cover a period of five years after marketing of isavuconazonium.
- 2) The applicant has provided their proposal for the carcinogenicity studies to be conducted as postmarketing requirements for these NDA applications.

In addition to the above PMR, the review division has proposed a postmarketing commitment for a registry to collect information on outcomes of isavuconazonium treatment of patients with Mucorales infections, and infections due to *Aspergillus* species other than *A. fumigatus*. At the time of this writing, the postmarketing commitment was still being discussed internally.

[REDACTED] (b) (4)

- Recommended Comments to Applicant

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOHN J ALEXANDER  
02/10/2015