CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208562
Submission Date	01/09/2017
Drug Product	Voriconazole for Injection
OCP Reviewer	Zhixia (Grace) Yan, Ph.D.
OCP Team Leader	Seong Jang, Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Xellia Pharmaceuticals ApS
Submission Type	505(b)(2), Resubmission/Class 1
Formulation	For injection: lyophilized powder for reconstitution, each vial containing 200 mg voriconazole and 3200 mg of hydroxypropyl-β-cyclodextrin (HPβCD)
Indication	• Invasive aspergillosis • Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds • Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy
Dosage and Administration	See nested table below

Infection	IV Loading Dose	IV Maintenance Dose
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h
Candidemia in non-neutropenics and other deep tissue *Candida* infections		3 – 4 mg/kg q12h
Scedosporiosis and Fusariosis		4 mg/kg q12h

1. BACKGROUND

This is a resubmission/Class 1 for a 505(b)(2) New Drug Application (NDA) originially submitted on 07/24/2015 for Voriconazole for Injection, 200 mg/vial. The strength, route of administration, dosage regimen of the Sponsor's voriconazole product are identical to those of the reference listed drug (RLD), VFEND ® (voriconazole) for Injection (NDA 21267; approved in 2002). The proposed product differs from VFEND by replacement of sulfobutylether-β-cyclodextrin (SBECD) with hydroxypropyl-β-cyclodextrin (HPβCD) (1:1, w/w replacement).

The original submission was granted a tentative approval on 05/24/2016 due to a patent issue with one of the listed drugs (i.e., SPORANOX® [Itraconazole] Injection containing HPβCD as excipient) upon which this application relies. Clinical Pharmacology labeling recommendations were conveyed to the Sponsor for the original submission.

Reference ID: 4060977

2. LABELING RECOMMENDATION

In this resubmission, no new Clinical Pharmacology information was submitted. The Clinical Phamacology review team reviewed Section 12.3 of the labeling for the proposed Voriconazole for Injection product. The added pharmacokinetic information of HPβCD is supported by the SPORANOX labeling. However, we recommend the following additional changes to the currently proposed labeling, indicated as underline (additions) and strikethrough (deletions).

12.3 Pharmacokinetics

The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the intravenous dose from 3 mg/kg every 12h to 4 mg/kg every 12h produces an approximately 2.5-fold increase in exposure (Table 8).

Table 8: Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

	6 mg/kg intravenously (loading dose)	3 mg/kg intravenously every 12h	4 mg/kg intravenously every 12h
N	35	23	40
AUC_{12} (µg·h/mL)	13.9 (32)	13.7 (53)	33.9 (54)
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)
C_{min} (µg/mL)	--	0.46 (97)	1.73 (74)

Note: Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies. AUC_{12} = area under the curve over 12 hour dosing interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration. CV = coefficient of variation.

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12–18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg intravenously, the median of the calculated mean plasma concentrations was 1.60 µg/mL (inter-quartile range 0.28 to 2.73 µg/mL). When the recommended intravenous loading dose regimen is administered to healthy subjects, plasma concentrations close to steady state are achieved within the first 24 hours of dosing (e.g., 6 mg/kg intravenously every 12h on day 1 followed by 3 mg/kg intravenously every 12h). Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma

concentrations (approximate range: 0.9–15 µg/mL). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 [*see Drug Interactions (7)*].

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15–20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3–5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radiolabelled dose of intravenous voriconazole, preceded by multiple intravenous dosing, approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after (b) (4) intravenous dosing.

(b) (4)

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

Clinical Efficacy and Safety-In 10 clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (N=1121) was 2.51 µg/mL (inter-quartile range 1.21 to 4.44 µg/mL) and 3.79 µg/mL (inter-quartile range 2.06 to 6.31 µg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, pharmacokinetic/pharmacodynamic analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances *[see Adverse Reactions (6)]*.

Electrocardiogram-A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female subjects was conducted with three single oral doses of voriconazole and ketoconazole. Serial ECGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole and after ketoconazole 800 mg were all <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown [*see Contraindications (4) and Drug Interactions (7)*].

Specific Populations

Gender-In a multiple oral dose study, the mean C_{max} and AUC_τ for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18–45 years), after tablet dosing. In the same study, no significant differences in the mean C_{max} and AUC_τ were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean Cmax was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric-In an oral multiple dose study the mean C_{max} and AUC_τ in healthy elderly males (≥ 65 years) were 61% and 86% higher, respectively, than in young males (18–45 years). No significant differences in the mean C_{max} and AUC_τ were observed between healthy elderly females (≥ 65 years) and healthy young females (18–45 years).

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80% to 90% higher than those in the younger patients (≤65 years) after either intravenous or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly [*see Use in Specific Populations (8.5)*].

Pediatric-A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2 to <12 years old who were included in two pharmacokinetic studies of intravenous voriconazole (single dose and multiple dose). Twenty-four of these patients received multiple intravenous maintenance doses of 3 mg/kg and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults (medians of 1.19 µg/mL and 1.16 µg/mL in children and adults, respectively) [*see Use in Specific Populations (8.4)*].

Hepatic Impairment

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the mean systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic insufficiency were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic insufficiency compared to controls.

In an oral multiple dose study, AUC_τ was similar in 6 subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group.

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) [*see Dosage and Administration (2.6)*].

Renal Impairment

In a multiple dose study of intravenous voriconazole (6 mg/kg intravenous loading dose × 2, then 3 mg/kg intravenous × 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30–50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 subjects with normal renal function.

(b) (4)

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetacyclodextrin (HPβCD), an ingredient of Voriconazole for injection, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85 %) of an 8 g dose of HPβCD is eliminated in the urine. In a study investigating another antifungal drug, itraconazole, following a single intravenous 200 mg dose, clearance of hydroxypropyl-ß-cyclodextrin was reduced in subjects with renal impairment, resulting in higher exposure to hydroxypropyl-ß-cyclodextrin. In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions

Comment [A4]: To the Applicant: We recommend you delete this subtitle to be consisitent with the VFEND for Injection labeling.

may result in accumulation of HPβCD until steady state is reached. HPβCD is removed by hemodialysis (b) (4)
(b) (4)

Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole [*see Dosage and Administration (2.7)*].

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/min (b) (4)
(b) (4) A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Comment [A5]: To the Applicant: We recommend you delete this information as it is not included in the SPORANOX labeling.

Formatted: Body Text, Right: 0.19", Space Before: 0 pt, Line spacing: Exactly 12.6 pt

Comment [A6]: To the Applicant: See our comment above.

Drug Interactions

Effects of Other Drugs on Voriconazole

Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of *in vitro* metabolism studies indicate that the affinity of voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4. Inhibitors or inducers of these three enzymes may increase or decrease voriconazole systemic exposure (plasma concentrations), respectively.

The systemic exposure to voriconazole is significantly reduced or is expected to be reduced by the concomitant administration of the following agents and their use is contraindicated:

***Rifampin* (potent CYP450 inducer)**–Rifampin (600 mg once daily) decreased the steady state C_{max} and AUC_τ of voriconazole (200 mg every 12h × 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg every 12h does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

***Ritonavir* (potent CYP450 inducer; CYP3A4 inhibitor and substrate)**–The effect of the coadministration of voriconazole and ritonavir (400 mg and 100 mg) was investigated in two separate studies. High-dose ritonavir (400 mg every 12h for 9 days) decreased the steady state C_{max} and AUC_τ of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. Low-dose ritonavir (100 mg every 12h for 9 days) decreased the steady state C_{max} and AUC_τ of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 8 days) by an average of 24% and 39%, respectively, in healthy subjects. Although repeat oral administration of voriconazole did not have a significant effect on steady state Cmax and AUCτ of high-dose ritonavir in healthy subjects, steady state C_{max} and AUC_τ of low-dose ritonavir decreased slightly by 24% and 14% respectively, when administered concomitantly with oral voriconazole in healthy subjects. **Coadministration of voriconazole and high-dose ritonavir (400 mg every 12h) is contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

***St. John's Wort* (CYP450 inducer; P-gp inducer)**–In an independent published study in healthy volunteers who were given multiple oral doses of St. John's Wort (300 mg LI 160 extract three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole $AUC_{0-\infty}$ was observed. In contrast, coadministration of single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole $AUC_{0-\infty}$. Because long-term use of St. John's Wort could lead to reduced voriconazole exposure, **concomitant use of voriconazole with St. John's Wort is contraindicated** [*see Contraindications (4)*].

***Carbamazepine and long-acting barbiturates* (potent CYP450 inducers)**–Although not studied *in vitro* or *in vivo*, carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole concentrations. **Coadministration of voriconazole with carbamazepine or long-acting barbiturates is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole-related adverse events/toxicity:

***Fluconazole* (CYP2C9, CYP2C19 and CYP3A4 inhibitor)**: Concurrent administration of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg

every 24h for 4 days) to 6 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 hours of the last dose of fluconazole [*see Warnings and Precautions (5.1)*].

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

Cimetidine **(non-specific CYP450 inhibitor and increases gastric pH)**–Cimetidine (400 mg every 12h × 8 days) increased voriconazole steady state C_{max} and AUC_{τ} by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg every 12h × 7 days to healthy subjects.

Ranitidine **(increases gastric pH)**–Ranitidine (150 mg every 12h) had no significant effect on voriconazole C_{max} and AUC_{τ} following oral doses of 200 mg every 12h × 7 days to healthy subjects.

Macrolide antibiotics–Coadministration of **erythromycin** (CYP3A4 inhibitor; 1g every 12h for 7 days) or **azithromycin** (500 mg every 24h for 3 days) with voriconazole 200 mg every 12h for 14 days had no significant effect on voriconazole steady state C_{max} and AUC_{τ} in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects of Voriconazole on Other Drugs

In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole. *In vitro* studies also show that the major metabolite of voriconazole, voriconazole N-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the systemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

Sirolimus **(CYP3A4 substrate)**–Repeat dose administration of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy male subjects. **Coadministration of voriconazole and sirolimus is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Terfenadine, astemizole, cisapride, pimozide and quinidine **(CYP3A4 substrates)**–Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*. **Coadministration of voriconazole and terfenadine, astemizole, cisapride, pimozide and quinidine is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Ergot alkaloids–Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Everolimus **(CYP3A4 substrate, P-gp substrate)**–Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of everolimus, which could potentially lead to exacerbation of everolimus toxicity. Currently there are insufficient data to allow dosing recommendations in this situation. Therefore, co-administration of voriconazole with everolimus is not recommended [*see Drug Interactions (7)*].

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

Alfentanil **(CYP3A4 substrate)**–Coadministration of multiple doses of oral voriconazole (400 mg every 12h on day 1, 200 mg every 12h on day 2) with a single 20 mcg/kg intravenous dose of alfentanil with concomitant naloxone

resulted in a 6-fold increase in mean alfentanil AUC_0–∞ and a 4-fold prolongation of mean alfentanil elimination half-life, compared to when alfentanil was given alone. An increase in the incidence of delayed and persistent alfentanil-associated nausea and vomiting during co-administration of voriconazole and alfentanil was also observed. Reduction in the dose of alfentanil or other opiates that are also metabolized by CYP3A4 (e.g., sufentanil), and extended close monitoring of patients for respiratory and other opiate-associated adverse events, may be necessary when any of these opiates is coadministered with voriconazole [*see Warnings and Precautions (5.1)*].

***Fentanyl* (CYP3A4 substrate):** In an independent published study, concomitant use of voriconazole (400 mg every 12h on Day 1, then 200 mg every 12h on Day 2) with a single intravenous dose of fentanyl (5 µg/kg) resulted in an increase in the mean AUC_0–∞ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold). When voriconazole is co-administered with fentanyl intravenous, oral or transdermal dosage forms, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and fentanyl dosage should be reduced if warranted [*see Warnings and Precautions (5.1)*].

***Oxycodone* (CYP3A4 substrate):** In an independent published study, coadministration of multiple doses of oral voriconazole (400 mg every 12h, on Day 1 followed by five doses of 200 mg every 12h on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and AUC_0–∞ of oxycodone by 1.7-fold (range 1.4- to 2.2-fold) and 3.6-fold (range 2.7- to 5.6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0-fold (range 1.4- to 2.5-fold). Voriconazole also increased the visual effects (heterophoria and miosis) of oxycodone. A reduction in oxycodone dosage may be needed during voriconazole treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolized by CYP3A4 is recommended [*see Warnings and Precautions (5.1)*].

***Cyclosporine* (CYP3A4 substrate)**–In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg every 12h for 8 days) increased cyclosporine C_{max} and AUC_τ an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary [*see Warnings and Precautions (5.1)*].

***Methadone* (CYP3A4, CYP2C19, CYP2C9 substrate)**–Repeat dose administration of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 4 days) increased the C_{max} and AUC_τ of pharmacologically active Rmethadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30–100 mg every 24h). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103% (90% CI: 85%, 124%), respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed [*see Warnings and Precautions (5.1)*].

***Tacrolimus* (CYP3A4 substrate)**–Repeat oral dose administration of voriconazole (400 mg every 12h × 1 day, then 200 mg every 12h × 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_τ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary [*see Warnings and Precautions (5.1)*].

***Warfarin* (CYP2C9 substrate)**–Coadministration of voriconazole (300 mg every 12h × 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2 times that of placebo in healthy subjects. Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended if warfarin and voriconazole are coadministered and the warfarin dose adjusted accordingly [*see Warnings and Precautions (5.1)*].

***Oral Coumarin Anticoagulants* (CYP2C9, CYP3A4 substrates)**–Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of coumarin anticoagulants and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with

voriconazole, the prothrombin time or other suitable anti-coagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly [*see Warnings and Precautions (5.1)*].

Statins **(CYP3A4 substrates)**–Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin concentrations in plasma have been associated with rhabdomyolysis [*see Warnings and Precautions (5.1)*].

Benzodiazepines **(CYP3A4 substrates)**–Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (e.g., midazolam, triazolam, and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration [*see Warnings and Precautions (5.1)*].

Calcium Channel Blockers **(CYP3A4 substrates)**–Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro* (human liver microsomes). Therefore, voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during coadministration. Dose adjustment of the calcium channel blocker may be needed [*see Warnings and Precautions (5.1)*].

Sulfonylureas **(CYP2C9 substrates)**–Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Frequent monitoring of blood glucose and appropriate adjustment (i.e., reduction) of the sulfonylurea dosage is recommended during coadministration [*see Warnings and Precautions (5.1)*].

Vinca Alkaloids **(CYP3A4 substrates)**–Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered [*see Warnings and Precautions (5.1)*].

Non-Steroidal Anti-Inflammatory Drugs **(NSAIDs; CYP2C9 substrates):** In two independent published studies, single doses of ibuprofen (400 mg) and diclofenac (50 mg) were coadministered with the last dose of voriconazole (400 mg every 12h on Day 1, followed by 200 mg every 12h on Day 2). Voriconazole increased the mean C_{max} and AUC of the pharmacologically active isomer, S (+)-ibuprofen by 20% and 100%, respectively. Voriconazole increased the mean C_{max} and AUC of diclofenac by 114% and 78%, respectively.

A reduction in ibuprofen and diclofenac dosage may be needed during concomitant administration with voriconazole. Patients receiving voriconazole concomitantly with other NSAIDs (e.g., celecoxib, naproxen, lornoxicam, meloxicam) that are also metabolized by CYP2C9 should be carefully monitored for NSAID-related adverse events and toxicity, and dosage reduction should be made if warranted [*see Warnings and Precautions (5.1)*].

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with the following agents. Therefore, no dosage adjustment for these agents is recommended:

Prednisolone **(CYP3A4 substrate)**–Voriconazole (200 mg every 12h × 30 days) increased C_{max} and AUC of prednisolone (60 mg single dose) by an average of 11% and 34%, respectively, in healthy subjects.

Digoxin **(P-glycoprotein mediated transport)**–Voriconazole (200 mg every 12h × 12 days) had no significant effect on steady state C_{max} and AUC_τ of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

Mycophenolic acid **(UDP-glucuronyl transferase substrate)**–Voriconazole (200 mg every 12h × 5 days) had no significant effect on the C_{max} and AUC_τ of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 g single oral dose of mycophenolate mofetil.

Two-Way Interactions

Concomitant use of the following agents with voriconazole is contraindicated:

Rifabutin **(potent CYP450 inducer)**–Rifabutin (300 mg once daily) decreased the C_{max} and AUC_τ of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady state C_{max} and AUC_τ of

voriconazole following an increased dose of 400 mg twice daily were on average approximately 2 times higher, compared with voriconazole alone at 200 mg twice daily. Coadministration of voriconazole at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_{τ} of rifabutin by an average of 3-times (90% CI: 2.2, 4.0) and 4 times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **Coadministration of voriconazole and rifabutin is contraindicated [*see Contraindications (4)*].**

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

***Efavirenz*, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)**–Standard doses of voriconazole and efavirenz (400 mg every 24h or higher) must not be coadministered [*see Drug Interactions (7)*]. Steady state efavirenz (400 mg PO every 24h) decreased the steady state Cmax and AUCτ of voriconazole (400 mg PO every 12h for 1 day, then 200 mg PO every 12h for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO every 12h for 1 day, then 200 mg every 12h for 8 days) increased the steady state C_{max} and AUC_{τ} of efavirenz (400 mg PO every 24h for 9 days) by an average of 38% and 44%, respectively, in healthy subjects.

Coadministration of standard doses of voriconazole and efavirenz (400 mg every 24h or higher) is contraindicated. [*see Contraindications (4) and Drug Interactions (7)*].

***Phenytoin* (CYP2C9 substrate and potent CYP450 inducer)**–Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_{τ} of orally administered voriconazole (200 mg every 12h × 14 days) by an average of 50% and 70%, respectively, in healthy subjects.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours [*see Dosage and Administration (2.4) and Drug Interactions (7)*].

Repeat dose administration of voriconazole (400 mg every 12h × 10 days) increased the steady state C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2 times the C_{max} and AUC estimates when phenytoin is given without voriconazole. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole [*see Warnings and Precautions (5.1)*].

***Omeprazole* (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**–Coadministration of omeprazole (40 mg once daily × 10 days) with oral voriconazole (400 mg every 12h × 1 day, then 200 mg every 12h × 9 days) increased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended.

Coadministration of voriconazole (400 mg every 12h × 1 day, then 200 mg × 6 days) with omeprazole (40 mg once daily × 7 days) to healthy subjects significantly increased the steady state C_{max} and AUC_{τ} of omeprazole an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half [*see Warnings and Precautions (5.1)*].

The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these drugs.

***Oral Contraceptives* (CYP3A4 substrate; CYP2C19 inhibitor)**–Coadministration of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 3 days) and oral contraceptive (Ortho-Novum1/35® consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, every 24h) to healthy female subjects at steady state increased the C_{max} and AUC_{τ} of ethinyl estradiol by an average of 36% (90% CI: 28%, 45%) and 61% (90% CI: 50%, 72%), respectively, and that of norethindrone by 15% (90% CI: 3%, 28%) and 53% (90% CI: 44%, 63%), respectively in healthy subjects. Voriconazole Cmax and AUC_{τ} increased by an average of 14% (90% CI: 3%, 27%) and 46% (90% CI: 32%, 61%), respectively. Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended during coadministration [*see Warnings and Precautions (5.1)*].

No significant pharmacokinetic interaction was seen and no dosage adjustment of these drugs is recommended:

***Indinavir* (CYP3A4 inhibitor and substrate)**–Repeat dose administration of indinavir (800 mg TID for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg every 12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg every 12h for 7 days) did not have a significant effect on steady state C_{max} and AUC_{τ} of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

Other Two-Way Interactions Expected to be Significant Based on *In Vitro* and *In Vivo* Findings:

***Other HIV Protease Inhibitors* (CYP3A4 substrates and inhibitors)**–*In vitro* studies (human liver microsomes) suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g., saquinavir, amprenavir and nelfinavir). *In vitro* studies (human liver microsomes) also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors (e.g., saquinavir and amprenavir). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors [*see Warnings and Precautions (5.1)*].

***Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)* (CYP3A4 substrates, inhibitors or CYP450 inducers)**–*In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by a NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy male subjects suggest that the metabolism of voriconazole may be induced by a NNRTI. This *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI [*see Drug Interactions (7) and Warnings and Precautions (5.8)*]. Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and other NNRTIs (e.g., nevirapine and delavirdine) [*see Warnings and Precautions (5.1)*]. Dose adjustments are required when voriconazole is co-administered with efavirenz [*see Drug Interactions (7) and Warnings and Precautions (5.1)*].

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

/s/

ZHIXIA YAN
02/24/2017

SEONG H JANG
02/24/2017

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208562
Submission Date	07/24/2015
Drug Product	Voriconazole for Injection
OCP Reviewer	Zhixia (Grace) Yan, Ph.D.
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Xellia Pharmaceuticals ApS
Submission Type	505(b)(2)
Formulation	For injection: lyophilized powder for reconstitution, each vial containing 200 mg voriconazole and 3200 mg of hydroxypropyl-β-cyclodextrin (HPβCD)
Indication	• Invasive aspergillosis • Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds • Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy
Dosage and Administration	See nested table below

Infection	IV Loading Dose	IV Maintenance Dose
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h
Candidemia in non-neutropenics and other deep tissue *Candida* infections		3 – 4 mg/kg q12h
Scedosporiosis and Fusariosis		4 mg/kg q12h

1. BACKGROUND

Xellia Pharmaceuticals submitted a 505(b)(2) New Drug Application (NDA) on 07/24/2015 for Voriconazole for Injection, 200 mg/vial. The strength, route of administration, dosage regimen of the Sponsor's voriconazole product are identical to those of the reference listed drug (RLD), VFEND ® (voriconazole) for Injection (NDA 21267; approved in 2002). The proposed product differs from VFEND by replacement of sulfobutylether-β-cyclodextrin (SBECD) with hydroxypropyl-β-cyclodextrin (HPβCD) (1:1, w/w replacement). The comparison of the proposed product and the RLD is presented in **Table 1**.

Reference ID: 3923931

Table 1. Formulation Comparison between the RLD (VFEND®) and the Proposed Product, Xellia's Voriconazole for Injection

Ingredient		Function	Quantity	
Xellia's Product	VFEND (NDA 021267)		mg/vial	mg/mL*
Voriconazole	Voriconazole	Active Ingredient	200	10
Hydroxypropyl ß-cyclodextrin (HPβCD)	Sulfobutylether ß-cyclodextrin (SBECD)	(b) (4)	3,200	160

* Following reconstitution with 19 mL of water for injection.

This NDA was submitted via a 505(b)(2) pathway and as such, relies on the Agency's prior findings of safety and efficacy for Voriconazole for Injection (VFEND®; NDA 021267). No clinical pharmacology studies have been conducted with the applicant's product. A waiver of in vivo bioavailability studies has been requested for the proposed voriconazole product. The submitted Summary of Biopharmaceutical Studies includes information on comparison of voriconazole PK between HPβCD and SBECD formulations and PK information for HPβCD and SBECD to support the bridging of applicant's product and the RLD. The clinical pharmacology review focused on 1) PK information for voriconazole between HPβCD and SBECD formulations; 2) PK information for HPβCD and SBECD, and 3) the proposed voriconazole label.

2. RECOMMENDATION

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the 505(b)(2) NDA 208562 submission for Voriconazole for Injection. No clinical pharmacology studies have been conducted with the applicant's proposed product. However, based on review of previously available PK information for voriconazole between the HPβCD and SBECD formulations for injection provided in this submission, replacement of SBECD with HPβCD (1:1 w/w) does not appear to affect the pharmacokinetics of voriconazole following intravenous administration. The Clinical Phamacology review team recommends approval of this NDA, provided the labeling recommendations given below are adequately addressed by the Sponsor.

3. LABELING COMMENTS/RECOMMENDATIONS

The PK information for HPβCD and SBECD provided in this submission appears (b) (4) **he Clinicla Pharmacology review team has concerns that these proposed changes to the Voriconazole for Injection labeling could potentially cause medication errors in clinical practice. Therefore, we recommend the Sponsor change the proposed labeling,** (b) (4) **similar to that of the labeling of VFEND for Injection.**

3 Page(s) have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Reference ID: 3923931

4.2 PK Information for HPβCD and SBECD

HPβCD and SBECD have comparable volumes of distribution, renal clearance, and elimination half-life (Stella and He, 2008). Following IV administration, both HPβCD and SBECD disappear rapidly from the systemic circulation and are excreted unchanged in the urine, with minimal or no metabolism. Following intravenous administration, HPβCD has a small volume of distribution in humans (Vd = 0.22-0.25 L/kg) and a short half-life ($t_{1/2}$ = 1.7-1.9 h). SBECD has a similar volume of distribution and half-life in humans following intravenous administration (Vd = 0.20 L/kg and $t_{1/2}$ ~1.6 h) (*Clinical Pharmacology/Biopharmaceutics Review for NDA 21267; VFEND*). Both excipients are excreted via glomerular filtration. The plasma clearance of HPβCD and SBECD in humans is 1.5 and 1.9 mL/min/kg, respectively. The half-life, clearance and volume of distribution are independent of dose and urine levels (Stella and He, 2008).

4.2.1 A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with a clearance of 121 mL/min. The intravenous vehicle, HPβCD, is hemodialyzed with clearance of 37.5 ± 24 mL/min (MHRA 2015). A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

4.2.2 The pharmacokinetic profile of HPβCD in renally impaired patients (mild, moderate and severe renal impairment) was established by Janssen following single dose IV administration of Sporanox (itraconazole) for Injection (*Sporanox® NDA 20966, 1999*). Renally impaired subjects received an intravenous administration of 200 mg of itraconazole and 8 g of HPβCD. The elimination of HPβCD appeared to be prolonged by renal impairment with the slowest rate in patients with severe impairment (**Table 5**).

Table 5. Mean Pharmacokinetic Parameters for HPβCD in Renally Impaired Patients Intravenously Administered 200 mg of Itraconazole and 8 g of HPβCD as a Single Dose of Sporanox for Injection conducted by Janssen

Parameter [a]	Renal Impairment Group				
	I (Normal) n=14	I (Mild) n = 8	III (Moderate) n=7	IV (Severe) n=7	Comparison P value [b]
Tmax (hr)	1.00	1.00	1.00	1.00	NS
Cmax (µg/mL) median	656 ± 100	617 ± 129	594 ± 147	785 ± 96	I, IV (0.022) II, IV (0.009) III,IV (0.004)
k (1/hr)	0.304 ± 0.077	0.207 ± 077	0.107 ± 0.046	0.050 ± 0.018	I, II (0.002) I,III (<0.001) I,IV (<0.001) II,III (0.005) II,IV (0.016)
t ½ (hr)	2.5 ± 0.84	4.1 ± 2.3	9.2 ± 8.4	15.6 ± 6.0	I,II (0.004) I,IV (<0.001) II,III (0.039) II,IV (<0.001) III,IV (0.016)
AUC_{last} (ng*hr/mL)	1842 ± 456	2570 ± 1131	4697 ± 2141	13074 ± 4928	I,III (0.015) I,IV (<0.001) II,IV (<0.001) III,IV (<0.001)
AUC_{∞} (ng*hr/mL)	1870 ± 450	2662 ± 1188	4781 ± 2260	13323 ± 5250	I,III (0.019) I,IV (<0.001) II,IV (<0.001) III,IV (<0.001)

Parameter [a]	Renal Impairment Group				
	I (Normal) n=14	I (Mild) n = 8	III (Moderate) n=7	IV (Severe) n=7	Comparison P value [b]
Cl (L/hr)	4.47 ± 0.90	3.48 ± 1.37	1.94 ± 0.73	0.67 ± 0.20	I,II (0.022) I,III (<0.001) I,IV (<0.001) II,III (<0.003) II,IV (<0.001) III,IV (0.015)
V_{ss} (L)	12.1 ± 2.41	14.6 ± 3.26	17.9 ± 6.57	12.9 ± 2.35	I,III (0.002) III, IV (0.017)
V_k (L)	15.2 ± 3.04	17.5 ± 4.15	20.1 ± 6.69	13.6 ± 2.52	I,III (0.016) III,IV (0.006)

NS Not statistically significant
[a] Mean reported for all parameters except Tmax for which median reported
[b] Based on untransformed data
Renal impairment groups:
Group I: CrCl ≥80 mL/min/1.73m²
Group II: CrCl 50-79 mL/min/1.73m²
Group III: CrCl 20-49 mL/min/1.73m²
Group IV: CrCl ≤19 mL/min/1.73m²

References

MHRA 2015: Voriconazole Teva 200 mg Powder for Solution For Infusion; Summary of Product Characteristics.

Valentino J. Stella and Quanren He; Cyclodextrins; Toxicologic Pathology, 36:30-42, 2008

Clinical Pharmacology/Biopharmaceutics Review for NDA 21267; VFEND

5. Clinical Pharmacology Labeling Recommendations

5.1 Proposed Labeling Changes by the Sponsor Pertaining to Clinical Pharmacology [Sponsor changes indicated as underline (additions) and ~~strikethrough~~ (deletions)]

HIGHLIGHTS OF PRESCRIBING INFORMATION

_____CONTRAINDICATIONS_____

- Hypersensitivity to voriconazole or its excipients (4)

(b) (4)

- Coadministration with terfenadine, astemizole, cisapride, pimozide or quinidine, sirolimus due to risk of serious adverse reactions (4, 7)
- Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir, rifabutin, ergot alkaloids, and St. John's Wort due to risk of loss of efficacy (4, 7)

___WARNINGS AND PRECAUTIONS___

- *Clinically Significant Drug Interactions*: Review patient's concomitant medications (5.1, 7)
- *Hepatic Toxicity*: Serious hepatic reactions reported. Evaluate liver function tests at start of and during voriconazole therapy (5.2)

(b) (4)

2 DOSAGE AND ADMINISTRATION

2.7 Use in Patients ~~W~~with Renal Impairment

(b) (4)

In patients with moderate or severe renal (b) (4) (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, hydroxypropyl ß-cyclodextrin (HPβCD (b) (4), occurs. (b) (4)

(b) (4)

4 CONTRAINDICATIONS

- Voriconazole for injection is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.
- (b) (4)

5 WARNINGS AND PRECAUTIONS

5.9 Patients ~~W~~with Renal Impairment

Hydroxypropyl-β-cyclodextrin, (b) (4) is eliminated through glomerular filtration. In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of (b) (4) (b) (4) HPβCD, occurs.- (b) (4) (b) (4)

(b) (4)

(b) (4) unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in (b) (4) patients. (b) (4) (b) (4) [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.7)*].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetacyclodextrin (HPβCD), an ingredient of Voriconazole for injection , has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85 %) of an 8 g dose of HPβCD is eliminated in the urine. In a study investigating another antifungal drug, itraconazole, following a single intravenous 200 mg dose, clearance of hydroxypropyl-ß-cyclodextrin was reduced in subjects with renal impairment, resulting in higher exposure to hydroxypropyl-ß-cyclodextrin. -In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of HPβCD until steady state is reached. HPβCD is removed by hemodialysis (b) (4)

(b) (4)

5.2 Clinical Pharmacology Assessment of the Proposed Labeling:

The Sponsor did not provide a head-to-head comparison of PK profiles of HPβCD and SBECD in patients with renal impairment. The VFEND for Injection label states, (b) (4) ***"in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group.*** (b) (4) ***in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min),*** (b) (4) ***The VFEND for Injection label does not contain SBECD PK information in patients with mild and severe renal impairment. The VFEND for Injection label also states, under Section 2.8 Use in Patients With Renal Impairment, "In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy".***

Per the Clinical Pharmacology/Biopharmaceutics Review for VFEND (NDA 21267), SBECD has been associated in animal studies with toxic effects in the kidney, specifically cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis, and urinary bladder. Therefore, IV voriconazole (containing SBECD) is not recommended in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) unless the benefit outweighs the risk in an individual patient. Oral voriconazole should be used instead, if possible. No information on SBECD PK was provided in patients with mild and severe renal impairment in the original Clinical Pharmacology/Biopharmaceutics Review of the NDA.

The Sponsor provided HPβCD pharmacokinetic results from a study conducted by Janssen in patients with renal impairment following a 200 mg single dose of SPORANOX (Itraconazole) containing 8 g of HPβCD (Table 5 above). The mean systemic exposure (AUC_∞) of HPβCD was increased by 1.4-, 2.6- and 7-fold, in the mildly, moderately, and severely impaired groups, respectively, compared to the normal control group; although the C_{max} of HPβCD remained relatively unchanged (Table 5). (b) (4)

(b) (4)

(b) (4)

SPORANOX (Itraconazole) IV Injection (current marketing status: discontinued) contains 8 g HPβCD per 200 mg itraconazole. The recommended dose of SPORANOX Injection is 200 mg BID for four doses, followed by 200 mg once daily for up to 14 days. The Sporanox labeling states that in patients with mild (defined as creatinine clearance 50-80 mL/min) and moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, SPORANOX Injection should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to modifying the antifungal regimen to an alternate medication with similar antimycotic coverage. SPORANOX Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).

(b) (4)

(b) (4) ***Finally, the VFEND label already states that serum creatinine levels should be closely monitored in patients with moderate and severe renal impairment, and oral voriconazole therapy should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. From a Clinical Pharmacology perspective, the recommendations in the VFEND label appear adequate to address the safety concern regarding the use of SBECD (or HPβCD) as an intravenous vehicle in the voriconazole IV formulation for patients with renal impairment.***

(b) (4)

Therefore, we recommend the Sponsor change the proposed labeling as provided below to be more consistent with the VFEND for Injection labeling. (b) (4)

of this drug product should be deleted or revised where applicable [Clinical Pharmacology recommended changes to the proposed labeling are indicated as underline (additions) and ~~strikethrough~~ (deletions) in BLUE].

HIGHLIGHTS OF PRESCRIBING INFORMATION

_____CONTRAINDICATIONS_____

- ~~Hypersensitivity to voriconazole or its excipients (4)~~
- (b) (4)
- Coadministration with terfenadine, astemizole, cisapride, pimozide or quinidine, sirolimus due to risk of serious adverse reactions (4, 7)
- Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir, rifabutin, ergot alkaloids, and St. John's Wort due to risk of loss of efficacy (4, 7)

___WARNINGS AND PRECAUTIONS___

- *Clinically Significant Drug Interactions:* Review patient's concomitant medications (5.1, 7)
- *Hepatic Toxicity:* Serious hepatic reactions reported. Evaluate liver function tests at start of and during voriconazole therapy (5.2)

(b) (4)

- Visual Disturbances (including optic neuritis and papilledema): Monitor visual function if treatment continues beyond 28 days (5.3)

2 DOSAGE AND ADMINISTRATION

2.7 Use in Patients with Renal Impairment

(b) (4)

~~In patients with moderate~~ (b) (4) ~~severe renal~~ (b) (4) ~~(creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, hydroxypropyl ß cyclodextrin~~ (b) (4) ~~occurs.~~ (b) (4)

(b) (4)

[redacted]

4 CONTRAINDICATIONS

- Voriconazole for injection is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.
- [redacted]
- Coadministration of Voriconazole for injection with high-dose ritonavir (400 mg q12h) is contraindicated because ritonavir (400 mg q12h) significantly decreases plasma voriconazole concentrations. [redacted] *[see Drug Interactions (7) and Clinical Pharmacology (12.3)].*

5 WARNINGS AND PRECAUTIONS

5.9 Patients with Renal Impairment

~~Hydroxypropyl β cyclodextrin,~~ [redacted] ~~, is eliminated through glomerular filtration In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of~~ [redacted] ~~HPβCD, occurs~~ [redacted].

[redacted] n patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of [redacted] HPβCD, occurs. [redacted] unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in [redacted] patients [redacted] if increases occur, consideration should be given to changing to [redacted] alternate [redacted] with similar [redacted] coverage *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.7)].*

7 DRUG INTERACTIONS

Table 7: Effect of Other Drugs on Voriconazole Pharmacokinetics
[see Clinical Pharmacology (12.3)]

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC_{τ} after 200 mg q12h)	Recommendations for Voriconazole Dosage Adjustment/ Comments
Rifampin* and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz (400 mg q24h)‡ (CYP450 Induction)	Significantly Reduced	**Contraindicated**
[redacted] (b) (4)		[redacted] (b) (4)
High-dose Ritonavir (400 mg q12h)‡ (CYP450 Induction)	Significantly Reduced	Contraindicated
Low-dose Ritonavir (100 mg q12h)‡ (CYP450 Induction)	Reduced	Coadministration of voriconazole and low-dose ritonavir (100 mg q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies
Carbamazepine (CYP450 Induction)	Not Studied In Vivo or In Vitro, but Likely to Result in Significant Reduction	Contraindicated
Long Acting Barbiturates (CYP450 Induction)	Not Studied In Vivo or In Vitro, but Likely to Result in Significant Reduction	Contraindicated
Phenytoin (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV q12h (b) (4) [redacted]
St. John's Wort (CYP450 inducer; P-gp inducer)	Significantly Reduced	Contraindicated
Oral Contraceptives‡ containing ethinyl estradiol and norethindrone (CYP2C19 Inhibition)	Increased	Monitoring for adverse events and toxicity related to voriconazole is recommended when coadministered with oral contraceptives

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 Inhibition)	Significantly Increased	Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is started within 24 h after the last dose of fluconazole.
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	In Vivo Studies Showed No Significant Effects of Indinavir on Voriconazole Exposure In Vitro Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism (Increased Plasma Exposure)	No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir Frequent monitoring for adverse events and toxicity related to voriconazole
Other NNRTIs‡ (CYP3A4 Inhibition or CYP450 Induction)	In Vitro Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism by Delavirdine and Other NNRTIs (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness
		(b) (4)

‡ Non-Nucleoside Reverse Transcriptase Inhibitors

Table 8: Effect of Voriconazole on Pharmacokinetics of Other Drugs [*see Clinical Pharmacology (12.3)*]

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	**Drug Plasma Exposure (C_{max} and AUC_{τ})**	**Recommendations for Drug Dosage Adjustment/Comments**
Sirolimus* (CYP3A4 Inhibition)	Significantly Increased	Contraindicated
Rifabutin* (CYP3A4 Inhibition)	Significantly Increased	Contraindicated

Efavirenz (400 mg q24h)† (CYP3A4 Inhibition)	Significantly Increased	Contraindicated
[redacted] (b) (4)		
High-dose Ritonavir (400 mg q12h)‡(CYP3A4 Inhibition) Low-dose Ritonavir (100 mg q12h)†	No Significant Effect of Voriconazole on Ritonavir Cmax or AUCτ Slight Decrease in Ritonavir Cmax and AUCτ	Contraindicated because of significant reduction of voriconazole Cmax and AUCτ Coadministration of voriconazole and low-dose ritonavir (100 mg q12h) should be avoided (due to the reduction in voriconazole Cmax and AUCτ) unless an assessment of the benefit/risk to the patient justifies the use of voriconazole
Astemizole, Cisapride, Pimozide, Quinidine (CYP3A4 Inhibition)	Vitro, but Drug Plasma Exposure Likely to be Increased	rare occurrence of torsade de pointes
Ergot Alkaloids (CYP450 Inhibition)	Not Studied In Vivo or In Vitro, but Drug Plasma Exposure Likely to be Increased	Contraindicated
Cyclosporine (CYP3A4 Inhibition)	AUCτ Significantly Increased; No Significant Effect on Cmax	When initiating therapy with Voriconazole for injection in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow with frequent monitoring of cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When Voriconazole for injection is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
Methadone (CYP3A4 Inhibition)	Increased	Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed

APPEARS THIS WAY ON ORIGINAL

Fentanyl (CYP3A4 Inhibition)	Increased	Reduction in the dose of fentanyl and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with Voriconazole for injection. Extended and frequent monitoring for opiate-associated adverse events may be necessary [see Drug Interactions (7)]
Alfentanil (CYP3A4 Inhibition)	Significantly Increased	Reduction in the dose of alfentanil and other opiates metabolized by CYP3A4 (e.g., sufentanil) should be considered when coadministered with Voriconazole for injection. A longer period for monitoring respiratory and other opiate-associated adverse events may be necessary [see Drug Interactions (7)].
Oxycodone (CYP3A4 Inhibition)	Significantly Increased	Reduction in the dose of oxycodone and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with Voriconazole for injection. Extended and frequent monitoring for opiate-associated adverse events may be necessary [see Drug Interactions (7)].
NSAIDs§ including. ibuprofen and diclofenac (CYP2C9 Inhibition)	Increased	Frequent monitoring for adverse events and toxicity related to NSAIDs. Dose reduction of NSAIDs may be needed [see Drug Interactions (7)].
Tacrolimus (CYP3A4 Inhibition)	Significantly Increased	When initiating therapy with Voriconazole for injection in patients already receiving tacrolimus, reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When Voriconazole for injection is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
Phenytoin (CYP2C9 Inhibition)	Significantly Increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin.
Oral Contraceptives containing ethinyl estradiol and norethindrone (CYP3A4 Inhibition)	Increased	Monitoring for adverse events related to oral contraceptives is recommended during coadministration.

Warfarin (CYP2C9 Inhibition)	Prothrombin Time Significantly Increased	Monitor PT or other suitable anti-coagulation tests. Adjustment of warfarin dosage may be needed.
Omeprazole (CYP2C19/3A4 Inhibition)	Significantly Increased	When initiating therapy with Voriconazole for injection in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	In Vivo Studies Showed No Significant Effects on Indinavir Exposure In Vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	No dosage adjustment for indinavir when coadministered with Voriconazole for injection Frequent monitoring for adverse events and toxicity related to other HIV protease inhibitors
Other NNRTIs¶ (CYP3A4 Inhibition)	A Voriconazole-Efavirenz Drug Interaction Study Demonstrated the Potential for Voriconazole to Inhibit Metabolism of Other NNRTIs (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to NNRTI
Benzodiazepines (CYP3A4 Inhibition)	In Vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	In Vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.

Dihydropyridine Calcium Channel Blockers (CYP3A4 Inhibition)	In Vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studied In Vivo or In Vitro, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
Vinca Alkaloids (CYP3A4 Inhibition)	Not Studied In Vivo or In Vitro, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring for adverse events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.
Everolimus (CYP3A4 Inhibition)	Not Studied In Vivo or In Vitro, but Drug Plasma Exposure Likely to be Increased	Concomitant administration of voriconazole and everolimus is not recommended.
[redacted] (b) (4)		

§ Non-Steroidal Anti-Inflammatory Drug
¶ Non-Nucleoside Reverse Transcriptase Inhibitors

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients. [redacted] (b) (4)

~~I~~In patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed voriconazole pharmacokinetics [redacted] (b) (4) were similar to those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, [redacted] (b) (4) increasing the intravenous dose from 3 mg/kg q12h to 4 mg/kg q12h produces an approximately 2.5-fold increase in exposure (Table 9).

Table 9: Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

	6 mg/kg IV (loading dose)	3 mg/kg IV q12h	4 mg/kg IV q12h	(b) (4)
N	35	23	40	
AUC_{12} (µg·h/mL)	13.9 (32)	13.7 (53)	33.9 (54)	
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)	
C_{min} (µg/mL)	- -	0.46 (97)	1.73 (74)	

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12–18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg IV, the median of the calculated mean plasma concentrations was 1.60 µg/mL (inter-quartile range 0.28 to 2.73 µg/mL).- (b) (4)

(b) (4)

Distribution–The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma concentrations (b) (4) (approximate range: 0.9–15 µg/mL). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Renal Impairment– [redacted]

In a multiple dose study of IV voriconazole (6 mg/kg IV loading dose × 2, then 3 mg/kg IV × 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30–50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 subjects with normal renal function.

Hydroxypropyl-ß-Cyclodextrin (HPβCD)
~~In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetacyclodextrin (HPβCD), an ingredient of Voriconazole for injection, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85 %) of an 8 g dose of HPβCD is eliminated in the urine.~~ In a study investigating another antifungal drug, itraconazole, following a single intravenous 200 mg dose, clearance of HPβCD was reduced in subjects with renal impairment, resulting in higher exposure to HPβCD. ~~In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of HPβCD until steady state is reached. HPβCD is removed by hemodialysis~~ [redacted]. In patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min), accumulation of the intravenous vehicle, HPβCD, occurs. ~~Intravenous voriconazole~~Voriconazole for Injection should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole [*see ~~Dosage and Administration (2.7)~~* [redacted]

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/min. [redacted] A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Drug Interactions

Significant drug interactions that may require dosage adjustment, [redacted] **or frequent monitoring of drug-related adverse events/toxicity:**

***Efavirenz*, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)**–Standard doses of voriconazole and efavirenz (400 mg q24h or higher) must not be coadministered [*see Drug Interactions (7)*]. Steady state efavirenz (400 mg PO q24h) decreased the steady state Cmax and AUCτ of voriconazole (400 mg PO q12h for 1 day, then 200 mg PO q12h for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO q12h for 1 day, then 200 mg q12h for 8 days) increased the steady state C_{max} and AUC_{τ} of efavirenz (400 mg PO q24h for 9 days) by an average of 38% and 44%, respectively, in healthy subjects.

[redacted]

[redacted]

Coadministration of standard doses of voriconazole and efavirenz (400 mg q24h or higher) is contraindicated. [redacted]

-[*see* [redacted] *Contraindications (4), and Drug Interactions (7)*].

***Phenytoin* (CYP2C9 substrate and potent CYP450 inducer)**–Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_{τ} of orally administered voriconazole (200 mg q12h × 14 days) by an average of 50% and 70%, respectively, in healthy subjects. [redacted]

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours - [redacted]

-[*see Dosage and Administration (2.4) and Drug Interactions (7)*].

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

/s/

ZHIXIA YAN
04/28/2016

PHILIP M COLANGELO
05/03/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
ADDENDUM

NDA	208562
Submission Date	07/24/2015
Drug Product	Voriconazole for Injection
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Xellia Pharmaceuticals ApS
Submission Type	505(b)(2)
Formulation	For injection: lyophilized powder for reconstitution, each vial containing 200 mg voriconazole and 3200 mg of hydroxypropyl-β-cyclodextrin (HPβCD)
Indication	• Invasive aspergillosis • Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds • Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy
Dosage and Administration	See nested table below

Infection	IV Loading Dose	IV Maintenance Dose
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h
Candidemia in non-neutropenics and other deep tissue *Candida* infections		3 – 4 mg/kg q12h
Scedosporiosis and Fusariosis		4 mg/kg q12h

(b) (4)

On 23 May 2016, the Sponsor provided a correspondence (b) (4) to clarify that the "bridge" between their product, Voriconazole for injection, and VFEND® for injection relies only upon *in vitro* studies conducted by the Sponsor and other *in vitro* and *in vivo* studies from the published literature that characterized various physical-chemical properties of voriconazole and/or the

two aforementioned cyclodextrin vehicles. The *in vitro* information is to support the bio-waiver submitted by Xellia in the original 505(b)(2) NDA submission.

(b) (4)

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

/s/

PHILIP M COLANGELO
05/24/2016

JOHN A LAZOR
05/24/2016