CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

MEDICAL REVIEW(S)

ADDENDUM to Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208562
Voriconazole for Injection, 200-mg

ADDENDUM II to Clinical Review, dated 02/22/17:

On 24 May 2016, FDA issued a Tentative Approval (TA) notice to the Applicant, Xellia Pharmaceuticals ApS, for approval via the NDA 505(b)(2) pathway, for an alternative formulation of voriconazole sterile lyophilized powder for injection (I.V.), 200-mg. The applicant, who originally submitted their 505(b)(2) application on 24 July 2015, intended to rely on the Agency's findings of efficacy and safety for Pfizer's VFEND® (voriconazole) for injection, for intravenous use (NDA 021267) in support of their Voriconazole for injection formulation (NDA 208562). The applicant's voriconazole formulation is similar to Pfizer's reference listed drug (RLD), VFEND® I.V. (voriconazole) for Injection in all aspects except in its use of the excipient hydroxypropyl β-cyclodextrin (HPβCD) (b) (4). Pfizer's VFEND® uses sulfobutylether β-cyclodextrin (SBEβCD).

While Xellia continues to rely on the Agency's findings of efficacy and safety for Pfizer's VFEND® (voriconazole), they also informed FDA that they are relying on SPORANOX® (itraconazole) Injection (NDA 020966) as a listed drug for the safety of HPβCD in patients with renal impairment. Xellia notified FDA that they issued a patent certification notice, on May 23, 2016, to Janssen Pharmaceuticals, the applicant for SPORANOX® Injection (NDA 020966). Despite having discontinued production of SPORANOX® Injection, Janssen Pharmaceutica maintains patent and exclusivity rights to this product until June 2019. Xellia previously issued a patent certification letter to Pfizer for the RLD VFEND®.

Briefly, on 21 May 2016, Xellia amended NDA 208,562 to include a Paragraph IV certification against U.S Patent No. 6,407,079 assigned to Janssen Pharmaceutica for right of reference to the HPβCD. On 29 June 2016, Janssen subsequently filed suit against Xellia alleging infringement of U.S. Patent No. 6,407,079 resulting in a 30-month stay of approval under FDCA 505(c)(3)(C). On 22 December 2016, the District Court of Delaware dismissed Janssen's lawsuit against Xellia stating, "All claims, counterclaims, and affirmative defenses between Plaintiff and Xellia which have been or could have been asserted in this action are dismissed with prejudice" and "[t]he 30-month stay of approval for New Drug Application No. 20-8562 pursuant to 21 U.S.C. §355(c)(3)(C) is hereby terminated."

Having received a final judgment in their favor, on 06 January 2017, the Applicant, Xellia, re-submitted "Request for Final Approval" for NDA 208,562. Included in their re-submission is updated Patent Information, updated labeling, and updated chemistry, manufacturing and controls data (CMC). Please see the CMC review for further details on CMC updates.

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/s/

CAROLINE J JJINGO
03/06/2017

THOMAS D SMITH
03/06/2017

CLINICAL REVIEW

Application Type	New Drug Application (NDA) 505(b)(2)
Application Number(s)	NDA 208,562
Applicant	Xellia Pharmaceuticals ApS
Established Name	Voriconazole
Referenced Licensed Drug	VFEND® (voriconazole) for injection, for intravenous use by Pfizer
Priority or Standard	Standard
Formulation(s)	Lyophilized powder for solution for injection
Dosing Regimen	Voriconazole for Injection, 200-mg
Applicant Proposed Indication(s)/Population(s)	Treatment of: • 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
Submit Date(s)	24 July 2015
Received Date(s)	24 July 2015
PDUFA Goal Date	24 May 2016
Division/Office	Division of Anti-Infective Products (DAIP)/ Office of Antimicrobial Products (OAP)
Reviewer Name(s)	Caroline J. Jjingo, MD, MPH
Medical Team Lead	Thomas Smith, MD
Review Completion Date	April 21, 2016
(Proposed) Trade Name	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of: • 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

Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208562
Voriconazole for Injection, 200-mg

Introduction

The applicant, Xellia Pharmaceuticals ApS, seeks approval, via the 505(b)(2) pathway, for an alternative formulation of voriconazole sterile lyophilized powder for injection (I.V.), 200-mg. The applicant's voriconazole formulation is purportedly similar to Pfizer's reference listed drug (RLD), VFEND® I.V. (voriconazole) for Injection in all aspects ***except*** in its use of the excipient hydroxypropyl β-cyclodextrin (HPβCD) (b) (4). Pfizer's VFEND® uses sulfobutylether β-cyclodextrin (SBEβCD). Despite this change in excipient, the applicant contends that replacing the cyclodextrin used in the RLD VFEND® will not alter the pharmacokinetics, pharmacodynamics, safety, or efficacy of this alternative formulation. The applicant intends to rely on the Agency's findings of efficacy and safety for Pfizer's VFEND® (voriconazole) for injection, for intravenous use (NDA 021267) in support of their Voriconazole for injection formulation (NDA 208562).

Voriconazole is a broad spectrum triazole antifungal. On 24 May 2002, Pfizer's VFEND® I.V. (voriconazole) obtained FDA approval under NDA 021267. The RLD, VFEND® (voriconazole) for injection (I.V.), is supplied as a sterile lyophilized powder in a single use vial (200-mg/vial). According to the VFEND® label, voriconazole is indicated for the treatment of invasive aspergillosis; candidemia in non-neutropenic patients with disseminated candidiasis in skin, abdomen, kidney, bladder wall and wound infections; esophageal candidiasis; and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. in patients, aged 12 years and older, who are intolerant of, or refractory to, other therapy (Pfizer VFEND® prescribing information Feb 2015). (b) (4)

Background

First discovered by the French scientist A. Villiers in 1891, cyclodextrins (CD) are cyclic oligosaccharides, composed of varying numbers of alpha-1-4 linked glucose units. CD can be used as a drug delivery system increasing the amount of available drug for solubilization in an aqueous vehicle. These donut-shaped molecules have a hydrophobic inner surface lined with hydrogen bonds and etherlike oxygen linkages that repel water, and permit the entry of lipophilic guest molecules. The outer surface of the "donut" is hydrophilic due to its hydroxyl group projections, thereby permitting the solubilization of the complex in water and protecting the lipophilic guest molecule (Stevens, DA Pharmacology 1999). β-cyclodextrins (β-CD) are the most accessible, useful and cheapest of the natural parent cyclodextrin (CD) compounds. Hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether-β-cyclodextrin (SBEβCD) are the most pharmaceutically relevant CD derivatives (Brewster, ME et al Adv Drug Del Rev 2007), and as such they are the best studied in humans.

The substitution of a hydroxyl group with a hydroxypropyl group modifies the parent β-CD into HPβCD. As a modified derivative of the parent molecule β-CD, HPβCD is 30 times as soluble and less subject to hydrolysis by gut amylases; moreover less than 3% of the modified compound is absorbed and, in humans, the bioavailability is nearly less than 0.5% (Stevens, DA Pharmacology 1999). In 1997, SPORANOX® (itraconazole)/2-HP-β-CD became the first approved CD-containing drug to enter the US pharmaceutical market (Del Valle, EM Process Biochem 2004). In addition, VIBATIV® (telavancin), the lipoglycopeptide and vancomycin derivative FDA approved in 2009, is a highly lipophilic drug that is only minimally soluble in water, and therefore, uses HPβCD as the intravenous vehicle for telavancin delivery. The applicant additionally notes that an I.V. voriconazole formulation containing HPβCD and lactose monohydrate was recently approved in Europe in November 2013 (Module 3 Description and Composition of Drug Product page 5 of 6).

Voriconazole is a lipophilic poorly water soluble drug characterized by nonlinear pharmacokinetics, high inter-individual pharmacokinetics, and hepatic elimination. A 200-mg vial of VFEND® for Injection lyophilized powder contains 3,200-mg of SBEβCD, which amounts to 10-mg/mL of voriconazole and 160-mg/mL of SBEβCD upon reconstitution (Pfizer VFEND® (voriconazole) U.S. Prescribing Information Feb 2015). In comparison, a 200-mg vial of Xellia's Voriconazole for injection also contains 3,200-mg of HPβCD and upon reconstitution amounts to 10-mg/mL of voriconazole and 160 mg/mL of HPβCD (Please see Table 1).

Table 1: Comparison of Xellia Formulation with VFEND Injection 200-mg

Components	Xellia's Voriconazole for Injection 200 mg	VFEND for Injection 200 mg
Active Pharmaceutical Ingredient	Voriconazole 200 mg (10 mg/mL)[a]	Voriconazole 200 mg (10 mg/mL)[a]
Inactive Ingredients	HPβCD 3200 mg (160 mg/mL)[a]	SBECD 3200 mg (160 mg/mL)[a]

[a] Following reconstitution with 19 mL of WFI

(b) (4) the dosage form and strength of Xellia's proposed voriconazole product will be equivalent to VFEND® powder for solution infusion. Although the molar concentrations between these two excipients differ, the applicant indicates that both formulations (b) (4)

(b) (4)

CMC
(Module 2 Section 2.3 Abbreviated Quality Overall Summary)
(Module 2 Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Voriconazole for Injection is to be supplied as a sterile, lyophilized powder, single dose vial (200-mg/vial) with a target fill volume of (b) (4) mL per vial (Section 2.7.1 page 1 of 12). The lyophilized powder is described as a white to off-white cake or powder which is contained in a clear vial with a rubber stopper and aluminum seal white red plastic flip off button. Voriconazole for Injection's lyophilized powder contains 200-mg voriconazole and 3,200-mg hydroxypropyl β-cyclodextrin, as does the RLD. After reconstitution with Water for Injection, a clear, colorless solution is obtained, a solution which contains 10-mg/mL of Voriconazole, USP and 160-mg/mL of the substituted β-cyclodextrin vehicle (Section 2.3. P page 19 of 81). The applicant informs the Agency that their voriconazole formulation will contain HPβCD in the same quantity and concentration of product as the quantity and concentration of SBEβCD in the RLD VFEND®.

The composition of the to-be marketed drug product is found below:

Table 2: Composition of the Voriconazole Drug Product (Section 2.7.1 page 1 of 12)

Name of Ingredient	Quantity per Unit		Function	Reference to Standard
	Mg/vial	% (w/w)		
Voriconazole	200	(b) (4)	Active substance	USP
Hydroxypropyl β-cyclodextrin (HPβCD)	3,200		(b) (4)	NF
(b) (4)				
TOTAL (solids)	(b) (4)	**100.0**		

[i] Water is removed during lyophilization process and is present in finished product only in residual amounts.
[ii] Used as a processing aid for moving the solution through filtration train and backfilling of vials prior to stoppering.

The applicant also states the following (Section 2.2 Introduction Summary page 2 of 22):

- "Xellia intends to rely on the history of safe use of the excipient, HPβCD, which is found at comparable levels in other FDA-approved products with similar patient populations and duration of use, to support its use in the Xellia product.
- Xellia intends to rely on publicly available information and analytical data to support the safety of drug-related impurities that may be present in the drug substance and drug product.
- Xellia intends to rely on analytical data to support the safety of extractables and leachables from the container closure for the drug product."

Nonclinical Pharmacology/Toxicology (Module 2 Section 2.6.6 Toxicology Summary)
The applicant has not conducted any nonclinical toxicology studies in support of this NDA, and does not intend to conduct any nonclinical studies of HPβCD, single-dose or repeat-dose toxicity studies, genotoxicity studies, carcinogenicity, or reproductive and development toxicity studies. (b) (4)

Clinical Pharmacology (Module 2 Section 2.7.2 Summary of Clinical Pharmacology Studies)
The applicant did not conduct any original clinical pharmacology studies in support of this NDA, (b) (4) hey do not believe that the replacement of SBEβCD with HPβCD will affect voriconazole's bioavailabilty.

(b) (4)

(b) (4)

Clinical Microbiology (Module 2 Section 2.6.2 Pharmacology Written Summary)
The applicant conducted an *in vitro* study comparing the antifungal activity of their voriconazole formulation against Pfizer's RLD VFEND® obtained from UK (2 batches) and US (2 batches) manufacturers. Under identical experimental conditions, the applicant simultaneously performed 11 tests, to determine the mean inhibitory concentrations (MIC) of these 3 voriconazole finished products (2 VFENDs and 1 from the applicant) against 3 *Candida* strains (*Candida albicans* ATCC 90028, *Candida krusei* ATCC 22019 and *Candida parapsilosis* ATCC 6258). From this data, the applicant concluded that the antifungal activity against the RLD and their drug product was "fully comparable . . . when tested against [three] *Candida* quality control strains (Report No. 13/2012) (page 1 of 1)."

No additional new clinical microbiology information was included in the application, as the applicant intends to solely rely on any information that had been previously described in the approved RLD product application.

Clinical/Statistical-Efficacy (Module 2 Section 2.7.3 Summary of Clinical Efficacy)
The applicant did not conduct any original clinical efficacy studies in support of this NDA. "Xellia is relying on the findings of safety and efficacy for the Reference Listed Drug VFEND® (voriconazole) for injection (NDA 021267) (page 1 of 1)."

Safety (Module 2 Section 2.6.6 Toxicology Written Summary)
The applicant intends to rely on safety data from several other previously FDA-approved products containing the excipient HPβCD, such as intravenous itraconazole (SPORANOX®, NDA 020966), in support of HPβCD's safety. SPORANOX® (itraconazole) Injection is an antifungal indicated for the treatment of several fungal infections in both immunocompromised and non-immunocompromised patients and for empiric therapy of febrile neutropenic patients with suspected fungal infections. "SPORANOX® (itraconazole) Injection is a sterile pyrogen-free clear, colorless to slightly yellow solution for intravenous infusion. Each mL contains 10 mg of itraconazole, solubilized by hydroxypropyl-β-cyclodextrin (400 mg) as a molecular complex, . . . SPORANOX® Injection is packaged in 25 mL colorless glass ampules, containing 250 mg of itraconazole, the contents of which are diluted in 50 mL 0.9% Sodium Chloride Injection, USP (Normal Saline) prior to infusion. When properly administered, contents of one ampule will supply 200 mg of itraconazole (Janssen Pharmaceuticals SPORANOX® (itraconazole) U.S. Prescribing Information, revised March 2009, page 2)" and 8,000 mg of HPβCD.

Table 4: Sporanox and Xellia's Voriconazole for Injection Exposure Comparisons of Hydroxypropyl-β-cyclodextrin (page 3 of 7)

Parameter	Sporanox®	Xellia's Voriconazole
Patient population	Patients with fungal infections	Patients with fungal infections
Label dose of Drug Substance	200 mg bid for two days, then 200 mg qd for five days	6 mg/kg bid for 24 hours, then 3-4 mg bid
Content of HPβCD per mg Drug Substance	40 mg HPβCD/mg itraconazole	16 mg HPβCD/mg Voriconazole
Exposure to HPβCD	8,000 mg bid for two days, then 8,000 mg qd for five days	Not applicable; dose varies according to body weight
Exposure to HPβCD expressed as mg/kg for a 50 kg adult	320 mg/kg/day for two days, then 160 mg/kg/day for 5 days	192 mg/kg/day for 24 hours, then 96-128 mg/kg/day

The SPORANOX® (itraconazole) Injection prescribing information provides a warning which conveys "SPORANOX® (itraconazole) Injection contains the excipient hydroxypropyl-β-cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown." The SPORANOX® (itraconazole) Injection label also cautions, "The excipient hydroxypropyl β-cyclodextrin is eliminated through glomerular filtration. Therefore, SPORANOX® IV is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30-mL/min)." The label further states "Following a single intravenous dose of itraconazole 200 mg, clearance of hydroxypropyl-β-cyclodextrin was reduced in subjects with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these subjects, 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 hydroxypropyl-β-cyclodextrin until steady state is reached. Hydroxypropyl-β-cyclodextrin is removed by hemodialysis (Janssen Pharma SPORANOX® (itraconazole) U.S.P.I., pages 4, 9)."

Telavancin (VIBATIV®, NDA 022110) for injection, FDA approved in 2009, is a lipoglycopeptide antibacterial indicated for use in adult patients with complicated skin and skin structure infections (cSSSI) and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). Telavancin comes in 250-mg vials and 750-mg vials and contains HPβCD as an excipient, (2500-mg of HPβCD and 7500-mg of HPβCD, respectively).

Table 4 Vibativ and Xellia's Voriconazole for Injection Exposure Comparisons of Hydroxypropyl-β-Cyclodextrin (page 4 of 7)

Parameter	Vibativ	Xellia's Voriconazole
Patient population	Patients with bacterial infections	Patients with fungal infections
Label dose of Drug Substance	10 mg/kg infusions; qd for 7-14 days	6 mg/kg bid for 24 hours, then 3-4 mg bid
Content of HPβCD per mg Drug Substance	10 mg HPβCD/mg telavancin	16 mg HPβCD/mg Voriconazole
Exposure to HPβCD expressed as mg/kg	100 mg/kg/day	192 mg/kg/day for 24 hours, then 96-128 mg/kg/day

Patients with Renal Impairment
(Module 2 Section 2.7 Clinical Summary; 2.7.1 Summary of Biopharmaceutic Studies)
The primary route of elimination for both HPβCD and SBEβCD is through renal excretion via glomerular filtration. Since both of these β-CDs have a fairly high clearance and small V_d values, the half-lives ($t_{1/2}$) of these molecules are very short. Consequently, immediately after IV administration of either HPβCD or SBEβCD, these molecules appear in the renal proximal tubules (Stella, VJ Toxicol Pathol 2008). Because cyclodextrins are renally eliminated, renal impairment may cause cyclodextrin accumulation and increase elimination half-life regardless of which drug vehicle (HPβCD or SBEβCD) is used.

Existing PK data demonstrate that the volumes of distribution, renal clearance and elimination half-life of IV SBEβCD and HPβCD are comparable. Therefore, IV SBEβCD and HPβCD are found to be rapidly eliminated from the systemic circulation and are excreted unchanged in the urine with minimal to no metabolism (page 10 of 12). In renally impaired individuals, cyclodextrin will accumulate and will result in an increase in the elimination half-life of either SBEβCD or HPβCD. Previous studies showed the elimination of HPβCD was most prolonged in persons with severe impairment. The RLD product instructs all users to avoid intravenous administration in patients with moderate to severe renal impairment (creatinine clearance [CrCl] <50 mL/min). (b) (4)

Medical Reviewer's Comments
The clinical pharmacology review team believes that the applicant should include the same warning in patients with moderate to severe impairment as that found in the RLD VFEND®'s U.S.P.I and (b) (4) In persons with moderate to severe renal dysfunction (CrCl<50 mL/min), Dr.Zhixia (Grace) Yan, clinical pharmacology reviewer, recommends that an alternate antifungal therapy be considered. Please refer to Dr. Zhixia (Grace) Yan's review for full details.

Literature Review (Module 2 Section 2.7 Summary of Clinical Safety; 2.7.4.6. Post-marketing Data)
Label
Non-clinical (Module 2 Section 2.4 Nonclinical Overview)
(b) (4) the applicant conducted a search of the published literature to identify any new nonclinical toxicology and pharmacokinetics information on voriconazole which they deemed may impact the current product labeling. They performed a MEDLINE® search using the PubMed® interface at www.pubmed.gov and searched the database for articles on voriconazole published between August 2014 and present (May 22, 2015). The abstracts of all articles identified in the search were reviewed. No nonclinical data with the potential to impact current nonclinical safety labeling were identified (page 1).

Clinical-Safety (Module 2 Section 2.7 Summary of Clinical Safety; 2.7.4.6. Post-marketing Data)
The applicant conducted a review of the literature and FDA Adverse Events Reporting System (AERS) to identify post-marketing safety findings associated with the use of voriconazole as requested by the FDA

(April 24, 2015 Pre-NDA preliminary meeting responses and May 13, 2015 email communication from Naseya Minor).

In accordance with the Agency's request, the applicant conducted a PubMed literature search using the keyword voriconazole, to "identify literature reporting safety findings associated with voriconazole use" since August 2014, since the relevant literature was reviewed for the VFEND® label revision in February 2015 (page 2 of 47). Their search yielded a total of ten relevant safety-related articles, published study reports, retrospective reviews or case reports pertaining to such *expected adverse events* as periostitis due to fluorosis, toxic epidermal necrolysis, and cutaneous squamous cell carcinoma. In addition, they identified two studies in which the concentrations of voriconazole plasma levels were elevated in the setting of inflammation. Another study reported an instance of "immune reconstitution inflammatory" in neutropenic patients with invasive pulmonary aspergillosis treated with voriconazole, a finding purportedly not uncommon in such situations.

Several publications identified drug-drug interactions (DDI) between voriconazole and other medications, including interactions between fentanyl and voriconazole and voriconazole and the HIV ART combination of darunavir-ritonavir. These DDIs are already included in the VFEND® label. They additionally noted an interaction between voriconazole and flucloxacillin that resulted in sub-therapeutic voriconazole drug levels. A retrospective analysis identified a possible association between muscle weakness in 11 patients treated concomitantly with voriconazole and corticosteroids.

The sponsor concluded that they identified no new safety signals which, in their estimation, would warrant a modification to the pre-existing approved VFEND® label.

Medical Reviewer
In March 2016, the medical reviewer conducted a PubMed/MeSH search using the MeSH search criteria ("Voriconazole"/"adverse events" [MeSH]) OR ("Voriconazole/toxicity" [MeSH]) and the restrictions "human" and "English language." This search yielded a total of 41 publications. Applying the publication date restriction of 01 October 2014 to 31 March 2016, the search was further narrowed to 25 publications. These dates were selected to be inclusive of the time period shortly before and a year after the most recently approved 3 February 2015 VFEND® label. Of these 25 publications, the two most commonly cited safety related topics included voriconazole-induced periostitis (6 publications) and voriconazole-induced squamous cell carcinomas (5 publications). There was one article addressing voriconazole associated alopecia and nail changes. Other publications pertained to drug-drug interactions, such as those between voriconazole and sirolimus, and voriconazole and everolimus. Applying the "clinical trials filter" to the above-outlined search criteria yielded four publications. Each of these publications was reviewed for adverse events; however, none of these studies identified new safety AEs. Identified AEs included such well-known voriconazole related AEs such as: hepatobiliary disorders (hyperbilirubinemia, abnormal hepatic function), eye disorders (visual impairment, photophobia, reduced visual acuity, etc.), and psychiatric disorders (hallucinations including visual hallucinations and agitation), all of which are included in the most recent iteration of the VFEND® USPI from 3 February 2015.

The medical reviewer additionally subscribed to PubMed Alerts; however, the reviewer found no new articles with concerning safety signals.

Adverse Event Reporting System (AERs) (Section 2.7 2.7 Summary of Clinical Safety)
Applicant
To identify any post-marketing adverse event safety findings, the applicant conducted an FDA AERS safety search of both generic voriconazole and VFEND® from the time period covering 1 January 2014 through 30 September 2014 -- the most recently available AERS quarterly report data at the time of the applicant's NDA submission. In so doing, the applicant identified a total of 516 reports containing a total of 1,724 adverse events, of which 1,524 were identified as serious and 200 as non-serious.

The most commonly reported adverse events reported in AERS, those with a frequency of >2%, were death (3.5%) and drug ineffective (2.0%). The applicant surmised that such findings reflect the fact that voriconazole is often used in critically ill patients with a host of co-morbid conditions (often including neutropenia) who are additionally taking multiple concomitant medications (pages 2-3 of 47).

Office of Surveillance and Epidemiology (OSE)
Dr. Kelly Cao from OSE/DPVII confirmed that as of 2/18/16, OSE was not aware of any new signals with voriconazole that require regulatory action at this time.

Pediatrics - PREA
PREA does not apply to this change in excipient of the voriconazole formulation, (b) (4) Therefore, neither a pediatric assessment and/or pediatric study plan are needed.

Labeling
The RLD VFEND® was FDA approved in 24 May 2002. In February 2015, Pfizer changed: the WARNING and PRECAUTIONS section of the VFEND® package insert and updated it with regards to hepatic toxicity, arrhythmias and QT prolongation, and Dermatological Reactions; the DOSAGE AND ADMINISTATION section were updated regarding concomitant use of voriconazole and blood products or short-term infusion of concentrated electrolytes; and the CLINICAL PHARMACOLOGY section, Microbiology subsection were updated . In February 2014, the CONTRAINDICATIONS section and CLINICAL PHARMACOLOGY subsections of the package insert were updated to indicate that co-administration of standard doses of voriconazole with efavirenz dose of 400-mg every 24-hours or higher is contraindicated, due to significant decreases in plasma voriconazole concentrations resulting from efavirenz administration. The label was updated to include the following information: "voriconazole may increase plasma concentrations of everolimus, which could potentially lead to exacerbation of everolimus toxicity."

Recommendations/Risk Benefit Assessment
From a clinical standpoint, this reviewer's recommendation is to approve this formulation of voriconazole for the following indications:

- 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

The applicant, Xellia, will only be manufacturing the IV formulation of the RLD. They will not manufacture the oral tablet or oral suspension formulations. (b) (4)

(b) (4)

No new data from clinical or non-clinical studies were included in this submission. A waiver of bioequivalence studies was granted. This formulation of voriconazole is assessed as bioequivalent to the approved RLD, VFEND®. No new safety information was presented or identified that would alter the favorable risk/benefit assessment of voriconazole in the treatment of the labeled indications. No post-marketing risk evaluation and management strategies or post-marketing requirements or commitments are recommended for Xellia's voriconazole formulation.

References

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Del Valle E.M.M. Cyclodextrins and their uses: a review. Proc Biochem. 39(2004) 1033-1046.

Janssen Pharmaceuticals Sporanox® (itraconazole) U.S. Prescribing Information, revised March 2009

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Pfizer VFEND® (Voriconazole) Prescribing Information. 2015 Feb.

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Stevens DA. Itraconazole in cyclodextrin solution. Pharmacotherapy. 1999 May;19(5):603-11.

Theravance Biopharma VIBATIV® (Telavancin) Prescribing Information 2014 Feb.

Xellia Pharmaceuticals ApS NDA Application NDA 208,562; 24 July 2015.

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/s/

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04/28/2016

THOMAS D SMITH
04/28/2016

ADDENDUM to Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208562
Voriconazole for Injection, 200-mg

ADDENDUM to Clinical Review, dated 4/28/16:

The applicant, Xellia Pharmaceuticals ApS, seeks approval, via the 505(b)(2) pathway, for an alternative formulation of voriconazole sterile lyophilized powder for injection (I.V.), 200-mg. The applicant, who originally submitted their 505(b)(2) application on 24 July 2015, intends to rely on the Agency's findings of efficacy and safety for Pfizer's VFEND® (voriconazole) for injection, for intravenous use (NDA 021267) in support of their Voriconazole for injection formulation (NDA 208562). The applicant's voriconazole formulation is purportedly similar to Pfizer's reference listed drug (RLD), VFEND® I.V. (voriconazole) for Injection in all aspects except in its use of the excipient hydroxypropyl β-cyclodextrin (HPβCD) (b) (4). Pfizer's VFEND® uses sulfobutylether β-cyclodextrin (SBEβCD).

(b) (4) In support of this application, Xellia performed a series of *in vitro* PK experiments demonstrating the bioequivalence of voriconazole in HPβCD vs. SBEβCD. These experiments were "designed to test the influence of the type of substituted ß-cyclodextrin (HPßCD vs. SBECD) on the dissociation of voriconazole from voriconazole:β-cyclodextrin complexes in an aqueous media and in a lipophilic environment (Xellia report dated September 12, 2014)." In so doing, Xellia determined that "the stability constants for HPßCD-voriconazole and SBEßCD-voriconazole complexes were equal to 319 M^{-1} and 491 M^{-1}, respectively, well below 1×10^5 M^{-1} and thereby indicating that the release of voriconazole from both complexes would be instantaneous irrespective of the type of substituted ß-cyclodextrin. Furthermore, Xellia demonstrated that the kinetics of voriconazole release from both Xellia's product and VFEND® are similar in both aqueous (**Error! Reference source not found.** and **Error! Reference source not found.**) and lipophilic environments (Module 2 Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods page 4)." Based on this information, FDA granted the applicant's biowaiver request. Please refer to the Biopharmaceutics review by Dr. Gieser for additional details.

While Xellia continues to rely on the Agency's findings of efficacy and safety for Pfizer's VFEND® (voriconazole) for all other aspects of Xellia's proposed NDA, (b) (4), they have additionally informed FDA that they will be relying on SPORANOX® (itraconazole) Injection (NDA 020966) as a listed drug for the safety of HPβCD in patients with renal impairment. Xellia has notified FDA that they have issued a patent certification notice to Janssen Pharmaceuticals on May 23, 2016, the applicant for SPORANOX® Injection (NDA 020966), who despite having discontinued production of SPORANOX® Injection maintains a patent and exclusivity rights to this product until June 2019. Xellia previously issued a patent certification to Pfizer for the RLD VFEND®.

In summary, the applicant Xellia, (b) (4) have conducted *in vitro* experiments establishing that a change in solubilizing agent will not alter the pharmacokinetics, pharmacodynamics, safety, or efficacy of their formulation relative to the RLD VFEND®. They also will rely on the RLD SPORANOX® (itraconazole) Injection (NDA 020966) to establish the safety of HPβCD in patients with renal impairment. Xellia has secured and issued patent certifications for both RLDs.

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/s/

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05/24/2016

PETER W KIM
05/24/2016