CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Division of Anti-Infective Products
Clinical Microbiology Review

Clinical Microbiology Reviewer	Shukal Bala, PhD
Acting Microbiology Team Leader	Tamara Feldblyum, PhD
NDA #	208562
SDN	014
Applicant Name	Xellia Pharmaceuticals Aps
Date of Submission	01/09/2017
CDER Date Received	01/09/2017
Product Name	Voriconazole lyophilized product for infusion
Indications	• Invasive aspergillosis. • Candidemia (non-neutropenic) and disseminated infections in skin, abdomen, kidney, bladder wall, and wounds. • Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani* in patients intolerant of, or refractory to, other therapy.
Recommended Action	Approval

The Applicant had submitted a NDA for approval of its proposed voriconazole injection product by the 505(b)(2) regulatory pathway. The Applicant was issued a tentative approval letter on May 24, 2016 due to patent protection of one of the drugs that the application was relying upon. Issues regarding the patent protection have been resolved; therefore the Applicant is now requesting Final Approval.

Based on the current Division practice, minor edits were made in sub-sections 12.1 and 12.4 of the labeling. There are no further recommendations from microbiology perspective. The NDA should be approved.

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/s/

SHUKAL BALA
02/17/2017

TAMARA V FELDBLYUM
02/17/2017

Division of Anti-Infective Products
Clinical Microbiology Review

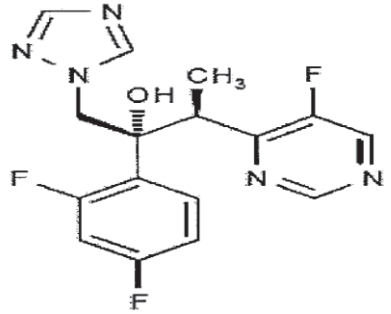
NDA: 208562 (SDN-001 and -002)
Date Submitted: 07/24/2016; 10/28/2016
Date Received by CDER: 07/24/2016; 10/28/2016
Date Assigned: 07/27/2016; 10/28/2016
Date Review Completed: 02/25/2016
Reviewer: Shukal Bala

APPLICANT

Xellia Pharmaceuticals Aps
C/O The Weinberg Group
1129 20th St Northwest Ste 600
Washington, DC 20036

DRUG PRODUCT NAME

Proprietary name: None
Non-proprietary name: Voriconazole
Chemical name: (2R,3 S)-2-(2, 4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4triazol-1-yl)-2-butanol (aR,pS)-a-(2,4-difluorophenyl)-5-fluoro-P-methyl-a-(1H -1 ,2,4-triazol-1-ylmethyl)-4- pyrimidine ethanol
Molecular/Structural formula: $C_{16}H_{14}F_3N_5O$



Molecular weight: 349.3

PROPOSED INDICATIONS

1. Invasive aspergillosis.
2. Candidemia (non-neutropenic) and disseminated infections in skin, abdomen, kidney, bladder wall, and wounds.
3. Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani* in patients intolerant of, or refractory to, other therapy.

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Dosage form: Lyophilized product; will be reconstituted for injection.
Route of administration: Intravenous infusion.
Dosage: 200 mg in a vial; for doses to be administered see Table below.
Duration of treatment: The dosing regimen is the same as the intravenous dosing regimen for the reference listed drug (RLD) VFEND® (NDA 021267). Single to multiple daily doses will be administered depending on the indication as shown below in the Table.

Table: Recommended dosing regimen

(b) (4)

Source: Applicant's submission

DISPENSED
Rx

RELATED DOCUMENTS
NDA 021267 VFEND® (The Applicant: Pfizer Inc.); Pre IND 124450

REMARKS and CONCLUSIONS
The applicant submitted a NDA for approval of its proposed voriconazole injection product by the 505(b)(2) regulatory pathway. The proposed indications for the applicant's formulation are (b) (4)

(b) (4)

The difference in formulation between the applicant's intravenous product and the RLD (VFEND®) is the composition of excipients, which include substitution of sulfobutyl ether beta-cyclodextrin sodium (SBE-β-CD) with hydroxy propyl beta-cylcodextrin sodium (HP-β-CD) (b) (4). The *in vitro* activity of the applicant's formulation is similar to that of the RLD against the three strains of *Candida* species tested. No clinical trials were performed in subjects with invasive aspergillosis, candidemia or serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species.

The microbiology section of the labeling for the applicant's formulation is same as the RLD (VFEND®) labeling. This is appropriate.

COMMENTS
From microbiology standpoint, the NDA should be approved. Minor changes are recommended in the microbiology section of the labeling to be consistent with the current Division practice (for details see section 3.3 below).

1. Introduction and Background

The subject of this NDA is voriconazole. Voriconazole (VFEND®, Pfizer, NDA 021267) the reference listed drug (RLD) was approved in 2002 for use in patients 12 years of age and older for the treatment of

- invasive aspergillosis.
- candidemia (non-neutropenic) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds.
- esophageal candidiasis.
- serious infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* species including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy.

The applicant submitted a NDA for approval of its proposed voriconazole injection product by the 505(b)(2) regulatory pathway. The difference in the intravenous formulation between the applicant's product and the RLD (VFEND®) is the composition of excipients, which include substitution of sulfobutyl ether beta-cyclodextrin sodium (SBE-β-CD) with hydroxy propyl beta-cylcodextrin sodium (HP-β-CD) (b) (4) (Table 1).

Table 1: Formulation comparison between (b) (4) voriconazole for injection and VFEND® IV (RLD)

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.
Source: NDA

The applicant submitted a NDA for approval of its proposed voriconazole injection product by the 505(b)(2) regulatory pathway. The proposed indications for the applicant's formulation (b) (4) (b) (4)

2. Nonclinical microbiology studies

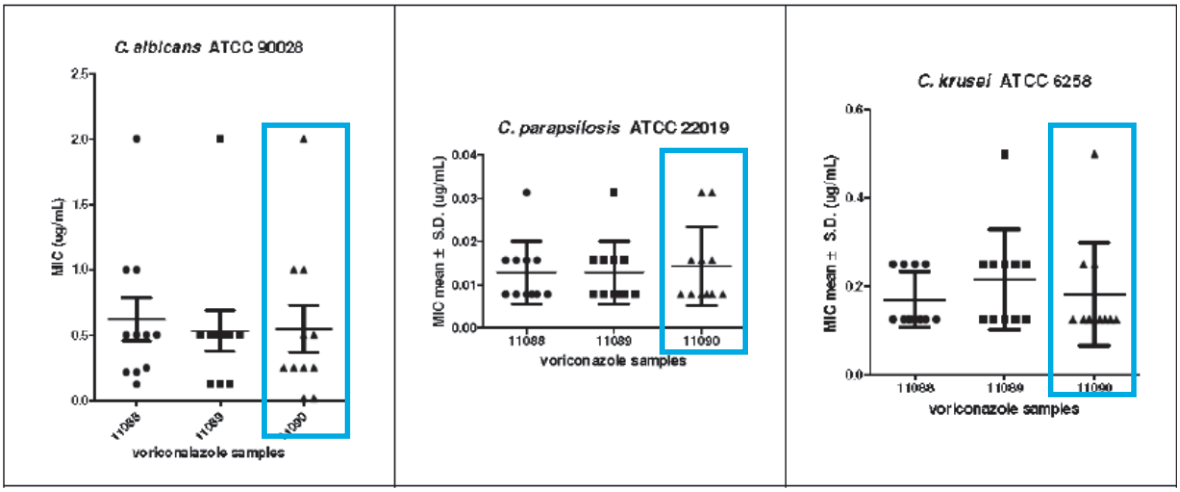
The applicant included a study report to support comparability of the anti-fungal activity of the voriconazole formulation containing HP-β-CD as the cyclodextrin containing voriconazole for injection (Sample Code No. 11090) to the activity of voriconazole of the RLD product, obtained from UK (Sample Code No. 11088) and the US (Sample Code No. 11089) against three quality control (QC) *Candida* strains (*Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, and *Candida krusei* ATCC 6258).[1] The testing was performed by the broth microdilution method according to the Antifungal Susceptibility Testing Subcommittee of European Committee on Antibiotic Susceptibility testing (AFST-

[1] Xellia Report No. 13/2012.

EUCAST) guidelines for the determination of minimum inhibitory concentrations (MICs).[2] Two of the QC strains (*C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019) are the same as those listed in the VFEND® approved labeling and those published by the Clinical Laboratory and Standards Institute (CLSI)[3] for MIC QC ranges; there is no MIC range published for the QC strain *C. albicans* ATCC 90028 in the CLSI document nor in the FDA approved labeling for VFEND®.

The determination of MICs of three voriconazole drug products was carried out simultaneously 11 times under the same experimental conditions. The results show that the MICs of the applicant's and RLD formulations are similar against the strains tested (Figure 1).

Figure 1: MIC Distributions for Voriconazole with HPβCD and SBEβCD



Comments:

- *Overall, the results suggest antifungal activity of the formulation containing HP-β-CD is comparable to that of the RLD VFEND®.*
- *A literature search was conducted to identify new nonclinical studies on voriconazole; no reports were identified with information that would impact product labeling.*

2.2. Clinical microbiology studies

The applicant relied on the information in the RLD, VFEND®, in the proposed NDA submission. No clinical trials were performed.

[2] EUCAST Definitive Document EDef 7.1: method for the determination of broth dilution MICs of antifungal agents for fermentative yeasts. *Clin Microbiol Infect* (2008) 14: 398–405.

[3] Clinical and Laboratory Standards Institute (CLSI). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Third Edition*. CLSI document M27-A3. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2008.

3. The Labeling

3.1. Applicant's proposed labeling:

12.1 Mechanism of Action
Voriconazole is an antifungal drug [*see Microbiology (12.4)*]

12.4 Microbiology

Mechanism of Action
Voriconazole is an azole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole.

(b) (4) Resistance

Voriconazole drug resistance development has not been adequately studied *in vitro* against *Candida, Aspergillus, Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

(b) (4)

Voriconazole has been shown to be active against most strains of the following microorganisms, **both *in vitro* and in clinical infections.**

Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus
Candida albicans
Candida glabrata (In clinical studies, the voriconazole MIC90 was 4 µg/mL)[1]
Candida krusei
Candida parapsilosis
Candida tropicalis
Fusarium spp. including *Fusarium solani*
Scedosporium apiospermum

The following data are available, **but their clinical significance is unknown.**

(b) (4)

(b) (4) not been established in adequate and well-controlled clinical trials:

Candida lusitaniae
Candida guilliermondii

[1]In clinical studies, voriconazole MIC90 for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC90 was 1 µg/mL (see Table 12).

Susceptibility Testing Methods[1,2]

***Aspergillus* species and other filamentous fungi**

No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

***Candida* species**

The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours.[1,2]

Broth Microdilution Techniques–Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours.[1] Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in Table 10.

Diffusion Techniques–Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* spp. to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations.[2] This procedure uses paper disks impregnated with 1 µg of voriconazole to test the susceptibility of yeasts to voriconazole at 24 hours. Disk diffusion interpretive criteria are also provided in Table 10.

Table 10: Susceptibility Interpretive Criteria for Voriconazole[1,2]

	Broth Microdilution at 48 hours (MIC in µg/mL)			Disk Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	Intermediate (I)	Resistant (R)	Susceptible (S)	Intermediate (I)	Resistant (R)
Voriconazole	≤1.0	2.0	≥4.0	≥17	14–16	≤13

NOTE: Shown are the breakpoints (µg/mL) for voriconazole against *Candida* species.

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *intermediate* (I) (b) (4) A report of *Resistant* (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to ensure the accuracy of the technical aspects of the test procedures. Standard voriconazole powder and 1 µg disks should provide the following range of values noted in Table 11.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Table 11: Acceptable Quality Control Ranges for Voriconazole to be used in Validation of Susceptibility Test Results

QC Strain	Broth Microdilution (MIC in µg/mL) at 48-hour	Disk Diffusion (Zone diameter in mm) at 24-hour
Candida parapsilosis ATCC 22019	0.03–0.25	28–37
Candida krusei ATCC 6258	0.12–1.0	16–25
Candida albicans ATCC 90028	*	31–42

ATCC is a registered trademark of the American Type Culture Collection.
* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

15 REFERENCES

1. Clinical Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved Standard M27-A3. Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2008.
2. Clinical Laboratory Standards Institute (CLSI). Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts. Approved Guideline M44-A2. Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2009.

3.2. Comments:

- *The information in sections 12.1 and 12.4* [redacted] (b) (4) [redacted] *The applicant's proposal is appropriate. However, few changes are recommended to be consistent with the current Division practice.*

3.3. FDA version of the labeling:
(The deleted text is striked out and additions double underlined)

12.1 Mechanism of Action
Voriconazole is an azole antifungal drug [*see Microbiology (12.4)*]

12.4 Microbiology

Mechanism of Action
Voriconazole is an azole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole.

[redacted] (b) (4) Resistance
Voriconazole drug resistance development has not been adequately studied *in vitro* against *Candida, Aspergillus, Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

[redacted] (b) (4) *Antimicrobial Activity*
Voriconazole has been shown to be active against most strains of the following microorganisms, **both *in vitro* and in clinical infections.**

Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus
Candida albicans
Candida glabrata (In clinical studies, the voriconazole MIC90 was 4 µg/mL)[1]
Candida krusei
Candida parapsilosis
Candida tropicalis
Fusarium spp. including *Fusarium solani*
Scedosporium apiospermum

The following data are available, **but their clinical significance is unknown.**

(b) (4)

(b) (4) The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following fungi exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for voriconazole against isolates of similar genus or organism group. However, the efficacy of voriconazole in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials:

Candida lusitaniae
Candida guilliermondii

[1]In clinical studies, voriconazole MIC90 for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC90 was 1 µg/mL (see Table 12).

Susceptibility Testing Methods[1,2]

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No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

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Broth Microdilution Techniques

Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours.[1] Standardized procedures are based on a microdilution method (broth) with standardized

inoculum concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in Table 10.

Diffusion Techniques
Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* spp. to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations.[2] This procedure uses paper disks impregnated with 1 µg of voriconazole to test the susceptibility of yeasts to voriconazole at 24 hours. Disk diffusion interpretive criteria are also provided in Table 10.

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Voriconazole	≤1.0	2.0	≥4.0	≥17	14–16	≤13

NOTE: Shown are the breakpoints (µg/mL) for voriconazole against *Candida* species.

A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *intermediate (I)* (b) (4) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant (R)* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control
Standardized susceptibility test procedures require the use of quality control organisms to ensure the accuracy of the technical aspects of the test procedures. Standard voriconazole powder and 1 µg disks should provide the following range of values noted in Table 11.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

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(See appended electronic signature page)
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CC:
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02/25/2016

AVERY C GOODWIN
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