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APPLICATION NUMBER:

208562Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
PHARMACOLOGY/TOXICOLOGY NDA REVIEW

Application number:	208562
Supporting document #:	14
Applicant's letter date:	January 6, 2017
CDER stamp date:	January 6, 2017
Product:	VORICONAZOLE for injection
Indications:	(1) Invasive aspergillosis (2) Candidemia (non-neutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds (3) Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy
Applicant:	Xellia Pharmaceuticals ApS Dalslandsgade 11 Copenhagen S Denmark
Review Division:	Division of Anti-infective Products
Reviewer:	Owen G. McMaster, Ph.D.
Supervisor/Team Leader:	Terry Miller, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Naseya Minor, MPH

Background

On July 24, 2015, Xellia Pharmaceuticals ApS submitted a New Drug Application for Voriconazole for Injection, 200 mg, under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The basis for this 505(b)(2) NDA is the Reference Listed Drug (RLD), Pfizer's VFEND® I.V. (voriconazole), 200 mg, which was approved in 2002. The active ingredient, (b) (4), route of administration, dosage form and strength of the applicant's product are the same as those of the RLD but the RLD is formulated with sulfobutyl ether β-cyclodextrin (SBECD) while the applicant's product is formulated with hydroxypropyl β-cyclodextrin (HPBCD). Xellia's 505(b)(2) NDA also refers to and relies upon data contained in the Janssen Pharmaceutica's NDA for SPORANOX® (NDA #020966).

On May 24, 2016, Xellia received the Tentative Approval letter for NDA #208562 for

Voriconazole for Injection, 200 mg. The approval was only tentative because of a lawsuit over patent protection for SPORANOX®. On December 22, 2016, the lawsuit filed by Janssen against Xellia in the District of Delaware, Civil Action No. 16-cv-00554-LPS, was dismissed by the district court.

Table 1. Comparison of the Xellia Formulation with VFEND injection

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

There are no safety concerns regarding the substitution of SBECD with HPBCD. HPBCD has been approved for use in the US in drugs such as Sporanox (Itraconazole) Injection and Vibativ (telavancin for injection). Xellia is relying on FDA's prior finding of the safety and effectiveness of the reference listed drug.

There are no Pharmacology or Toxicology issues which would preclude the approval of Xellia's Voriconazole for injection.

Labeling Recommendations

The applicant should strike the following statement from Section (b) (4) of the label:

(b) (4)

Reviewer comment:

(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/

OWEN G MCMASTER
02/14/2017

TERRY J MILLER
02/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
PHARMACOLOGY/TOXICOLOGY NDA REVIEW

Application number:	208562
Supporting document/s:	1
Applicant's letter date:	July 24, 2015
CDER stamp date:	July 24, 2015
Product:	VORICONAZOLE for injection
Indications:	(1) Invasive aspergillosis (2) Candidemia (non-neutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds (3) Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy
Applicant:	Xellia Pharmaceuticals ApS Dalslandsgade 11 Copenhagen S Denmark
Review Division:	Division of Anti-infective Products
Reviewer:	Owen G. McMaster, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Naseya Minor, MPH

Background

Xellia Pharmaceuticals ApS submitted a New Drug Application for Voriconazole for Injection, 200 mg, under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The basis for this 505(b)(2) NDA is the Reference Listed Drug (RLD), VFEND® I.V. (voriconazole), 200 mg, which was approved in 2002. The active ingredient, (b) (4) route of administration, dosage form and strength of the applicant's product are the same as those of the RLD but the RLD is formulated with sulfobutyl ether β-cyclodextrin (SBECD) while the applicant's product is formulated with hydroxypropyl β-cyclodextrin (HPBCD).

Table 1. Comparison of the Xellia Formulation with VFEND injection

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Inactive Ingredients	HPβCD 3200 mg (160 mg/mL)[a]	SBECD 3200 mg (160 mg/mL)[a]

[a] Following reconstitution with 19 mL of WFI

There are no safety concerns regarding the substitution of SBECD with HPBCD. HPBCD has been approved for use in the US in drugs such as Sporanox (Itraconazole) Injection and Vibativ (telavancin for injection). No nonclinical toxicology studies were conducted to support this NDA. Xellia is relying on FDA's prior finding of the safety and effectiveness of the reference listed drug.

There are no Pharmacology or Toxicology issues which would preclude the approval of Xellia's Voriconazole for injection.

Labeling Recommendations

The following labeling recommendations are edits based on publicly available information about the RLD.

Under **'HIGHLIGHTS OF PRESCRIBING INFORMATION',** subsection INDICATIONS AND USAGE, the label should read:

'Voriconazole for injection is an azole antifungal (b) (4) '

Reviewer's comment:

The term (b) (4) should be deleted because the established pharmacologic class for voriconazole is *azole antifungal*. The term 'azole antifungal' should also be used in the following sections:

11 (Description),

Voriconazole for injection, an azole antifungal (b) (4) is available as ….

12.1 (Mechanism of action)

Voriconazole is an azole antifungal ~~drug~~.

12.4 Microbiology

Mechanism of action.

Voriconazole is an azole antifungal (b) (4)

Under the section **FULL PRESCRIBING INFORMATION: CONTENTS**

8 **USE IN SPECIFIC POPULATIONS** the label should be edited as follows:

8.1 Pregnancy
(b) (4) Risk Summary
(b) (4) 8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
(b) (4)

13 NONCLINICAL TOXICOLOGY the label should be edited as follows:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
(b) (4)

Reviewer's comment:
These changes are updates per PLLR.

Under section 8 **USE IN SPECIFIC POPULATIONS** the label should read:

8.1 Pregnancy

(b) (4)

(b) (4) Risk Summary

Voriconazole can cause fetal harm when administered to a pregnant woman and should not be taken in pregnancy except in patients where the benefit to the mother clearly outweighs the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In animals, voriconazole administration was associated with teratogenicity, embryotoxicity, increased gestational length, dystocia and embryomortality at 0.3 times the RMD (recommended maintenance dose) in rats and 6 times the RMD in rabbits *[See Data]*.

(b) (4)

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

AnimalData

Oral voriconazole was teratogenic in rats and embryotoxic in rabbits. Cleft palates and hydronephrosis/hydroureter were observed in rat pups exposed to voriconazole during organogenesis at and above 10 mg/kg (0.3 times the recommended maintenance dose (RMD) of 200 mg every 12 hours based on body surface area comparisons). Embryotoxicity was observed in rabbits orally dosed at 100 mg/kg (6 times the RMD based on body surface area comparisons). Other effects in rats dosed by the oral route, included reduced ossification of sacral and caudal vertebrae, skull, pubic and hyoid bone, supernumerary ribs, anomalies of the sternebrae and dilatation of the ureter/renal pelvis. Plasma estradiol in pregnant rats was reduced at all dose

levels. Rats exposed to voriconazole from implantation to weaning experienced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. Rabbit pups showed increased embryomortality, reduced fetal weight and increased incidence of skeletal variations, cervical ribs and extrasternal ossification sites.

(b) (4) 8.2 Lactation

(b) (4)

Risk Summary

No data are available regarding the presence of voriconazole in human milk, the effects of the drug on the breast fed infant, or the effects the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Voriconazole for injection and any potential adverse effects on the breastfed child from Voriconazole for injection or from the underlying maternal condition.

(b) (4) 8.3 (b) (4) Females and Males of (b) (4) Reproductive Potential

(b) (4)

Contraception

(b) (4) Females of reproductive potential should use effective contraception during treatment. The coadministration of voriconazole with the oral contraceptive, Ortho-Novum® (35 mcg ethinyl estradiol and 1 mg norethindrone), results in an interaction between these two drugs, but is unlikely to reduce the contraceptive effect. Monitoring for adverse reactions associated with oral contraceptives and voriconazole is recommended [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

(b) (4)

Reviewer's comment: The label has been updated according to PLLR

Under section **10 OVERDOSAGE**

In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, HPβCD, is hemodialyzed with clearance of 37.5±24 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and HPβCD from the body.

(b) (4)

Reviewer's comment:

(b) (4).

Under section **13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a ~~mg/m2~~ body surface area basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a ~~mg/m2~~ body surface area basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole administration induced no impairment of male or female fertility in rats dosed at 50 mg/kg, or 1.6 times the RMD (recommended maintenance dose).

(b) (4)

Reviewer's comment: The label has been updated according to PLLR.

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/s/

OWEN G MCMASTER
05/03/2016

WENDELYN J SCHMIDT
05/03/2016