Office of Clinical Pharmacology Review

NDA Numbers	NDA 21266: VFEND® (voriconazole) tablets, for oral use NDA 21267: VFEND® (voriconazole) for injection, for intravenous use NDA 21630: VFEND® (voriconazole) for oral suspension
Link to EDR	NDA 21266/S-039: \\CDSESUB1\evsprod\NDA021266\0094 NDA 21267/S-050: \\CDSESUB1\evsprod\NDA021267\0110 NDA 21630/S-029: \\CDSESUB1\evsprod\NDA021630\0096
Submission Date	06/01/2017
Submission Type	Pediatric Labeling Supplement; dosing regimen and PK information for pediatric patients 2 years of age and older
Dosage Forms and Strengths	• Tablets: 50 mg, 200 mg • For Oral Suspension: 45 grams of powder; after reconstitution 40 mg/mL • For Injection: lyophilized powder containing 200 mg voriconazole and 3,200 mg of sulfobutyl ether beta-cyclodextrin sodium (SBECD); after reconstitution 10 mg/mL of voriconazole and 160 mg/mL of SBECD
Proposed Indications	• Invasive aspergillosis • Candidemia in nonneutropenics and other deep tissue *Candida* infections • Esophageal candidiasis • Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including Fusarium solani, in patients intolerant of, or refractory to, other therapy

Applicant	Pfizer Inc.
OCP Review Team	Zhixia (Grace) Yan, Ph.D.; Clinical Pharmacology Reviewer Fang Li, Ph.D.; Pharmacometrics Reviewer Kevin Krudys, Ph.D.; Pharmacometrics Team Leader Philip M. Colangelo, Pharm.D., Ph.D.; Clinical Pharmacology Team Leader

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1. EXECUTIVE SUMMARY

VFEND® (voriconazole) is an azole antifungal that was approved in the U.S. in 2002 for the treatment of adults with serious fungal infections including invasive aspergillosis, candidemia, esophageal candidiasis, and other serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species.

The recommended dosage regimen for adults is shown in the table below (Adapted from VFEND labeling).

Recommended Dosage (2.3)			
Infection	**Loading dose**	**Maintenance Dose**	
	IV	**IV**	**Oral**
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h
Candidemia in nonneutropenics and other deep tissue *Candida* infections		3-4 mg/kg q12h	200 mg q12h
Scedosporiosis and Fusariosis		4 mg/kg q12h	200 mg q12h
Esophageal Candidiasis	Not Evaluated	not evaluated	200 mg q12h

- Adult patients weighing less than 40 kg: oral maintenance dose 100 or 150 mg q12 hours

This current supplemental New Drug Application (sNDA) submission is intended to provide appropriate IV and oral dosage regimens in pediatric patients (ages 2 years and older) for the same indications. This sNDA includes full reports for 2 prospective clinical studies, A1501080 and A1501085, in pediatric patients (ages 2 years and older) with invasive aspergillosis (IA) and invasive candidiasis including candidemia (ICC) and esophageal candidiasis (EC) using the IV and oral dosage regimens that were previously developed via modeling and simulation by the OCP pharmacometrics reviewers, and subsequently agreed upon between the Agency and Applicant. The key clinical pharmacology review questions for this current review focus on assessment of the appropriateness of the proposed IV and oral dosage regimens in pediatric patients (ages 2 years and older) with IA, ICC, and EC.

1.1 Recommendation

The Clinical Pharmacology review team has reviewed the pediatric PK information contained in this submission and recommends approval of this pediatric labeling supplement for NDA 21266/S-039, NDA 21267/S-050, and NDA 21630/S-029 for VFEND, provided that agreement is reached between the Applicant and the Agency on the labeling (see Section 2.3 below).

Review Issue	Recommendations and Comments
Pivotal or Supportive	The primary evidence of effectiveness for VFEND in pediatric patients (ages 2 years and older) with IA, ICC, and EC comes from matching

<table>
<tr><td>evidence of effectiveness</td><td>voriconazole exposure in pediatric patients receiving the proposed dosage regimen to that in adult patients.

Supportive evidence of effectiveness was provided by the descriptive efficacy results from the 2 prospective, multicenter, open label, pediatric studies, A1501080 and A1501085.</td></tr>
<tr><td>Dosing in pediatric patients (2 to less than 12 years of age and 12 to 14 years of age with body weight less than 50 kg)</td><td>(b) (4)

FDA’s recommendation separated by indication:
<table>
<tr><td></td><td>Loading Dose</td><td colspan="2">Maintenance Dose</td></tr>
<tr><td></td><td>Intravenous infusion</td><td>Intravenous infusion</td><td>Oral</td></tr>
<tr><td>Invasive Aspergillosis</td><td rowspan="3">9 mg/kg every 12 hours for the first 24 hours</td><td rowspan="3">8 mg/kg every 12 hours after the first 24 hours</td><td rowspan="3">9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)</td></tr>
<tr><td>Candidemia in nonneutropenics and other deep tissue Candida infections</td></tr>
<tr><td>Scedosporiosis and Fusariosis</td></tr>
<tr><td>Esophageal Candidiasis</td><td>Not Evaluated</td><td>4 mg/kg every 12 hours</td><td>9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)</td></tr>
</table></td></tr>
</table>

Dosing in pediatric patients (12 to 14 years of age with a body weight greater than or equal to 50 kg and those 15 years of age and above regardless of body weight)	Administer the adult dosing regimen of VFEND
Labeling	The review team has specific content and formatting change recommendations.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pediatric Dosing

Background

[redacted] (b) (4) However, the Clinical Pharmacology review team (during that time) did not agree with the Pop PK model developed by the Applicant and the resulting dosing recommendations. Thus, the FDA requested 3 additional PK studies to confirm Applicant's proposed pediatric dosing regimens. After the completion of these additional PK studies (A1501081, A1501088 and A1501092), the Applicant conducted an integrated population PK analysis with pooled concentration data (from children, adolescents and adults) to derive pediatric dosing regimens. Following multiple rounds of communications between FDA and Applicant, in a meeting held on 19 April 2010, mutual agreement was reached on the appropriate IV and oral dosing regimens of VFEND (Table 2.1-1) to be evaluated in pediatric patients ages 2 years and older in two prospective pediatric studies, A1501080 and A1501085 (Table 2.1-2).

(b) (4)

Table 2.1-2. Summary of study design for the two prospective pediatric studies, A1501080 and A1501085.

Study No.	Design	Disease	VFEND Dosage Regimen	Population Size
A1501080	Prospective, open-label, non-comparative, multicenter	Invasive aspergillosis (IA) or infections with rare molds (such as *Scedosporium* or *Fusarium*)	Same as the agreed upon dosage regimen shown in Table 2.1-1[a].	N=31
A1501085		Invasive candidiasis including candidemia (ICC) and esophageal candidiasis (EC) requiring either primary or salvage therapy	For ICC: Same as the agreed upon dosage regimen shown in Table 2.1-1[b]. For EC[c]: Pediatric patients ages 2 to less than 12 years and 12 to 14 years with body weight less than 50 kg received an intravenous VFEND 4 mg/kg dose every 12 hours followed by an oral VFEND dose of 9 mg/kg every 12 hours (maximum dose of 350 mg) when criteria for oral switch were met. All other pediatric patients ages 12 to less than 18 years received the adult VFEND dosage regimen.	N=22

[a]*After completing 7 days of intravenous therapy, patients had an option to switch to oral VFEND. Patients received VFEND for at least 6 weeks and up to a maximum of 12 weeks.*

[b]*VFEND was administered for at least 14 days after the last positive culture. A maximum of 42 days of treatment was permitted.*

[c] *VFEND was administered for at least 7 days after the resolution of clinical signs and symptoms. A maximum of 42 days of treatment was permitted.*

- It is important to note that since Studies A1501080 and A1501085 were both open label and non-comparative, they were not considered adequately designed or powered to statistically evaluate the efficacy and/or safety of VFEND following the IV and oral dosage regimens outlined in Table 2.1-1 above. Efficacy and safety were evaluated only on a descriptive basis by the Medical Officer (Dr. Caroline Jjingo).

Summary of Efficacy Results

Invasive Aspergillosis (IA)

Study A1501080 enrolled 31 patients with possible, proven, or probable IA. Fourteen of 31 patients, 5 of whom were 2 to less than 12 years old and 9 of whom were 12 to less than 18 years old, had proven or probable IA and were included in the modified intent to treat (MITT) efficacy analyses. No patients with rare mold were enrolled. A successful global response was defined as resolution or improvement in clinical signs and symptoms and at least 50% resolution of radiological lesions attributed to IA (Table 2.1-3). The overall rates of successful global response at end of treatment (EOT) are summarized in Table 2.1-3.

Table 2.1-3. Global Response[a] in Patients with Invasive Aspergillosis, Modified Intent-to-Treat (MITT)[b] Population (Study A1501080)

Parameter	Global Response at Week 6		
	Ages 2-<12 years N=5	**Ages 12-<18 years N=9**	**Overall N=14**
Number of successes, n (%)	2 (40%)	7 (78%)	**9 (64%)**

[a] Global response rate was defined as the number of subjects with a successful response (complete or partial) as a percentage of all subjects (including subjects with an indeterminate or missing response) at 6 weeks in the MITT population.

[b] The Modified Intent-to-Treat (MITT) population was defined as all subjects who received at least 1 dose of study drug and who were diagnosed

Candida Infection (ICC and EC)

Study A1501085 enrolled 22 patients with invasive candidiasis including candidemia (ICC) and esophageal candidiasis (EC) requiring either primary or salvage therapy. Seventeen of these patients had confirmed *Candida* infection and were included in the MITT efficacy analyses. Of the 17 patients included in the MITT analyses, 9 were 2 to less than 12 years old (7 with ICC and 2 with EC) and 8 were 12 to less than18 years old (all with EC). For ICC and EC, a successful global response was defined as clinical cure or improvement with microbiological eradication or presumed eradication. The overall rates of successful global response at EOT are summarized in Table 2.1-4.

Table 2.1-4. Global Response[a] at the End of Treatment (EOT) in the treatment of Invasive Candidiasis with Candidemia (ICC) and Esophageal Candidiasis (EC), Modified Intent-to-Treat (MITT) Population[b](Study A1501085)

Parameter	Global Response at End of Treatment			
	EC N=10			ICC[c] N=7
	Ages 2-<12 N=2	Ages 12-<18 N=8	Overall N=10	Overall N=7
Number of successes, n (%)	2 (100%)	5 (63%)	**7 (70%)**	**6 (86%)**

[a] Global response was determined based on the investigator's assessment of clinical and microbiological response in the Modified Intent-to-Treat (MITT) analysis population at end of treatment.

[b]The MITT population was defined as all subjects who received at least 1 dose of study drug and who had microbe/ologically confirmed invasive candidiasis with candidemia (ICC) and esophageal candidiasis (EC), or subjects with EC who had at least confirmation of oropharyngeal candidiasis without confirmation on esophagoscopy. Subjects with missing data or whose response was deemed indeterminate were considered failures.

[c]All subjects with ICC were aged 2 to less than 12.

- Please refer to the Medical Officer's review (Dr. Caroline Jjingo) for more information regarding efficacy and safety.

Summary of Pharmacokinetic Results

Limited voriconazole trough plasma samples were collected to facilitate dose adjustment in pediatric patients ages 2 to less than 18 years with invasive aspergillosis or invasive candidiasis including candidemia, and esophageal candidiasis in Studies A1501080 and A1501085. A 4 mL blood sample was collected just prior to dosing on Day 3 and on the third day after each IV dose adjustment (if applicable). In addition, a blood sample was collected just prior to dosing on the third day after switching to oral voriconazole therapy as well as on the third day after each oral dose adjustment (if applicable). The IV or oral voriconazole dose was adjusted in 1 mg/kg or 50 mg increments, respectively, based on patient response/tolerance to the dose and measured trough concentrations (e.g., increase dose if Ctrough < 0.5 mcg/mL; reduce dose if Ctrough > 6 mcg/mL).

In eleven pediatric patients ages 2 to less than 12 years and ages 12 to 14 years, with body weight less than 50 kg, who received 9 mg/kg intravenously every 12 hours as a loading dose on the first day of treatment, followed by 8 mg/kg every 12 hours as an intravenous maintenance dose, or 9 mg/kg every 12 hours as an oral maintenance dose, the mean trough concentration of voriconazole was 3.6 mcg/mL (range 0.3 to 10.7 mcg/mL). In four pediatric patients ages 2 to less than 12 years and ages 12 to 14 years, with body weight less than 50 kg, who received 4 mg/kg intravenously every 12 hours, the mean trough concentration of voriconazole was 0.9 mcg/mL (range 0.3 to 1.6 mcg/mL).

The Applicant developed a new population PK model using the limited PK data from Studies A1501080 and A1501085. However, upon review of this population model and the limited PK

data, the Clinical Pharmacology Review Team concluded that the new population PK model is not robust enough to provide reliable prediction of voriconazole plasma exposure (AUC and Cmin) in pediatric patients. Therefore, the population PK model developed from the previous analyses with pooled pediatric concentration data was deemed more appropriate to describe the voriconazole PK in pediatric patients. The pediatric IV and oral dosage regimens were derived based on matching the voriconazole plasma exposure in pediatric patients to that in adults (i.e., steady-state AUC_{12h} of approximately 14 and 34 mcg.hr/mL following 3 mg/kg and 4 mg/kg Q12h intravenous dose, respectively).

A comparison of the pediatric and adult population pharmacokinetic data indicated that the predicted steady-state exposure (AUC_{12h}) in pediatric patients ages 2 to <12 years following administration of a 9 mg/kg Q12 hr intravenous loading dose was comparable to that in adults following a 6 mg/kg Q12 hr intravenous loading dose. The predicted total exposures in pediatric patients ages 2 to <12 years following intravenous maintenance doses of 4 and 8 mg/kg Q12 hr were comparable to those in adults following intravenous maintenance doses of 3 and 4 mg/kg Q12 hr, respectively. The predicted steady-state exposure in pediatric patients ages 2 to <12 years following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) Q12 hr was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg Q12 hr intravenous dose regimen will provide steady-state voriconazole exposure approximately 2-fold higher than a 9 mg/kg Q12 hr oral dose regimen in pediatric patients ages 2 to <12 years.

Steady-state voriconazole exposures in pediatric patients ages 12 to <17 years were comparable to those in adults receiving the same dosing regimens.

Given the comparable PK results between pediatric and adult patients and an acceptable safety profile in pediatric patients (see Medical Officer (Dr. Caroline Jjingo) review), the Clinical Pharmacology Review Team concluded that the proposed IV and oral dosage regimens (evaluated in Studies A1501080 and A1501085) were acceptable for pediatric patients ages 2 years and older with IA, ICC, and EC.

2.2 Outstanding Issues

None.

2.3 Summary of Labeling Recommendations

Section/heading	Acceptable to OCP?			Comment
	A	AWE	NA	
Highlights/Section 2.4 Recommended Dosing Regimen in Pediatric Patients	☐	☐	☒	• Separate the pediatric dosing regimens by indication • Add treatment duration under the pediatric dosing table.
2.4 Recommended Dosing Regimen in Pediatric Patients, Method for Adjusting the Dosing Regimen in Pediatric Patients	☐	☒	☐	• Modify wording on dose adjustment method
12.3 Specific Populations, Pediatrics	☐	☐	☒	• Delete the information on the (b) (4) • Delete the information based on speculation • Add information on the observed trough concentrations in pediatric patients from 2 prospective pediatric studies

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Clinical Pharmacology Review Questions

3.1.1 Is the proposed dosing regimen appropriate for pediatric patients with invasive aspergillosis (IA) and invasive candidiasis including candidemia (ICC)?

The pediatric dosing of voriconazole in study A1501080 and A1501085 aimed at matching exposure in adults. The proposed dosing regimen was derived from a previously developed population PK modeling and simulation analysis using data from multiple pediatric and adult studies. The dosing regimen for pediatric studies A1501080 and A1501085 was reviewed in previous submissions and agreed upon with the Applicant.

While a limited number of PK samples were collected in Studies A1501080 and A1501085, and a new Pop PK model was developed by the Applicant with data from the two studies to estimate steady-state AUC and Ctrough in pediatric patients, the model was not considered reliable due to limited PK samples (see Appendix) by the Clinical Pharmacology review team. Information from the observed voriconazole trough concentration (Ctrough) data is not deemed to be

adequate to inform or change previous conclusions on dosing in children with IA/ICC. However, since the efficacy in Studies A1501080 and A1501085 was deemed to be qualitatively similar to that in adults, and the safety profile in pediatric patients appears to be acceptable, the proposed IV and oral dosing regimens for treatment of pediatric patients with IA/ICC is deemed acceptable.

A summary of PK results from Studies A1501080 and A1501085 is described as follows.

Study A1501080 was an open-label, non-randomized study to investigate the safety and tolerability of voriconazole for treatment invasive aspergillosis and molds such as *Scedosporium* or *Fusarium* Species. Patients received a total of 6-12 weeks of therapy. Study A1501085 was conducted to describe the safety, tolerability and efficacy of voriconazole in pediatric patients from 2 to <18 years of age who had ICC or EC. A total of 53 patients were enrolled: Study A1501080 enrolled 31 patients including 14 mITT patients with IA; and Study A1501085 enrolled 22 patients including 17 mITT patients with ICC or EC

The dosing regimens tested in Studies A1501080 and A1501085 are summarized in Table 3.1.1-1.

Table 3.1.1-1. Dosing Regimens in Pediatric Studies (A1501080 and A1501085)

Children (2-11 years) & young adolescents (12-14-year-olds weighing <50 kg)	**Loading Dose**	**Maintenance Dose**	
	IV	**IV**	**If switched to oral voriconazole**
IA/ICC	9 mg/kg IV q12h for the first 24 h	8 mg/kg IV q12h	9 mg/kg (maximum 350 mg) PO q12h
EC	No loading dose	4 mg/kg IV q12h	9 mg/kg (maximum 350 mg) PO q12h

Adolescents (12-17 years) (excluding 12-14-year-olds weighing <50 kg)	**Loading Dose**	**Maintenance Dose**	
	IV	**IV**	**If switched to oral voriconazole[a]**
IA/ICC	6 mg/kg IV q12h for the first 24 h	4 mg/kg IV q12h	200 mg PO q12h
EC	No loading dose	3 mg/kg IV q12h	200 mg PO q12h

[a] At the investigator's discretion, a dose of 300 mg PO q12h may be used in adolescents with IA.

Source: Table S1 on page 4 of Applicant's population modeling and analysis report (PMAR-245)

Of note, the dosing regimen in adolescents (12 to 17 years) excluding 12-14 years old weighing < 50 kg is the same as in adults. The agreed upon dosing regimen (9 mg/kg IV, 8 mg/kg IV, 9 mg/kg PO) was for children with IA/ICC. Children with EC were dosed based on PK similarity as discussed in section 3.1.2.

The demographics of pediatric patients in Pediatric Studies A1501080 and A1501085 are presented in Table 3.1.1-2.

Table 3.1.1-2. Demographics of Pediatric Patients in Pediatric Study A1501080 and A1501085

Characteristics	Median (Range) or Counts
Age (years)	12 (2 - 17)
Baseline body weight (kg)	37.6 (11 - 94)
Sex (male/female)	22/ 26
Race (white/black/Asian/Other)	18/ 1/ 23/ 6
CYP2C19 genotyping status (EM/HEM/PM/Unknown[a])	17/ 12/ 3/ 16

EM = homozygous extensive metabolizers, HEM = heterozygous extensive metabolizers, PM = poor metabolizers.

Source: Table S2 on page 5 of Applicant's population modeling and analysis report (PMAR-245)

A limited number of trough PK samples (Ctrough) were collected in Studies A1501080 and A1501085. A total of 96 concentrations from 48 pediatric patients were collected for analysis but not all of them were collected at trough. Among the 96 PK samples, 42 samples are trough concentrations; 32 following IV and 10 following oral administration, and only 12 trough concentrations following the recommended and agreed upon doses for IA/ICC (see also Section 2 above).

- For Study A1501080, the voriconazole Ctrough in pediatric patients with IA/ICC following the agreed upon and recommended IV and oral dose regimens that will be included in the labeling is summarized in Table 3.1.1-3.

Table 3.1.1-3. Observed voriconazole Ctrough in pediatric patients with IAA/IC ages 2 to <12 years and 12 to 14 years with weight <50 kg (Study A1501080)

Infection	Loading Dose		Maintenance Dose		Ctrough (µg/mL)			
	IV	Oral	IV	Oral	N=12			
					Mean	Median	Min	Max
IA/ICC	9 mg/kg q12h for the first 24 hours	Not (b) (4)	8 mg/kg q12h after the first 24 hours	9 mg/kg q12h (maximum dose of 350 mg q12h)	3.6	2.1	0.3	10.7

Given the complexity of voriconazole PK, such limited PK data is not able to provide reliable estimates of AUC_{tau}, Cmax, and Ctrough.

3.1.2 Is the proposed dosing regimen appropriate for pediatric patients with esophageal candidiasis (EC)?

In Study A1501085, patients with primary or salvage EC ages 2 to less than 12 years and 12 to 14 years with body weight less than 50 kg received an intravenous VFEND 4 mg/kg dose every 12 hours followed by an oral VFEND dose of 9 mg/kg every 12 hours (maximum dose of 350 mg) when criteria for oral switch were met. All other pediatric patients ages 12 to less than 18 years received the adult VFEND dosage regimen. Of note, no intravenous dose, only the oral dose of 200 mg every 12 hours is recommended in adult patients with EC. The strategy of assessing the appropriateness of the proposed intravenous dose of 4 mg/kg in pediatric patients with EC is to determine whether the intravenous dose of 4 mg/kg provides the comparable voriconazole exposure to the agreed upon oral dose of 9 mg/kg in pediatric patients with EC.

Based on the previous population PK analyses, the predicted voriconazole exposure in pediatric patients ages 2 to <12 years following intravenous dose of 4 mg/kg every 12 hours was comparable to those in adults following intravenous maintenance dose of 3 mg/kg every 12 hours. The predicted voriconazole exposure in pediatric patients ages 2 to <12 years following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) every 12 hours was comparable to that in adults following 200 mg oral every 12 hours.

As shown in Table 3.1.2-1, the observed voriconazole exposure in adults receiving intravenous dose of 3 mg/kg every 12 hours was comparable to that in adults receiving oral dose of 200 mg every 12 hours.

Given the above information, the proposed the intravenous dose of 4 mg/kg would achieve the comparable voriconazole exposure to the agreed upon oral dose of 9 mg/kg in pediatric patients with EC. Therefore, the proposed intravenous dosing regimen (4mg/kg) is considered appropriate for pediatric patients with EC.

Table 3.1.2-1. Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens (Adapted from VFEND label)

	6 mg/kg IV (loading dose)	**3 mg/kg IV q12h**	**4 mg/kg IV q12h**	**400 mg Oral (loading dose)**	**200 mg Oral q12h**	**300 mg Oral q12h**
N	35	23	40	17	48	16
AUC_{12} (μg·h/mL)	13.9 (32)	13.7 (53)	33.9 (54)	9.31 (38)	12.4 (78)	34.0 (53)
C_{max} (μg/mL)	3.13 (20)	3.03 (25)	4.77 (36)	2.30 (19)	2.31 (48)	4.74 (35)
C_{min} (μg/mL)	--	0.46 (97)	1.73 (74)	--	0.46 (120)	1.63 (79)

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.

A limited number of trough PK samples were collected in Study A1501085. In four pediatric patients ages 2 to less than 12 years and ages 12 to 14 years, with body weight less than 50 kg, who received 4 mg/kg intravenously every 12 hours, the mean trough concentration of voriconazole was 0.9 mcg/mL (range 0.3 to 1.6 mcg/mL).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

In Studies A1501080 and A1501085, trough PK samples were collected to facilitate dose adjustment. To enable rapid turnaround analysis and availability of voriconazole plasma concentrations, plasma samples were shipped to and analyzed by the following 3 non-GLP assay laboratories:

1. (b) (4)
2.
3.

Validated methodology and assay procedures for determination of voriconazole plasma concentrations were summarized for each non-GLP assay laboratory (Table 4.1-1).

Table 4.1-1. Bioanalytical Methods for Determination of Voriconazole Plasma Concentrations in 3 Non-GLP Assay Laboratories

Criterion	(b) (4)		
Method	HPLC		
Calibration Range	0.2 -10 mcg/mL	0.1 -10 mcg/mL	0.2 -10 mcg/mL
Linearity, mean R^2	0.996	0.997	0.9997
Quality Control	0.8, 3.5, 7.5 mcg/mL	0.2, 0.75, 5 mcg/mL	0.2, 1, 10 mcg/mL
Accuracy, % bias	0.33-17.33%	Within ±16%	Within ±8%
Precision, CV	7.78-22.85%	Within 15%	Within 12%
Stability	Samples were stored at -20 ºC. Sample stability was not determined under this condition.	24 hours at room temperature; 2 weeks at -20 ºC	Sample stability was not determined.

Reviewer Comment: Although the labs used for bioanalytical assay of voriconazole plasma concentrations were non-GLP, due to the extenuating circumstances to rapidly adjust the

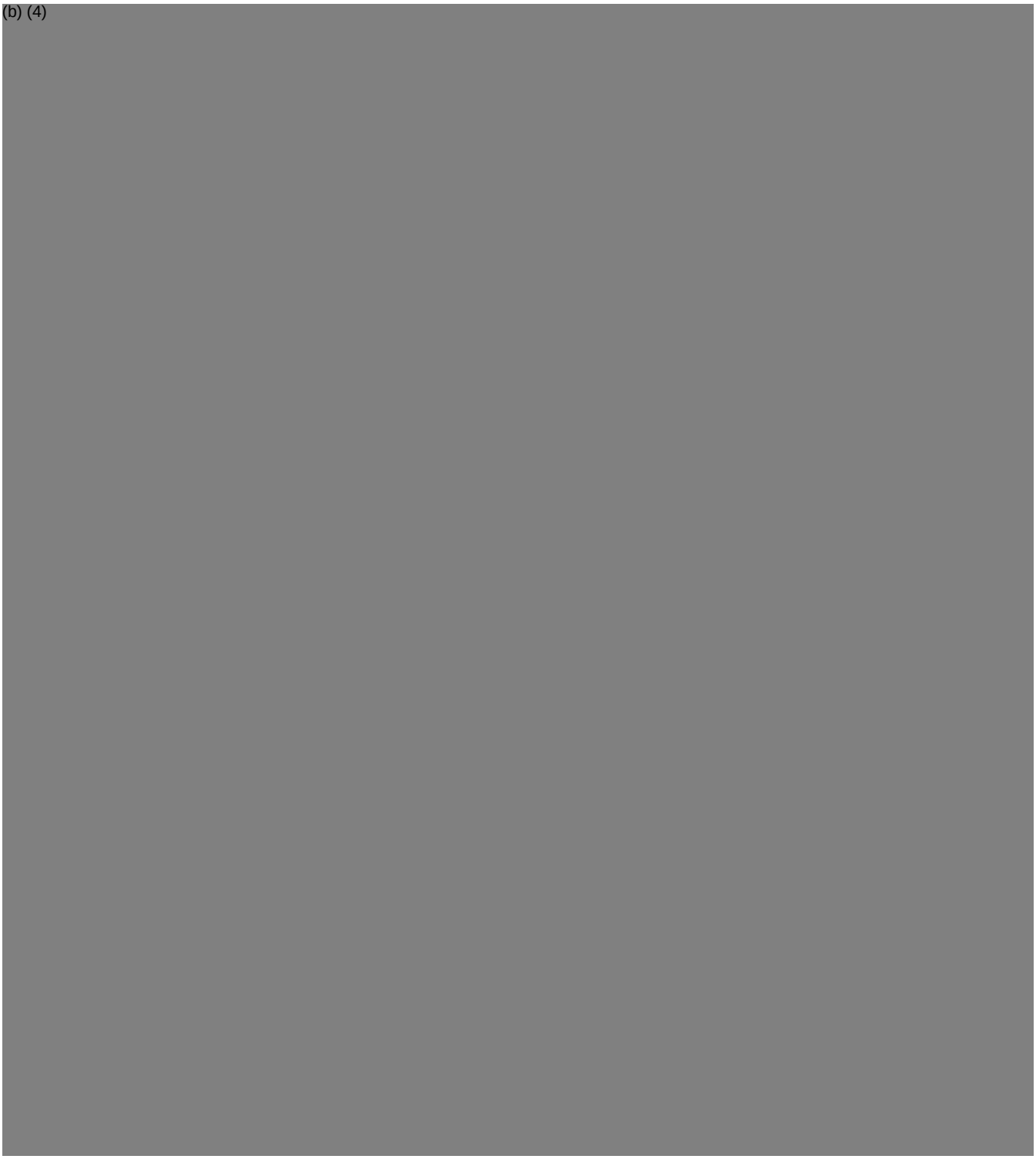
VFEND dose in the pediatric patients in a timely manner, the reviewer deems the results of the assay validation and methods to be acceptable.

4.2 Detailed Labeling Recommendations

The following proposed package insert has been marked by revisions made by the Review Team, indicated with ~~strikethrough~~ for deleted text and underlined for inserted text. Affected sections include Highlights, Dosage and Administration-Recommended Dosing Regimen in Pediatric Patients (2.4), and Clinical Pharmacology-Pharmacokinetics, Specific Populations, *Pediatric Patients* (12.3).

(b) (4)

(b) (4)



(b) (4)

4.3 Population PK / PD Analyses

The Applicant submitted a new population PK/PD report (PMAR-EQDD-A150f-DP4-245) entitled "Population pharmacokinetic-pharmacodynamic analysis report of voriconazole in pediatric patients with fungal infections (studies A1501080 and A1501085)." PK data from other studies were not included in the analysis.

Objectives: the primary objectives of the submitted population PK/PD analysis were to:

- To describe the PK of voriconazole in the target pediatric patient population based on limited sparse PK samples, if data permit
- To predict individual exposure parameters (eg, area under the curve over 12-hour dosing interval [AUC0-12] and trough concentration [C_{min}]) based on the final PK parameter estimates, if data permit
- To explore the relationship between voriconazole exposure parameters (AUC0-12 and C_{min}) and key efficacy endpoints (survival and global response), if data permit
- To explore the relationship between voriconazole exposure parameters (AUC0-12 and C_{min}) and key safety endpoints (hepatic, visual, psychiatric, skin and subcutaneous tissue AEs), if data permit
- To identify and characterize patient factors which influence the variability in the PK and PD of voriconazole (eg, CYP2C19 genotyping status), if data permit
- To evaluate the model performance of voriconazole PK and PD models, if data permit
- To explore the relationship between voriconazole PK/PD index [eg, AUC0-12/minimum inhibitory concentration (MIC)] and efficacy endpoints in a subset of patients, if data permit.

Data:

A total of 53 patients were enrolled in pediatric studies: Study A1501080 enrolled 31 patients including 14 mITT patients with IA; and Study A1501085 enrolled 22 patients including 17 mITT patients with ICC or EC. The final PK dataset contained 96 voriconazole concentrations from 48 patients. The demographics of the patients included in the PK analysis are presented in Table 4.1-1.

Table 4.1-1. Demographics of Pediatric Patients Included in PK Analysis (N=48)

Characteristics	Median (Range) or Counts
Age (years)	12 (2 - 17)
Baseline body weight (kg)	37.6 (11 - 94)
Sex (male/female)	22/ 26
Race (white/black/Asian/Other)	18/ 1/ 23/ 6
CYP2C19 genotyping status (EM/HEM/PM/Unknown[a])	17/ 12/ 3/ 16

EM = homozygous extensive metabolizers, HEM = heterozygous extensive metabolizers, PM = poor metabolizers.

Population PK Models

A previously developed PK model for voriconazole was adopted to the current data. This was a two-compartment model with first-order absorption and mixed linear and time-dependent nonlinear (Michaelis-Menten) elimination. The Normal-Inverse-Wishart prior approach was used to stabilize the current data analysis due to sparse sample collection, and the pre-study concentrations were modeled by a

zero-order rate parameter. The FOCE method was used on log-transformed concentrations. To improve model fitting, different modifications of the previous PK model were evaluated. In addition, a simplified model (linear elimination only) was evaluated given the very limited concentration data available.

Attempts were made to explore if there were any new covariates on other voriconazole PK parameters besides the ones already identified in previous analyses. To be included in the final model, a covariate needed to produce a reduction in the objective function value (OFV) of at least 7.88 (corresponding to a p-value of 0.005 with one degree of freedom, difference of loglikelihoods from nested models is approximately asymptotically $\chi 2$ distributed).

Model selection was based on goodness-of-fit criteria, that included basic diagnostic plots, precision of parameter estimates, and the OFV. Estimates of parameter precision were obtained from the asymptotic standard errors of the estimated parameters. The parameter uncertainty was described as a percent relative standard error. In addition, visual predictive check was utilized to assess the predictive performance of the models.

In order to predict voriconazole exposures at the recommended dosing regimens, a simulation dataset was created for patients with individual estimated PK parameters incorporated. Then the concentrations were simulated and AUC_{0-12} values were computed in NONMEM; the C_{min} was estimated at 12 hours post-dose at steady state. These exposure parameters were summarized and compared with adult exposures.

Based on the parameter estimates and the diagnostic plots, two runs (Run 6 and Run 13) showed better performance than other runs (ie, lower OFV, improved diagnostic plots, improved precision of parameter estimates, and successful convergence). These two runs represent two different model structures. Run 6 is a two-compartment model with first-order absorption and mixed linear and time-dependent nonlinear elimination, which is similar to the previous PK model. Run 13 is a simplified model with less parameters for the elimination phase: a two-compartment model with first-order absorption and linear elimination only. These two runs had similar results, and Run 13 had slightly better performance than Run 6. The simplified model (Run 13) was selected as the final PK model.

No new covariates were identified in the current analysis

Table 4.1-2. Summarized the Parameter Estimate of the Two Models in Comparison with Those from Previous Analysis.

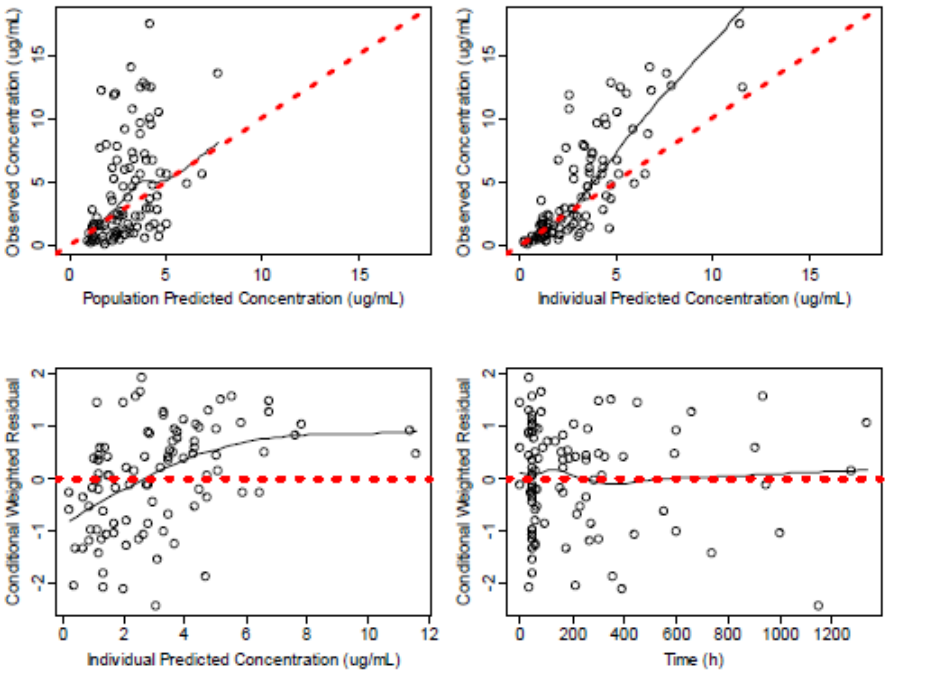
Parameter	Typical value (%RSE[a])					Interindividual variability[c] / SD[b] (%RSE[a])					
	Original Ped Data (N = 112)	Adult Data (N = 305)	Japanese Ped Data (N = 21)	Current Run 6 (N = 48)	Current Run 13 (N = 48)		Original Ped Data (N = 112)	Adult Data (N = 305)	Japanese Ped Data (N = 21)	Current Run 6 (N = 48)	Current Run 13 (N = 48)
k_m (µg/mL)						$k_{m,i} = k_m * \exp(\eta_{km\text{-}Vmax,1})$					
θ_{km}	1.15 (28)	1.15 (10)	0.922 (30)	9.52 (55)	-	$\omega_{km\text{-}Vmax,1}$	1.36 (21)	1.91 (28)	1.36 (11)	NS	-
$V_{max,1}$ (mg/h/70kg^d)						$V_{max,1,i} = V_{max,1} * \exp(\eta 1 * \theta_{Vmax,scale})$					
$\theta_{Vmax,1}$	114 (16)	0.113 (10)	118 (14)	117 (8.5)	-	$\omega_{km\text{-}Vmax,1}$	1.36 (21)	1.91 (28)	1.36 (11)	NS	-
						$\theta_{Vmax,scale}$	0.584 (10)	0.583 (10)	1.25 (12)		
$V_{max,inh}$*											
$\theta_{Vmax,inh}$	1.50 (9.3)	1.50 (9.3)	2.61 (19)	2.03 (80)	-		NS	NS		NS	-
$\theta_{AGE<12}$	-0.39 (39)										
T_{50} (h)											
θ_{T50}	2.41 (6.6)	2.42 (5.7)	2.45 (6.3)	8.60 (72)	-		NS	NS		NS	-
CL (L/h/70kg^d)											
θ_{CL}	6.16 (13)	5.30 (4.2)	6.02 (11)	5.31 (33)	7.79 (14)	ω_{CL}	0.435 (18)	0.634 (11)	0.696 (10)	0.686 (29)	0.675 (23)
V_2 (L/70kg)											
θ_{V2}	79.0 (3.1)	77.6 (2.9)	75.0 (32)	72.7 (14)	72.3 (14)	ω_{V2}	0.136 (21)	0.139 (25)	0.142 (11)	NS	NS
V_3 (L/70kg)											
θ_{V3}	103 (6.0)	89.5 (5.4)	101 (6.1)	101 (10)	100 (10)	ω_{V3}	0.769 (15)	0.831 (26)	0.784 (11)	NS	NS
Q (L/h/70kg^d)											
θ_Q	25.4 (6.8)	15.9 (5.7)	24.6 (4.4)	24.7 (37)	23.3 (43)	ω_Q	0.424 (22)	0.459 (27)	0.434 (11)	NS	NS
F1						$\text{logit}(F1,i) = \text{logit}(F1) + ETATR,i$; $ETATR,i = (\exp(\eta_{F1} * \theta_{BC\text{-}F}) - 1) / \theta_{BC\text{-}F}$					
θ_{F1}	0.585 (13)	0.595 (13)	0.597 (13)	0.805 (93)	1.77 (69)	ω_{F1}	1.67 (19)	0.713 (24)	1.69 (11)	NS	NS
						$\theta_{BC\text{-}F}$	0.367 (42)	0.411 (34)	0.330 (23)		
k_a (h^{-1})											
θ_{ka}	1.19 (20)	1.2 (FIX)	1.38 (14)	5.12 (118)	0.08 (69)		0.898 (35)		0.894 (11)	NS	NS
Alag (h)											
θ_{Alag}	0.12 (0.4)	1 (0.52)	0.121(2.8)	0.12(8333)	-		NS	NS	NS	NS	-
Rate (mg/h)											
θ_{rate}	-	12.8 (9.1)	-	25.7 (29)	28.4 (48)	ω_{R2}	-	0.910 (20)	-	NS	NS

Residual Error Parameter									
Original Ped Data		Adult Data		Japanese Ped Data		Current Data	Run 6	Run 13	
$W = SQRT(\theta^3)$	0.365(4.3)	σ_{IV}^2 (%)	53 (6.7)	$W = SQRT(\theta^2)$	0.239 (5.8)	σ_{IV}^2 (%)	82 (24)	72 (26)	
		σ_{oral}^2 (%)	61 (28)			σ_{oral}^2 (%)	69 (30)	64 (28)	

Source: Table 6 on page 50 of applicant's population PK report PMAR-245

Model Evaluation:The goodness-of-fit (GOF) plots are presented in Figure 4.1-1 and Figure 4.1-2. Visual Predictive Check (VPC) was also created to show the time course of the predicted mean and spread of concentrations (5th to 95th percentile) versus the observed data (Figure 4.1-3).

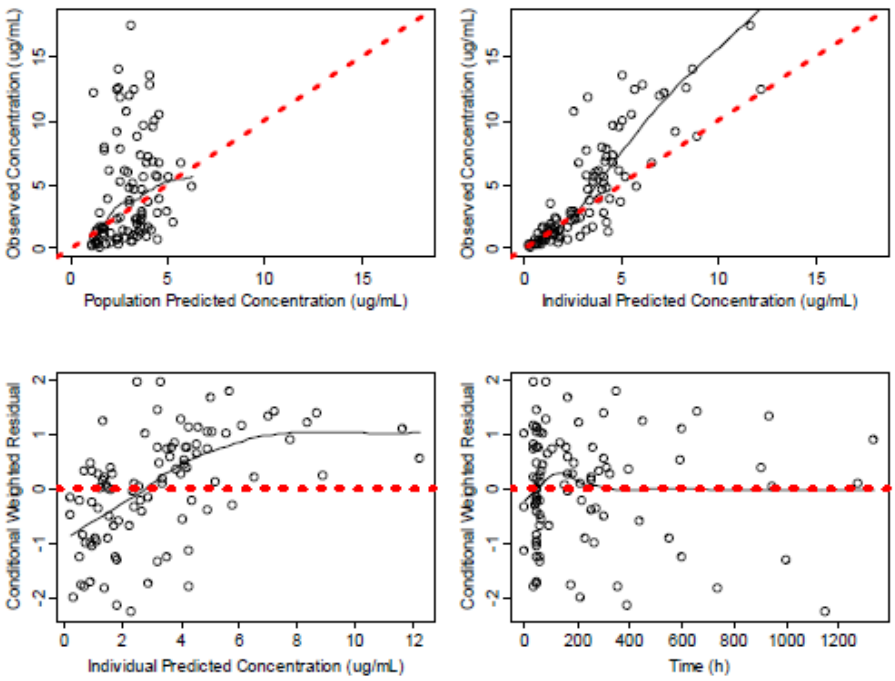
Figure 4.1-1. Goodness-of-fit Plots (Run 6-Mixed Linear and Nonlinear Elimination)



Key – open symbols are observed data, dashed line is the line of identity or unity, solid line is the loess smooth.

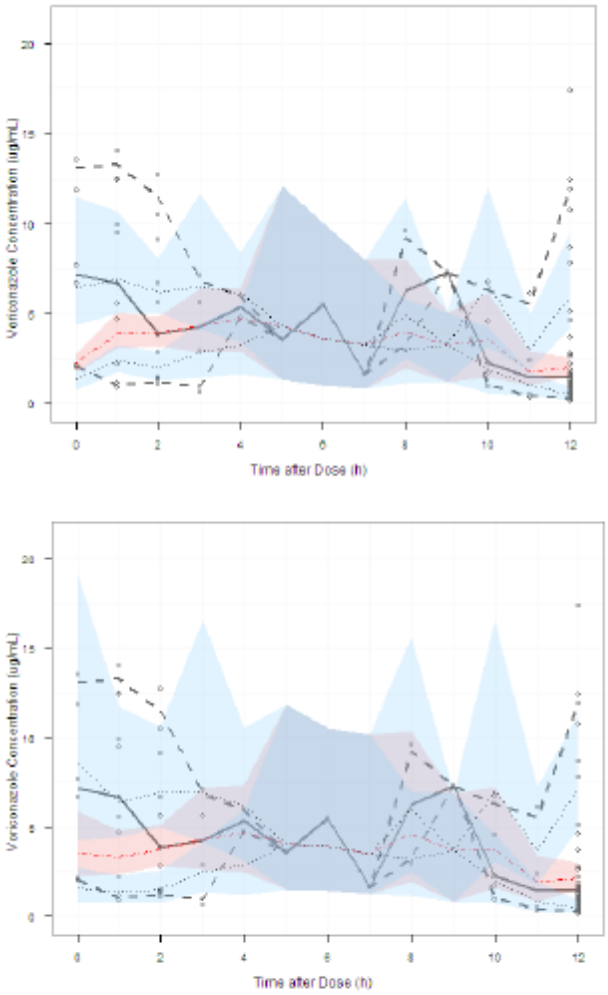
Source: Figure 1 on page 52 of applicant's population PK report PMAR-245

Figure 4.1-2. Goodness-of-fit Plots (Run 13- Linear Elimination)



Key – open symbols are observed data, dashed line is the line of identity or unity, solid line is the loess smooth.

Figure 1.1-3. Visual Predictive Check: Observed and Simulated Median, 5th and 95th Percentile Voriconazole Concentrations, 90% Prediction Interval for Run6 (Upper Panel) and Run13 (Lower Panel)



Key – open symbols are observed data. Black solid and dashed lines represent the median, 5th and the 95th percentile of the observed concentrations, and red dash-dotted and black dotted lines represent the median, 5th and the 95th percentile of the simulated concentrations. The band around the simulated percentiles represents the 90% confidence intervals. 500 replicates were simulated.

Source: Figure 5 on page 55 of applicant's population PK report PMAR-245

Voriconazole Exposure in Pediatric Patients

Voriconazole exposure after the proposed dosing regimen in pediatric patients was estimated with the final model. Summary of $AUC_{0\text{-}12}$ and C_{min} in children and adolescents are presented in Table 4.1-3.

Table 4.1-3. Summary of Estimated Voriconazole Exposure in Pediatric Patients

	Voriconazole AUC_{0-12} (µg·h/mL)		Voriconazole C_{min} (µg/mL)	
Children (n = 21)				
Regimen	8 mg/kg IV q12h	9 mg/kg oral q12h[a]	8 mg/kg IV q12h	9 mg/kg oral q12h[a]
Geomean (CV%)	49.63 (57)	46.86 (60)	2.65 (77)	3.56 (64)
Median (Range)	51.54 (20.67 - 171.08)	45.66 (19.84 - 170.76)	2.95 (0.69 - 12.67)	3.48 (1.39 - 13.86)
Young adolescents aged 12 to 14 years weighing <50 kg (n = 10)				
Regimen	8 mg/kg IV q12h	9 mg/kg oral q12h[a]	8 mg/kg IV q12h	9 mg/kg oral q12h[a]
Geomean (CV%)	54.91 (40)	50.57 (43)	3.0 (52)	3.86 (46)
Median (Range)	68.24 (20.35 - 85.79)	62.02 (19.54 - 82.44)	4.19 (0.66 - 5.61)	4.84 (1.36 - 6.51)
All Other Adolescents (n = 17)				
Regimen	4 mg/kg IV q12h	200 mg oral q12h	4 mg/kg IV q12h	200 mg oral q12h
Geomean (CV%)	37.28 (59)	27.72 (65)	2.18 (75)	2.15 (67)
Median (Range)	33.78 (17.7 - 110.05)	25.07 (8.89 - 79.36)	1.97 (0.76 - 8.27)	1.94 (0.65 - 6.46)

Geomean = geometric mean, CV% = Coefficient of variation in percentage.

Reviewer's Comments:

- *The model fits presented in these analyses were not considered adequate and acceptable. As indicated in the goodness-of-fit plots and the VPC plots, both models (run6 and run13) were not able to fit the observed data adequately, specifically with evident underestimation of high concentrations.*
- *Previous population PK analysis with both children and adult data indicated voriconazole demonstrated time-dependent nonlinear clearance. But the model fitting in current analysis cannot support this feature. Notable limitations were observed. The voriconazole concentration data collected from the two pediatric studies were very limited. Only 96 PK samples were collected from 48 pediatric subjects. Most subjects just provided 1-2 PK samples. Given the high variability of voriconazole exposure and the complexity of its pharmacokinetics, the PK samples may be too sparse to estimate all parameters necessary to characterize the voriconazole PK accurately. The limitations were also acknowledged by the applicant.*
- *The previously developed model (PMAR-00204) was a more robust analysis using data from children, adolescents and adults, including rich PK and a wider range of voriconazole doses. The result is considered more informative than the current analysis. Observations in present analysis did not support or change conclusions of the previous analysis.*
- (b) (4) [redacted]

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/s/

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