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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Name:	VFEND® (voriconazole)
Pediatric Labeling Approval Date:	January 29, 2019
Application Type/Number:	NDA 21266 (oral tablet) NDA 21267 (injection) NDA 21630 (oral suspension)
Applicant:	Pfizer
OSE RCM #:	2021-589

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for VFEND (voriconazole) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with voriconazole in pediatric patients.

FDA approved voriconazole on May 24, 2002. Voriconazole is a broad-spectrum triazole antifungal agent indicated for the treatment of adult and pediatric patients ages 2 years of age and older with invasive aspergillosis, candidemia in non-neutropenic patients and other deep tissue *Candida* infections, esophageal candidiasis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani* in patients intolerant of, or refractory to, other therapy. Voriconazole was initially approved for adult and pediatric patients ages 12 years and older. On January 29, 2019, the pediatric indication was extended to include pediatric patients 2 years of age and older.

We reviewed all U.S. serious FAERS reports with voriconazole in the pediatric population (ages 0 - <18 years) from May 24, 2002, through February 28, 2022 and did not identify any cases for inclusion in our case series.

DPV did not identify any new pediatric safety concerns for voriconazole at this time. DPV will continue to monitor all adverse events associated with the use of voriconazole.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for voriconazole (VFEND) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with voriconazole in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Voriconazole was originally approved on May 24, 2002. Voriconazole is a broad-spectrum triazole antifungal agent indicated for the treatment of adult and pediatric patients ages 2 years of age and older with invasive aspergillosis, candidemia in non-neutropenic patients and other deep tissue *Candida* infections, esophageal candidiasis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani* in patients intolerant of, or refractory to, other therapy.[1] Voriconazole is available in three dosage formulations: tablets for oral use (50 mg and 200 mg), lyophilized powder for injection for intravenous use (200 mg), and powder for oral suspension (40 mg/mL when reconstituted).

At the time of initial approval voriconazole was approved for adult and pediatric patients 12 years of age and older. The approved pediatric labeling was based on data from pediatric patients aged 12 to 18 years with invasive aspergillosis that were included in the adult therapeutic studies. On January 29, 2019, the pediatric indication was extended to include pediatric patients 2 years of age and older. The safety and effectiveness of voriconazole was established in pediatric patients 2 years of age and older based on evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data.

A total of 105 pediatric patients aged 2 years to less than 12 years [N=26] and aged 12 years to less than 18 years [N=79] from two, non-comparative Phase 3 pediatric studies, and eight adult therapeutic trials provided safety information for voriconazole use in the pediatric population. The combined safety population of 105 patients was used to compare the frequency of pediatric safety events against those observed in adults. The Phase 3 pediatric studies were not powered to make efficacy determinations. Therefore, efficacy was extrapolated from adults because the pathophysiology of invasive fungal infections is similar in both populations. In spite of limited numbers and a non-comparative study design, it was noted that pediatric global response rates were higher than rates observed in adults with invasive aspergillosis (64% vs. 53% and 52% in two adult trials) and invasive candidiasis and candidemia (70.0 vs. 41%). Efficacy rates among pediatric patients with esophageal candidiasis were comparable to those in adults (85.7% vs. 87.5%). This difference may have resulted from smaller numbers of pediatric patients since adult and pediatric patients enrolled in these studies were equally ill.

DPV has not previously presented an evaluation of postmarketing adverse event reports for voriconazole in pediatric patients to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION

The Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, and Use in Specific Populations (from the Highlights of Prescribing Information), and Pediatric Use sections of the voriconazole (VFEND) product labeling are reproduced below.[1]

---------- CONTRAINDICATIONS ----------
• Hypersensitivity to voriconazole or its excipients (4)
• Coadministration with pimozide, quinidine, sirolimus or ivabradine due to risk of serious adverse reactions (4, 7)
• Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir, rifabutin, ergot alkaloids, and St. John's Wort due to risk of loss of efficacy (4, 7)
• Coadministration with naloxegol, tolvaptan, and lurasidone due to risk of adverse reactions (4, 7)
• Coadministration of VFEND with venetoclax at initiation and during the ramp-up phase in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to increased risk of adverse reactions (4, 7)

---------- WARNINGS AND PRECAUTIONS ----------
• *Hepatic Toxicity*: Serious hepatic reactions reported. Evaluate liver function tests at start of and during VFEND therapy (5.1)
• *Arrhythmias and QT Prolongation*: Correct potassium, magnesium and calcium prior to use; caution patients with proarrhythmic conditions (5.2)
• *Infusion Related Reactions (including anaphylaxis)*: Stop the infusion (5.3)
• *Visual Disturbances* (including optic neuritis and papilledema): Monitor visual function if treatment continues beyond 28 days (5.4)
• *Severe Cutaneous Adverse Reactions*: Discontinue for exfoliative cutaneous reactions (5.5)
• *Photosensitivity*: Avoid sunlight due to risk of photosensitivity (5.6)
• *Adrenal Dysfunction*: Carefully monitor patients receiving VFEND and corticosteroids (via all routes of administration) for adrenal dysfunction both during and after VFEND treatment. Instruct patients to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency (5.8)
• *Embryo-Fetal Toxicity*: Voriconazole can cause fetal harm when administered to a pregnant woman. Inform pregnant patients of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with VFEND (5.9, 8.1, 8.3)
• *Skeletal Adverse Reactions*: Fluorosis and periostitis with long-term voriconazole therapy. Discontinue if these adverse reactions occur (5.12)
• *Clinically Significant Drug Interactions*: Review patient's concomitant medications (5.13, 7)
• *Patients with Hereditary Galactose Intolerance, Lapp Lactase Deficiency or Glucose-Galactose Malabsorption*: VFEND tablets should not be given to these patients because it contains lactose (5.14)

---------- ADVERSE REACTIONS ----------
• *Adult Patients*: The most common adverse reactions (incidence ≥2%) were visual disturbances, fever, nausea, rash, vomiting, chills, headache, liver function test abnormal, tachycardia, hallucinations (6)

• *Pediatric Patients*: The most common adverse reactions (incidence ≥5%) were visual disturbances, pyrexia, vomiting, epistaxis, nausea, rash, abdominal pain, diarrhea, hypertension, hypokalemia, cough, headache, thrombocytopenia, ALT abnormal, hypotension, peripheral edema, hyperglycemia, tachycardia, dyspnea, hypocalcemia, hypophosphatemia, LFT abnormal, mucosal inflammation, photophobia, abdominal distention, constipation, dizziness, hallucinations, hemoptysis, hypoalbuminemia, hypomagnesemia, renal impairment, upper respiratory tract infection (6)

---------- DRUG INTERACTIONS----------
• CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers: Adjust VFEND dosage and monitor for adverse reactions or lack of efficacy (4, 7)
• VFEND may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce dosage of these other drugs and monitor for adverse reactions (4, 7)
• Phenytoin or Efavirenz: With co-administration, increase maintenance oral and intravenous dosage of VFEND (2.3, 2.7, 7)

---------- USE IN SPECIFIC POPULATIONS ----------
• *Pediatrics*: Safety and effectiveness in patients younger than 2 years has not been established
(8.4)

8.4 Pediatric Use
The safety and effectiveness of VFEND have been established in pediatric patients 2 years of age and older based on evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data. A total of 105 pediatric patients aged 2 to less than 12 [N=26] and aged 12 to less than 18 [N=79] from two, non-comparative Phase 3 pediatric studies and eight adult therapeutic trials provided safety information for VFEND use in the pediatric population *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness in pediatric patients below the age of 2 years has not been established. Therefore, VFEND is not recommended for pediatric patients less than 2 years of age.

A higher frequency of liver enzyme elevations was observed in the pediatric patients *[see Dosage and Administration (2.5), Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

The frequency of phototoxicity reactions is higher in the pediatric population. Squamous cell carcinoma has been reported in patients who experience photosensitivity reactions. Stringent measures for photoprotection are warranted. Sun avoidance and dermatologic follow-up are recommended in pediatric patients experiencing photoaging injuries, such as lentigines or ephelides, even after treatment discontinuation *[see Warnings and Precautions (5.6)]*.

VFEND has not been studied in pediatric patients with hepatic or renal impairment *[see Dosage and Administration (2.5, 2.6)]*. Hepatic function and serum creatinine levels should be closely monitored in pediatric patients *[see Dosage and Administration (2.6) and Warnings and Precautions (5.1, 5.10)]*.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*

Date of search	March 24, 2022
Time period of search	May 24, 2002† - February 28, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	VFEND Voriconazole
MedDRA search terms (Version 24.1)	All PT terms

* See Appendix A for a description of the FAERS database.
† Initial U.S. approval date for voriconazole.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from approval (May 24, 2002) to February 28, 2022, with voriconazole.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From Approval (May 24, 2002) to February 28, 2022 With Voriconazole

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	10,614 (3,790)	9,751 (3,048)	3,044 (988)
Pediatrics (0 - <18 years)	1,390‡ (309)	1,328‡ **(269)**	375‡ **(45)**

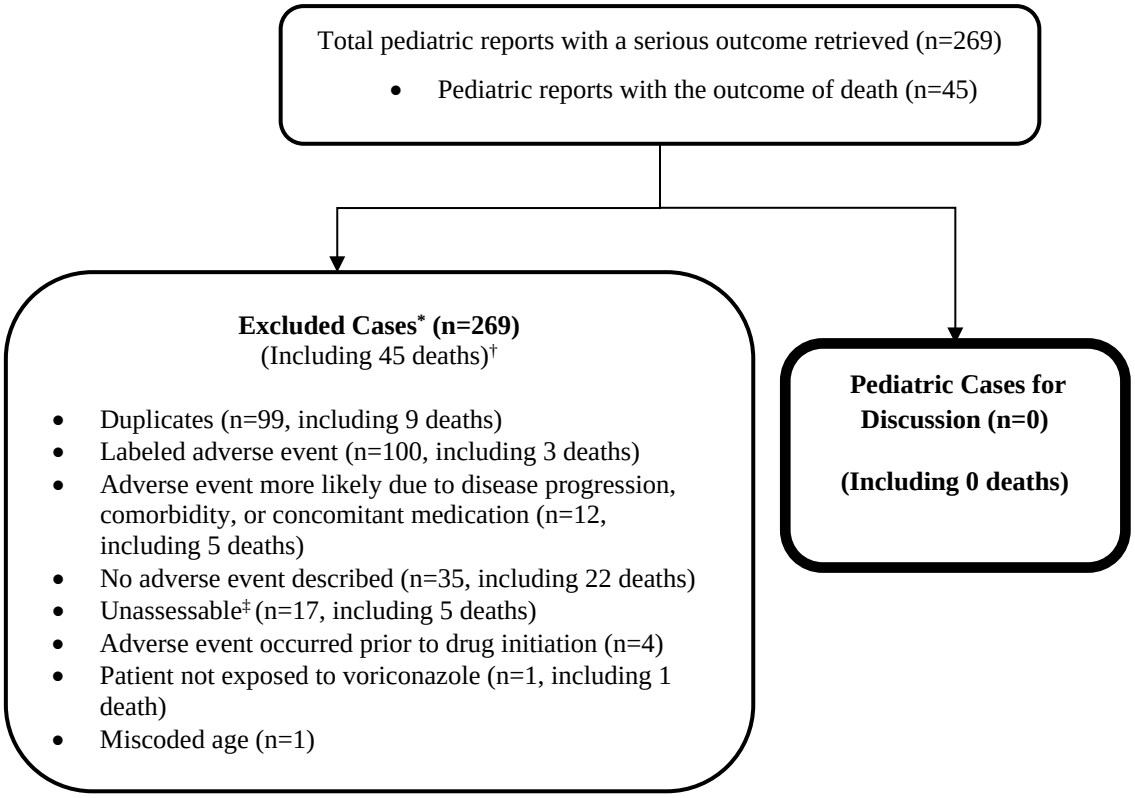
* May include duplicates and transplacental exposures and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. Ten additional U.S. reports of pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 269 U.S. serious pediatric reports from approval (May 24, 2002) to February 28, 2022.

No cases were identified for inclusion in the pediatric case series. We reviewed all FAERS U.S. pediatric reports with a serious outcome. We excluded all reports from the case series for various reasons, such as duplicate reporting, labeled adverse event, adverse event was more likely due to concomitant medications or comorbidities, no adverse event described, unassessable reports, lack of exposure to voriconazole, or miscoded reports. Figure 1 presents the reasons all U.S. pediatric reports with a serious outcome were excluded from the case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Voriconazole



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† Forty-five excluded reports described fatal outcomes. No deaths were attributed to voriconazole, but were due to overwhelming fungal infection despite voriconazole use, progression of an underlying medical condition, or were unassessable. These reports are not remarkable given the serious medical conditions of the patient population using the drug. Nine were duplicate reports. Three reports included labeled adverse events (photophobia, QT prolongation, increased liver enzymes) that were unrelated to the fatal outcome. These included a 14-year-old female who experienced photophobia after beginning voriconazole for pneumonia who died due to acute myeloid leukemia (AML) progression, an 8-year-old (gender not reported) with AML who experienced QT interval prolongation after beginning voriconazole and died 1 year later due to overwhelming fungal infection, and a 7-year-old female with T-cell lymphoma who experienced elevated gamma-glutamyl transpeptidase after beginning voriconazole who was switched back to caspofungin, and 1 month later died due to disseminated candidiasis. Another five reports described fatal events considered due to disease progression or comorbidities including cancer progression in a 15-year-old male and a 9-year-old female, worsening of pre-existing heart disease in a 15-year-old female who was

treated with voriconazole for sepsis, Epstein-Barr Virus (EBV)-lymphoproliferative disease in a 15-year-old female following bone marrow transplant (BMT) for AML, and hemophagocytic lymphohistiocytosis in a 5-week-old infant with X-linked chronic granulomatous disease and *Burkholderia cepacia* sepsis. Twenty-two reports did not report an adverse event, rather, reports described treatment failure or lack of effect and deaths were due to overwhelming fungal infection despite voriconazole use. Five reports had limited information and were considered unassessable; in two of these reports the cause of death was not reported, and in three reports the reported cause of death (cardiotoxicity, paroxysmal cardiac rhythm disorder, mitochondrial dysfunction) was confounded by concomitant medications or comorbidities. The last report was a 14-year-old BMT female with AML who was not exposed to voriconazole and died due to fungal infection.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with voriconazole in the pediatric population.

4 DISCUSSION

We reviewed 269 FAERS U.S. serious reports with voriconazole in the pediatric population (ages 0 - <18 years) from May 24, 2002 through February 28, 2022 and all were excluded from the case series. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with voriconazole.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for voriconazole at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of voriconazole.

7 REFERENCES

1. VFEND [package insert]. New York, NY. Pfizer, revised January 2022.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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