DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-266/S-025, S-027, S-029, S-030
NDA 21-267/S-025, S-029, S-032, S-033
NDA 21-630/S-014, S-018, S-020, S-021

**SUPPLEMENTS APPROVAL**

Pfizer, Inc.
Attention: Ms. Anne Palestroni
Director, US Regulatory Affairs
235 East 42nd Street 685/19/05
New York, NY 10017-5755

Dear Ms. Palestroni:

Please refer to your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| **NDA Number** Name of Drug Product and Formulation Strengths | **Supplement Number** | **Letter Date of Supplement** | **Receipt Date of Supplement** |
|---|---|---|---|
| **21-266** VFEND® (voriconazole) Tablets, 50 mg and 200 mg | S-025 | December 19, 2007 | December 20, 2007 |
| | S-027 | July 1, 2009 | July 1, 2009 |
| | S-029 | December 17, 2009 | December 17, 2009 |
| | S-030 | March 31, 2010 | March 31, 2010 |
| **21-267** VFEND® I.V. (voriconazole) for Injection, 10 mg/mL | S-025 | December 19, 2007 | December 20, 2007 |
| | S-029 | July 1, 2009 | July 1, 2009 |
| | S-032 | December 17, 2009 | December 17, 2009 |
| | S-033 | March 31, 2010 | March 31, 2010 |
| **21-630** VFEND® (voriconazole) for Oral Suspension, 45 mg/mL | S-014 | December 19, 2007 | December 20, 2007 |
| | S-018 | July 1, 2009 | July 1, 2009 |
| | S-020 | December 17, 2009 | December 17, 2009 |
| | S-021 | March 31, 2010 | March 31, 2010 |

We acknowledge receipt of your amendments dated April 10, 2008, December 17, 2009, April 8, April 29, and June 11 and June 17, 2010.

## SUMMARY OF LABELING SUPPLEMENTS

### (1) Visual Adverse Events - CBE Supplements NDA 21-266/S-025, NDA 21-267/S-025, and NDA 21-630/S-014

In letters dated December 19, 2007, "Changes Being Effected" (CBE) supplements NDA 21-266/S-025, NDA 21-267/S-025, and NDA 21-630/S-014 were submitted that proposed revisions to the **WARNINGS** and **ADVERSE EVENTS** sections, to the **VISUAL DISTURBANCES** sub-section of the package insert and to the "**What are possible side effects of VFEND? Eyesight (vision) changes**" section of the Patient Package Insert.

### (2) Drug-Drug Interactions Between Voriconazole And Long-Acting Opiates Supplements NDA 21-266/S-027, NDA 21-267/S-029, and NDA 21-630/S-018

In letters dated July 1, 2009, "Prior Approval Supplements" NDA 21-266/S-027, NDA 21-267/S-029, and NDA 21-630/S-018 were submitted that proposed revisions to the **CLINICAL PHARMACOLOGY** and the **PRECAUTIONS** sections of the package insert to add information regarding drug interactions between voriconazole and fentanyl, voriconazole and oxycodone, and voriconazole and non-steroidal anti-inflammatory drugs (NSAIDs).

### (3) Squamous Cell Carcinoma Adverse Events - CBE Supplements NDA 21-266/S-029, NDA 21-267/S-032, and NDA 21-630/S-020

In letters dated December 17, 2009, CBE labeling supplements NDA 21-266/ S-029, NDA 21-267/S-032, and NDA 21-630/S-020 were submitted to revise the VFEND label to update the **PRECAUTIONS/ Dermatological Reactions** subsection to reference several recently reported cases of squamous skin carcinoma that had developed in immunocompromised patients (primarily post-lung transplant) receiving long-term treatment with voriconazole.

### (4) Melanoma Adverse Events – CBE Supplements NDA 21-266/S-030, NDA 21-267/S-033, and NDA 21-630/S-021

In letters dated March 31, 2010, CBE labeling supplements NDA 21-266/S-030, NDA 21-267/ S-033, and NDA 21-630/S-021 were submitted to revise the VFEND label to update the **PRECAUTIONS/ Dermatological Reactions** subsection to include melanoma.

## REVISIONS TO THE PACKAGE INSERT

The revisions to the package insert (PI) that were agreed upon for the above twelve supplements are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

### (1) Visual Adverse Events - CBE Supplements

**a**. Under the **WARNINGS/VISUAL DISTURBANCES** subsection, a new sentence was added:

**VISUAL DISTURBANCES: The effect of VFEND on visual function is not known if treatment continues beyond 28 days.** There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema. If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored (see **PRECAUTIONS – Information for Patients and ADVERSE REACTIONS – Visual Disturbances**).

**b.** Under the **ADVERSE REACTIONS** section, the font for the heading **VISUAL DISTURBANCES** was changed and a new second paragraph was added:

~~**VISUAL DISTURBANCES**~~ ***Visual Disturbances*:** Voriconazole treatment-related visual disturbances are common. In therapeutic trials, approximately 21% of patients experienced abnormal vision, color vision change and/or photophobia. The visual disturbances were generally mild and rarely resulted in discontinuation. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema (see WARNINGS).

**c.** In the Patient Package Insert, under the **What are possible side effects of VFEND?** section and the **Eyesight (vision) changes** subsection**,** the second paragraph was revised:

These changes include blurred vision, color vision change, and being sensitive to light while you are taking VFEND. These changes are generally mild. Vision side effects lasting for more than one month have been reported by some patients. Your doctor should monitor your eyesight if you take VFEND for more than 28 days.

### (2) Drug-Drug Interactions Between Voriconazole And Long-Acting Opiates - Prior Approval Supplements

**a.** Under the **CLINICAL PHARMACOLOGY/Drug Interactions/Effect of Voriconazole on Other Drugs** subsection, three new paragraphs were added:

**Note:** Information for ***Fentanyl*** and ***Oxycodone*** was added between ***Alfentanil*** and ***Cyclosporine*** in this subsection.

***Fentanyl* (CYP3A4 substrate):** In an independent published study, concomitant use of voriconazole (400 mg Q12h on Day 1, then 200 mg Q12h on Day 2) with a single itravenous dose of fentanyl (5 μg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold). When voriconazole is co-administered with fentanyl IV, oral or transdermal dosage forms, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and fentanyl dosage should be reduced, if warranted. (see PRECAUTIONS – Drug Interactions).

***Oxycodone* (CYP3A4 substrate):** In an independent published study, coadministration of multiple doses of oral voriconazole (400 mg Q12h on Day 1 followed by five doses of 200 mg Q12h on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean Cmax and $AUC_{0-\infty}$ of oxycodone by 1.7-fold (range 1.4- to 2.2-fold) and 3.6-fold (range 2.7- to 5.6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0-fold (range 1.4- to 2.5-fold). Voriconazole also increased the visual effects (heterophoria and miosis) of oxycodone. A reduction in oxycodone dosage may be needed during voriconazole treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolized by CYP3A4 is recommended. (see PRECAUTIONS – Drug Interactions).

**Note:** Information for ***Non-Steroidal Anti-Inflammatory Drugs*** was added between ***Vinca Alkaloids*** and the paragraph beginning "No significant pharmacokinetic interactions were observed when voriconazole…"

***Non-Steroidal Anti-Inflammatory Drugs* (NSAIDS; CYP2C9 substrates):** In two independent published studies, single doses of ibuprofen (400 mg) and diclofenac (50 mg) were coadministered with the last dose of voriconazole (400 mg Q12h on Day 1, followed by 200 mg Q12h on Day 2). Voriconazole increased the mean Cmax and AUC of the pharmacologically active isomer, S (+)-ibuprofen by 20% and 100%, respectively. Voriconazole increased the mean Cmax and AUC of diclofenac by 114% and 78%, respectively. A reduction in ibuprofen and diclofenac dosage of NSAIDs may be needed during concomitant administration with voriconazole. Patients receiving voriconazole concomitantly with other NSAIDs (e.g., celecoxib, naproxen, lornoxicam, meloxicam) that are also metabolized by CYP2C9 should be carefully monitored for NSAID-related adverse events and toxicity, and dosage reduction should be made if warranted. (see PRECAUTIONS – Drug Interactions).

**b.** Under the **PRECAUTIONS/Drug Interactions** subsection, Table 12 was updated:

**Note:** Information on ***Fentanyl, Oxycodone*** and ***NSAIDs*** was added to Table 12

**Table 12: Effect of Voriconazole on Pharmacokinetics of Other Drugs**

| Drug/Drug Class (Mechanism of Interaction by Voriconazole) | Drug Plasma Exposure (Cmax and AUCτ) | Recommendations for Drug Dosage Adjustment/Comments |
|---|---|---|
| Fentanyl (CYP3A4 Inhibition) | Increased | Reduction in the dose of fentanyl and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with VFEND. Extended and frequent monitoring for opiate-associated adverse events may be necessary (see CLINICAL PHARMACOLOGY-Drug Interactions). |
| Oxycodone (CYP3A4 Inhibition) | Significantly Increased | Reduction in the dose of oxycodone and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with VFEND. Extended and frequent monitoring for opiate-associated adverse events may be necessary (see CLINICAL PHARMACOLOGY-Drug Interactions). |
| NSAIDs **** including ibuprofen and diclofenac (CYP2C9 Inhibition) | Increased | Frequent monitoring for adverse events and toxicity related to NSAIDs. Dose reduction -of NSAIDs may be needed. (see CLINICAL PHARMACOLOGY - Drug Interactions). |

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID voriconazole to healthy subjects
**Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for at least 2 days voriconazole to healthy subjects
*** Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for 4 days voriconazole to subjects receiving a methadone maintenance dose (30-100 mg QD)
**** Non-Steroidal Anti-Inflammatory Drugs
***** Non-Nucleoside Reverse Transcriptase Inhibitors

**(3) Squamous Cell Carcinoma Adverse Events - CBE Supplements**

**and**

**(4) Melanoma Adverse Events – CBE Supplements**

**a.** Under the **PRECAUTIONS/Dermatological Reactions** subsection, the first paragraph was revised and a new second paragraph was added:

**Dermatological ~~Reactions~~ Adverse Events**

Patients have rarely developed serious exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If a patient~~s~~ develop~~s~~ ~~a rash, they should be monitored closely and consideration given to discontinuation of VFEND~~ an exfoliative cutaneous reaction, VFEND should be discontinued~~. VFEND has been infrequently associated with photosensitivity skin reaction, especially during long-term therapy. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.~~

In addition, VFEND has been associated with photosensitivity skin reactions. Patients should avoid intesnse or prolonged exposure to direct sunlight during VFEND treatment. In patients with photosensitivity skin reactions, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VFEND should be discontinued.

**b.** Under the **ADVERSE REACTIONS**/*Dermatological Reactions* subsection, the first paragraph was revised and reformatted, and a new third paragraph was added:

*Dermatological Reactions:* Dermatological reactions were common in the patients treated with voriconazole. The mechanism underlying these dermatologic adverse events remains unknown. In clinical trials, rashes considered related to therapy were reported by 7% (110/1655) of voriconazole-treated patients. The majority of rashes were of mild to moderate severity. ~~Cases of photosensitivity reactions appear to be more likely to occur with long-term treatment.~~

Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND.~~ If patients develop a rash, they should be monitored closely and consideration given to discontinuation of VFEND. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.~~ If a patient develops an exfoliative cutaneous reaction, VFEND should be discontinued.

In addition, VFEND has been associated with photosensitivity skin reactions., Patients should avoid strong, direct sunlight during VFEND therapy. In patients with photosensitivity skin reactions, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VFEND should be discontinued.

**c.** Under the **ADVERSE REACTIONS/Less Common Adverse Events/**Skin and Appendages subsection, new information was added:

*Skin and Appendages:* alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanoma, melanosis, photosensitivity skin reaction, pruritus, pseudoporphyria, psoriasis, skin discoloration, skin disorder, skin dry, squamous cell carcinoma, Stevens-Johnson syndrome, sweating, toxic epidermal necrolysis, urticaria

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, including minor editorial revisions.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories. Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

## LABELING

Submit final printed labeling as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to the package insert.

The final printed labeling should be submitted electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**Final Printed Labeling for approved NDA 21-266/S-025, S-027, S-029, S-030; NDA 21-267/S-025, S-029, S-032, S-033; NDA 21-630/S-014, S-018, S-020,**

**S-021**." Approval of these submissions by FDA is not required before the labeling is used.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert (PI)
Patient Package Insert (PPI)

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21630 | SUPPL-21 | PFIZER INC | VFEND (VORICONAZOLE) ORAL SUSPENSION |
| NDA-21630 | SUPPL-20 | PFIZER INC | VFEND (VORICONAZOLE) ORAL SUSPENSION |
| NDA-21630 | SUPPL-18 | PFIZER INC | VFEND (VORICONAZOLE) ORAL SUSPENSION |
| NDA-21630 | SUPPL-14 | PFIZER INC | VFEND (VORICONAZOLE) ORAL SUSPENSION |
| NDA-21267 | SUPPL-33 | PFIZER INC | VFEND (VORICONAZOLE) 200MG IV |
| NDA-21267 | SUPPL-32 | PFIZER INC | VFEND (VORICONAZOLE) 200MG IV |
| NDA-21267 | SUPPL-29 | PFIZER INC | VFEND (VORICONAZOLE) 200MG IV |
| NDA-21267 | SUPPL-25 | PFIZER INC | VFEND (VORICONAZOLE) 200MG IV |
| NDA-21266 | SUPPL-30 | PFIZER INC | VFEND (VORICONAZOLE) 50/200MG TABLETS |
| NDA-21266 | SUPPL-29 | PFIZER INC | VFEND (VORICONAZOLE) 50/200MG TABLETS |
| NDA-21266 | SUPPL-27 | PFIZER INC | VFEND (VORICONAZOLE) 50/200MG TABLETS |
| NDA-21266 | SUPPL-25 | PFIZER INC | VFEND (VORICONAZOLE) 50/200MG TABLETS |

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/s/

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RENATA ALBRECHT
06/17/2010