DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-266/S-032
NDA 21-267/S-036
NDA 21-630/S-023

SUPPLEMENTS APPROVAL

Pfizer, Inc.
Attention: Maureen Garvey, Ph.D.
Senior Director
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Garvey:

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:

Drug Product Name	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-032	July 22, 2010	July 22, 2010
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-036	July 22, 2010	July 22, 2010
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-023	July 22, 2010	July 22, 2010

We acknowledge receipt of your amendments to all three supplements dated November 2 and 5, 2010.

SUMMARY OF LABELING SUPPLEMENTS

On July 22, 2010, Pfizer submitted Prior Approval Labeling Supplements that propose adding safety information to the package inserts (PI) related to the concomitant and sequential use of voriconazole and fluconazole. The patient package insert (PPI) was also submitted, but no changes were proposed.

REVISIONS TO THE PACKAGE INSERT

The additions to the package insert (PI) that were agreed upon for the above three supplements are noted with underline:

1. Under **the CLINICAL PHARMACOLOGY/ Drug Interactions/Effects of Other Drugs on Voriconazole** subsection, the following two paragraphs were added between paragraghs beginning with "***Carbamazepine and long-acting barbiturates* (potent CYP450 inducers)" and *"Minor or no significant pharmacokinetic interactions that do not require dosage adjustment" heading:**

Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole-related adverse events/toxicity:

***Fluconazole* (CYP2C9, CYP2C19 and CYP3A4 inhibitor):** Concurrent administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 6 healthy male subjects resulted in an increase in Cmax and AUC_τ of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 hours of the last dose of fluconazole. (see PRECAUTIONS - Drug Interactions).

2. In **Table 11: Effect of Other Drugs on Voriconazole Pharmacokinetics** safety information regarding Fluconazole was added:

Drug/Drug Class (Mechanism of Interaction by the Drug)	**Voriconazole Plasma Exposure (C_{max} and AUC_τ after 200 mg Q12h)**	**Recommendations for Voriconazole Dosage Adjustment/Comments**
Rifampin*, and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz** (CYP450 Induction)	Significantly Reduced	When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg Q12h and efavirenz should be decreased to 300 mg Q24h (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION-Dosage Adjustment)**
High-dose Ritonavir (400mg Q12h)** (CYP450 Induction)	Significantly Reduced	**Contraindicated** Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h)

Drug/Drug Class (Mechanism of Interaction by the Drug)	**Voriconazole Plasma Exposure (C_{max} and AUC_{τ} after 200 mg Q12h)**	**Recommendations for Voriconazole Dosage Adjustment/Comments**
Low-dose Ritonavir (100mg Q12h)** (CYP450 Induction)	Reduced	should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole
Carbamazepine (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Long Acting Barbiturates (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Phenytoin* (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV every 12 hrs or from 200 mg to 400 mg orally every 12 hrs (100 mg to 200 mg orally every 12 hrs in patients weighing less than 40 kg)
St. John's Wort (CYP450 inducer; P-gp inducer)	Significantly Reduced	**Contraindicated**
Oral Contraceptives** containing ethinyl estradiol and norethindrone (CYP2C19 Inhibition)	Increased	Monitoring for adverse events and toxicity related to voriconazole is recommended when coadministered with oral contraceptives
Fluconazole**(CYP2C9, CYP2C19 and CYP3A4 Inhibition)	Significantly Increased	Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is recommended especially if voriconazole is started within 24 h after the last dose of fluconazole.
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects of Indinavir on Voriconazole Exposure *In Vitro* Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism (Increased Plasma Exposure)	No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir Frequent monitoring for adverse events and toxicity related to voriconazole when coadministered with other HIV protease inhibitors
Other NNRTIs*** (CYP3A4 Inhibition or CYP450 Induction)	*In Vitro* Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism by Delavirdine and Other NNRTIs (Increased Plasma Exposure) A Voriconazole-Efavirenz Drug Interaction Study Demonstrated the Potential for the Metabolism of Voriconazole to be Induced by Efavirenz and Other NNRTIs (Decreased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg Q12h 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
*** Non-Nucleoside Reverse Transcriptase Inhibitors

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 these NDAs, 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 these supplemental applications.

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-032; NDA 21-267/S-036; NDA 21-630/S-023**." 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 these drug products (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 these NDAs, 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 approved NDAs (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}

Ozlem Belen, M.D.
Deputy Director of Safety
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)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
11/21/2010