DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

SUPPLEMENT APPROVAL

NDA 19-949/S-052
NDA 19-950/S-057
NDA 20-090/S-036

Pfizer, Inc.
Attention: Nancy Kirschbaum, Ph.D.
Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Kirschbaum:

Please refer to your supplemental New Drug Applications (sNDA)s dated December 8, 2010, received December 8, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product	**NDA Number**	**Supplement Number**
Diflucan (fluconazole) Tablets, 50 mg, 100 mg, and 200 mg	19-949	S-052
Diflucan (fluconazole) I.V., 2 mg/mL	19-950	S-057
Diflucan (fluconazole) for Oral Suspension, 10 mg/mL and 40 mg/mL	20-090	S-036

These Prior-Approval labeling supplements provide for revisions to the **CLINICAL PHARMACOLOGY/Drug Interaction Studies** and **PRECAUTIONS/Drug Interactions** subsections of the DIFLUCAN® (fluconazole) package insert (PI) to provide precautionary language regarding concomitant or sequential administration of VFEND® (voriconazole) and DIFLUCAN® (fluconazole), consistent with the language included in the VFEND® package insert submitted to FDA on November 2, 2010 and approved on November 21, 2010. The Patient Package Insert (PPI) has also been revised to be consistent with the package insert.

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.

Revisions to the Package Insert (PI)

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

a. Under the **CLINICAL PHARMACOLOGY/Drug Interaction Studies** subsection, a new paragraph was added after the *Azithromycin* paragraph:

*Voriconazole***:** Voriconazole is a substrate for both CYP2C9 and CYP3A4 isoenzymes. 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 AUCτ 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 h of the last dose of fluconazole. (See **PRECAUTIONS.**)

b. Under the **PRECAUTIONS/Drug Interactions** subsection, Voriconazole was added to the list of observed/documented interactions:

Drug Interactions: (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies** and **CONTRAINDICATIONS**.) DIFLUCAN is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole. Clinically or potentially significant drug interactions between DIFLUCAN and the following agents/classes have been observed. These are described in greater detail below:

Oral hypoglycemics
Coumarin-type anticoagulants
Phenytoin
Cyclosporine
Rifampin
Theophylline
Terfenadine
Cisapride
Astemizole

Rifabutin
Voriconazole
Tacrolimus
Short-acting benzodiazepines
Triazolam
Oral Contraceptives
Pimozide
Hydrochlorothiazide
Alfentanil
Amitriptyline, nortriptyline
Amphotericin B
Azithromycin
Carbamazepine
Calcium Channel Blockers
Celecoxib
Cyclophosphamide
Fentanyl
Halofantrine
HMG-CoA reductase inhibitors
Losartan
Methadone
Non-steroidal anti-inflammatory drugs
Prednisone
Saquinavir
Sirolimus
Vinca Alkaloids
Vitamin A
Zidovudine

c. Under the **PRECAUTIONS/Drug Interactions subsection**, a new paragraph was added after the *Rifabutin* paragraph:

Voriconazole: 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. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Revisions to Patient Package insert (PPI)

The revisions to the patient package insert (PPI) that were agreed upon for the above three supplements are as follow (additions are noted with underline):

d. The **What To Tell Your Doctor Before You Start DIFLUCAN?** section was revised as follows:

Do not take Diflucan if you take certain medicines. They can cause serious problems. Therefore, tell your doctor about all the medicines you take including:

- amphotericin B or voriconazole for fungal infections

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 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, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

Enclosures: Package Insert
Patient Package Insert

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

/s/

RENATA ALBRECHT
04/26/2011