



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-010
NDA 21-267/S-010
NDA 21-630/S-004

Pfizer, Inc.
Attention: Mr. Robert B. Clark
Vice President, U.S. Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug applications dated September 27, 2004, received September 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VFEND® (voriconazole) Tablets, 50 mg, 200 mg, VFEND® I.V. (voriconazole) for Injection, 200 mg vial and VFEND® (voriconazole) for Oral Suspension, 40 mg/mL.

We acknowledge receipt of your submissions dated November 16, 2004, March 7, 2005, and March 14, 2005.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined):

1. CLINICAL PHARMACOLOGY

The following paragraph was added to **Drug Interactions, Effects of Voriconazole on Other Drugs**:

Methadone (CYP3A4, CYP2C19, CYP2C9 substrate): Repeat dose administration of oral voriconazole (400mg Q12h for 1 day, then 200mg Q12h for 4 days) increased the C_{max} and AUC_{0-12h} of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30-100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103% (90% CI: 85%, 124%), respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed (see PRECAUTIONS - Drug Interactions).

2. PRECAUTIONS

The following information was added to Table 10 in **Drug Interactions, "Effect of Voriconazole on Other Drugs"**:

<u>Methadone*** (CYP3A4 Inhibition)</u>	<u>Increased</u>	<u>Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed</u>
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*** 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)

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (text for the package insert submitted March 14, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as "**FPL for approved supplements NDA 21-266/S-010, NDA 21-267/S-010, NDA 21-630/S-004.**" Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 21-266/S-010

NDA 21-267/S-010

NDA 21-630/S-004

Page 3

If you have any questions, call Robin Anderson, R.N., M.B.A., Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.

Director

Division of Special Pathogen and Immunologic Drug
Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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