



NDA 21-266/S-026
NDA 21-267/S-026
NDA 21-630/S-015

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attention: Mr. Robert B. Clark
Vice President, U.S. Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug applications dated and received on March 13, 2008 and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
VFEND [®] (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-026
VFEND [®] I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-026
VFEND [®] (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-015

We acknowledge receipt of your submissions dated May 22, 2008.

These supplemental applications, submitted as “Supplements – Changes Being Effected,” provide for the addition of safety information pertaining to a drug interaction between voriconazole and alfentanil to content of labeling for the package insert for VFEND[®].

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The revisions to the package insert were as follows (additions noted with underline):

1. A precaution between voriconazole and alfentanil was added to the **CLINICAL PHARMACOLOGY/Drug Interactions/Effects of Voriconazole on Other Drugs** subsection of the package insert as follows:

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

Alfentanil (CYP3A4 substrate): Coadministration of multiple doses of oral voriconazole (400 mg q12h on day 1, 200 mg q12h on day 2) with a single 20 mcg/kg intravenous dose of alfentanil with concomitant naloxone resulted in a 6-fold increase in mean alfentanil AUC_{0-∞}

and a 4-fold prolongation of mean alfentanil elimination half-life, compared to when alfentanil was given alone. An increase in the incidence of delayed and persistent alfentanil-associated nausea and vomiting during co-administration of voriconazole and alfentanil was also observed. Reduction in the dose of alfentanil or other opiates that are also metabolized by CYP3A4 (e.g., sufentanil), and extended close monitoring of patients for respiratory and other opiate-associated adverse events, may be necessary when any of these opiates is coadministered with voriconazole. (see PRECAUTIONS – Drug Interactions).

2. **Table 12: Effect of Voriconazole on Pharmacokinetics of Other Drugs** of the **PRECAUTIONS** section of the package insert was revised as follows:

Table 12: Effect of Voriconazole on Pharmacokinetics of Other Drugs

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_τ)	Recommendations for Drug Dosage Adjustment/Comments
<u>Alfentanil (CYP3A4 Inhibition)</u>	<u>Significantly Increased</u>	<u>Reduction in the dose of alfentanil and other opiates metabolized by CYP3A4 (e.g., sufentanil) should be considered when coadministered with VFEND. A longer period for monitoring respiratory and other opiate-associated adverse events may be necessary (see CLINICAL PHARMACOLOGY - Drug Interactions).</u>

3. Minor editorial changes throughout the labeling.

CONTENT OF LABELING

As soon as possible, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, “**SPL for approved NDA 21-266/S-026, NDA 21-267/S-026, and NDA 21-630/S-015.**”

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Rebecca D. Saville, Pharm.D., 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

**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
5/30/2008 02:57:36 PM