

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**21-266 / S-005, S-006**

**21-267 / S-005, S-006**

**21-630 / S-001**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-266/S-005, S-006  
NDA 21-267/S-005, S-006  
NDA 21-630/S-001

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

Dear Mr. Clark:

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

NDA Number	Drug Product	Supplement Number	Letter Date	Receipt Date
21-266	VFEND <sup>®</sup> (voriconazole) Tablets, 50 mg and 100 mg	S-005	October 21, 2003	October 21, 2003
		S-006	November 12, 2003	November 12, 2003
21-267	VFEND <sup>®</sup> I.V. (voriconazole) for Injection	S-005	October 21, 2003	October 21, 2003
		S-006	November 12, 2003	November 12, 2003
21-630	VFEND <sup>®</sup> (voriconazole) for Oral Suspension	S-001	January 20, 2004	January 21, 2004

We acknowledge receipt of your submissions dated:

December 24, 2003 (2)	February 2, 2004 (2)	February 12, 2004 (2)
March 31, 2004 (2)	April 21, 2004	

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

### 1. CLINICAL PHARMACOLOGY

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400 mg Q12h for 9 days) decreased the steady state  $C_{max}$  and  $AUC_{\tau}$  of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. The effect of ritonavir (100 mg Q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been

studied. Repeat oral administration of voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) did not have a significant effect on steady state  $C_{max}$  and  $AUC_T$  of ritonavir following repeat dose administration (400 mg Q12h for 9 days) in healthy subjects.

**Coadministration of voriconazole and ritonavir (400 mg Q12h) is contraindicated (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).**

- The following paragraph was added to **Drug Interactions, Two-Way Interactions** :

**Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate):** Steady state efavirenz (400 mg PO QD) decreased the steady state  $C_{max}$  and  $AUC_T$  of voriconazole (400 mg PO Q12h for 1 day, then 200 mg PO Q12h for 8 days) by an average of 61% and 77%, respectively, in healthy subjects. Voriconazole at steady state (400 mg PO Q12h for 1 day, then 200 mg Q12h for 8 days) increased the steady state  $C_{max}$  and  $AUC_T$  of efavirenz (400 mg PO QD for 9 days) by an average of 38% and 44%, respectively, in healthy subjects. **Coadministration of voriconazole and efavirenz is contraindicated (see CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions).**

- The following paragraph was modified in **Drug Interactions, Two-Way Interactions** :

**Other Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers):** *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by an NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy volunteers suggest that the metabolism of voriconazole may be induced by a NNRTI. This *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI. Although not studies *in vitro* or *in vivo*, the metabolism of voriconazole may be induced by an NNRTI, such as nevirapine. *In vitro* studies (human liver microsomes) show that voriconazole may also inhibit the metabolism of an NNRTI (e.g., delavirdine). **Efavirenz and voriconazole coadministration is contraindicated (see CLINICAL PHARMACOLOGY – Drug Interactions, CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions).** Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and ~~other~~ NNRTIs (e.g. nevirapine and delavirdine) (see PRECAUTIONS – Drug Interactions).

## 2. CONTRAINDICATIONS

- The following paragraphs were added to this section:

**Coadministration of VFEND with ritonavir (400 mg Q12h) is contraindicated because ritonavir (400 mg Q12h) significantly decreases plasma voriconazole concentrations in healthy subjects. The effect of ritonavir (100 mg Q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).**

**Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).**

### 3. PRECAUTIONS

- Table 8 and Table 9 in **Drug Interactions** were revised to include information concerning ritonavir and efavirenz:

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 products are safe and effective for use as recommended for use in the agreed upon labeling text (enclosed). Accordingly, these supplemental new drug applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted April 21, 2004).

Please submit the copies of the final printed labeling (FPL) electronically to each application according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated “FPL for approved supplements NDA 21-266/S-005, S-006; NDA 21-267/S-005, S-006; and NDA 21-630/S-001.” Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs 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.

If you have any questions, please call Rebecca Saville, Pharm.D., Regulatory Project Manager, 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

Enclosure

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/s/

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Renata Albrecht  
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