DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-019
NDA 21-267/S-021
NDA 21-630/S-011

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attn: Mr. Robert B. Clark
Vice President, U.S. Regulatory
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Clark:

Please refer to your supplemental new drug applications, dated May 31, 2006 and received on June 1, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-019
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-021
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-011

We acknowledge receipt of your submissions dated December 1, 2006.

These supplemental new drug applications provide for the addition of information to adjust the doses of efavirenz and voriconazole to allow for their concomitant use.

These supplemental new drug applications, as amended, provide for the following revisions to the text of the package insert (~~strikethrough~~ = deleted text and double-underlined = added text):

1. The following information was added in the **CLINICAL PHARMACOLOGY/ Drug Interactions/Effects of Voriconazole on Other Drugs** subsection of the package insert:

   ***Sirolimus* (CYP3A4 substrate):** Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy male subjects. **Coadministration of voriconazole and sirolimus is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

2. The following information was added in the **CLINICAL PHARMACOLOGY/ Drug Interactions/Effects of Voriconazole on Other Drugs/Two-way Interactions** subsection of the package insert:

***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_{τ} 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 male 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_{τ} of efavirenz (400 mg PO QD for 9 days) by an average of 38% and 44%, respectively, in healthy subjects. **Coadministration of standard doses of voriconazole and efavirenz is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions).

The pharmacokinetics of adjusted doses of voriconazole and efavirenz were studied in healthy male subjects following administration of voriconazole (300 mg or 400 mg PO Q12h on Days 2 to 7) with efavirenz (300 mg PO Q24h on Days 1-7), relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg PO Q12h for 2 days) or efavirenz (600 mg Q24h for 9 days).

Coadministration of voriconazole 300 mg Q 12h with efavirenz 300 mg Q24h, decreased voriconazole AUCτ and Cmax by 55% (90% CI: 45%, 62%) and 36% (90% CI: 21%, 49%), respectively; efavirenz AUCτ was equivalent and Cmax was decreased by 14% (90% CI: 7%, 21%).

Coadministration of voriconazole 400 mg Q 12h with efavirenz 300 mg Q24h, decreased voriconazole AUCτ by 7% (90% CI: -23%, 13%) and increased Cmax by 23% (90% CI: -1%, 53%); efavirenz AUCτ was increased by 17% (90% CI; 6%, 29%) and Cmax was equivalent. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg Q12h and efavirenz dose should be decreased to 300 mg Q24h.

3. The following information was revised in the **CLINICAL PHARMACOLOGY/ Drug Interactions/Effects of Voriconazole on Other Drugs/Two-way Interactions/Other Two-Way Interactions Expected to be Significant Based on *In Vitro* and *In Vivo* Findings** subsection of the package insert:

***Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)* (CYP3A4 substrates, inhibitors or CYP450 inducers)**: *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by a NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy male subjects ~~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. ~~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).

4. The following information was added in the **CONTRAINDICATIONS** section of the package insert as follows:

   Coadministration of standard doses of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations. Concomitant use of adjusted doses of voriconazole and efavirenz may be administered (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions, and DOSAGE AND ADMINISTRATION – Dosage Adjustment).

5. Information was revised and added to Table 9 in the **PRECAUTIONS/Drug Interactions** subsection of the package insert as follows (please see enclosure for the entirety of Table 9):

Table 9 Effect of Other Drugs on Voriconazole Pharmacokinetics

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*~~, Efavirenz**~~ and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz** (CYP450 Induction)	Significantly Reduced	**Coadministration of standard doses of efavirenz with voriconazole is Contraindicated.** 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)**

*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~~3~~ days voriconazole to healthy subjects
*** Non-Nucleoside Reverse Transcriptase Inhibitors

6. Information was revised and added to Table 10 in the **PRECAUTIONS/Drug Interactions** subsection of the package insert as follows (please see enclosure for the entirety of Table 10):

Table 10 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
Rifabutin* ~~and Efavirenz**~~ (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Efavirenz** (CYP3A4 Inhibition)	Significantly Increased	**Coadministration of standard doses of efavirenz with voriconazole is Contraindicated.** 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)**

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID 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~~3~~ days 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 4 days voriconazole to subjects receiving a methadone maintenance dose (30-100 mg QD)
**** Non-Nucleoside Reverse Transcriptase Inhibitors

7. The following text was added to the **DOSAGE AND ADMINISTRATION** section of the package insert:

   When voriconazole is coadministered with efavirenz, the voriconazole maintenance dose should be increased to 400 mg Q12h and the efavirenz dose should be decreased to 300 mg Q24h (see CLINICAL PHARMACOLOGY and PRECAUTIONS – Drug Interactions).

8. The **PATIENT PACKAGE INSERT** section of the package insert was revised as follows:

Who should not take VFEND?
Do NOT take VFEND if you are taking the medicines listed below. Serious or life-threatening side effects from these medicines, or a decrease in the effect of VFEND could result if any of these medicines are taken together with VFEND. Tell your doctor right away if you are taking any of these medications:

- terfenadine (Seldane®)
- astemizole (Hismanal®)
- cisapride (Propulsid®)
- pimozide (Orap®)
- ~~efavirenz (Sustiva®)~~
- sirolimus (Rapamune®)
- carbamazepine (Tegretol®)
- rifampin (Rifadin®)
- rifabutin (Mycobutin®)
- quinidine (like Quinaglute®)
- ergotamine, dihydroergotamine, methysergide (Sansert®), and bromocriptine (Parlodel®)
- long-acting barbiturates like phenobarbital (Luminal®)
- ritonavir (Norvir ®) and efavirenz (Sustiva®) (Some doses of ritonavir and efavirenz can be taken at the same time as VFEND, but you must check with your doctor first)

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.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

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