DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-015
NDA 21-267/S-015
NDA 21-630/S-008

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 September 12, 2005 and received on September 13, 2005, 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-015
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-015
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-008

We acknowledge receipt of your submissions dated February 23, 2006 and March 7, 2006.

These "Changes Being Effected in 30 days" supplemental new drug applications provide for the revision of the **CLINICAL PHARMACOLOGY/Drug Interactions subsection, the CONTRAINDICATIONS section**, and **PRECAUTIONS/Drug Interactions sub**section of the labeling to include information regarding the interaction between voriconazole and low dose ritonavir.

We note that the currently approved text for the package insert has information regarding the high-dose ritonavir interaction with voriconazole. Your February 23, 2006 submission contained updated labeling that reflected the addition of the patient package insert, approved on December 18, 2005, and provided for revision of the **"Who should not take VFEND?"** section of the patient package insert to update the information regarding the use of ritonavir with voriconazole.

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

1. The following revisions were made in the **CLINICAL PHARMACOLOGY/Drug Interactions** subsection of the package insert:

   Ritonavir **(potent CYP450 inducer; CYP3A4 inhibitor and substrate):** The effect of the coadministration of voriconazole and ritonavir (400 mg and 100 mg) was investigated in two separate studies. High-dose ~~R~~ritonavir (400 mg Q12h for 9 days) decreased the steady state C_{max} and AUC_{τ} 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~~ Low-dose ritonavir (100 mg Q12h for 9 days ~~as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied~~ decreased the steady state C_{max} and AUC_{τ} of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) by an average of 24% and 39%, respectively**,** in healthy subjects. Although ~~R~~repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_{τ} of high-dose ritonavir ~~following repeat dose dose administration (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days)~~ in healthy subjects~~.~~, steady state C_{max} and AUC_{τ} of low-dose ritonavir decreased slightly by 24% and 14% respectively, when administered concomitantly with oral voriconazole in healthy subjects. **Coadministration of voriconazole and high-dose ritonavir (400 mg Q12h) is contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

2. The **CONTRAINDICATIONS** section of the package insert was revised as follows:

   Coadministration of VFEND with high-dose 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.~~ Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

3. The following information pertaining to ritonavir in the tables from the **PRECAUTIONS/Drug Interactions sub**section of the package insert were revised as follows:

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**
High-dose Ritonavir (400mg Q12h ~~HIV Protease Inhibitor~~)** (CYP450 Induction)	Significantly Reduced	**Contraindicated** ~~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.~~
Low-dose Ritonavir (100mg Q12h)** (CYP450 Induction)	Reduced	Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole

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

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**
High-dose Ritonavir (400 mg Q12h ~~HIV Protease Inhibitor~~)**(CYP3A4 Inhibition)	No Significant Effect of Voriconazole on Ritonavir C_{max} or AUC_τ	**Contraindicated** because of significant reduction of voriconazole C_{max} and AUC_τ
Low-dose Ritonavir (100mg Q12h)**	Slight Decrease in Ritonavir C_{max} and AUC_τ	Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h) should be avoided (due to the reduction in voriconazole C_{max} and AUC_τ) unless an assessment of the benefit/risk to the patient justifies the use of voriconazole

*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 8 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

4. The **Who should not take VFEND?** section of the Patient Package Insert was modified as followed:

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 ~~medicines activity~~ 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®)
- cisapride (Propulsid®)
- ~~ritonavir (Norvir ®)~~
- carbamazepine (Tegretol®)
- rifabutin (Mycobutin®)
- astemizole (Hismanal®)
- pimozide (Orap®)
- efavirenz (Sustiva®)
- sirolimus (Rapamune®)
- rifampin (Rifadin®)
- quinidine (like Quinaglute®)
- ergotamine, dihydroergotamine, methysergide (Sansert®), and bromocriptine (Parlodel®)
- long-acting barbiturates like phenobarbital (Luminal®)
- ritonavir (Norvir ®) (Some doses of ritonavir 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. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in PDF format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 21-266/S-015, NDA 21-267/S-015, and NDA 21-630/S-008**." Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

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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