



NDA 21-266/S-018
NDA 21-267/S-019
NDA 21-630/S-010

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 November 18, 2005 and received on November 21, 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-018
VFEND [®] I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-019
VFEND [®] (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-010

We acknowledge receipt of your submissions dated May 18, 2006.

These supplemental new drug applications provide for the addition of information pertaining to a drug interaction between voriconazole and oral contraceptives to the **CLINICAL PHARMACOLOGY/ Drug Interactions** and **PRECAUTIONS/Drug Interactions** subsections of the package insert for VFEND[®].

These supplemental new drug applications, as amended, provide for the following revisions to the text of the package insert (~~striketrough~~ = 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/Two-way Interactions** subsection of the package insert:

Oral Contraceptives (CYP3A4 substrate; CYP2C19 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 3 days) and oral contraceptive (Ortho-Novum1/35[®] consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, Q24h) to healthy female subjects at steady state increased the C_{max} and AUC_τ of ethinyl estradiol by an average of 36% (90% CI: 28%, 45%) and 61% (90% CI: 50%, 72%), respectively, and that of norethindrone by 15% (90% CI: 3%, 28%) and 53% (90% CI: 44%, 63%), respectively in

healthy subjects. Voriconazole C_{max} and AUC_τ increased by an average of 14% (90% CI: 3%, 27%) and 46% (90% CI: 32%, 61%), respectively. Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended during coadministration. (see PRECAUTIONS - Drug Interactions).

- The following information pertaining to oral contraceptives was added to a new row in the tables in the **PRECAUTIONS/Drug Interactions** subsection of the package insert 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
<u>Oral Contraceptives** containing ethinyl estradiol and norethindrone (CYP2C19 Inhibition)</u>	<u>Increased</u>	<u>Monitoring for adverse events and toxicity related to voriconazole is recommended when coadministered with oral contraceptives</u>

*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 3 & 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
<u>Oral Contraceptives containing ethinyl estradiol and norethindrone (CYP3A4 Inhibition)**</u>	<u>Increased</u>	<u>Monitoring for adverse events related to oral contraceptives is recommended during coadministration.</u>

*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 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

- The **PRECAUTIONS/Drug Interactions** subsection of the package insert was revised to add the following information:

Women of Childbearing Potential

Women of childbearing potential should use effective contraception during treatment. The coadministration of voriconazole with the oral contraceptive, Ortho-Novum® (35 mcg ethinyl estradiol and 1 mg norethindrone), results in an interaction between these two drugs, but is unlikely to reduce the contraceptive effect (see CLINICAL PHARMACOLOGY-Drug Interactions-Oral Contraceptives; PRECAUTIONS-Drug Interactions)

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). Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions 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 these submissions "**FPL for approved supplements NDA 21-266/S-018, NDA 21-267/S-019, and NDA 21-630/S-010.**" 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
5/19/2006 04:25:10 PM