DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-012
NDA 21-267/S-011
NDA 21-630/S-005

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attn: Maureen H. Garvey, Ph.D.
Senior Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Garvey:

Please refer to your supplemental new drug applications (NDAs) dated January 6, 2005, received January 7, 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-012
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-011
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-005

We acknowledge receipt of your submissions dated January 25, 2005, February 2, 2005, and July 6, 2005.

These supplemental new drug applications provide for the correction of editorial errors and accidental deletions in the labeling for the package insert approved on December 21, 2004 for VFEND®. The following revisions (double underlined) were proposed:

1. In the **CLINICAL PHARMACOLOGY/Pharmacokinetic-Pharmacodynamic Relationships**/Electrocardiogram section, a sentence was corrected to read "No subject in any group had an increase in QTc of $\geq$ 60 msec from baseline."

2. The title of the **CLINICAL PHARMACOLOGY Other Two-Way Interactions Expected to be Significant Based on *In Vitro* and *In Vivo* Findings** was corrected.

3. The column of approved comparator data in Table 11 in the **ADVERSE REACTIONS** section was restored as follows:

Table 11
Treatment Emergent Adverse Events

Rate ≥ 2% on Voriconazole or Adverse Events of Concern in All Therapeutic Studies population, Studies 307/602-608 combined, or Study 305. Possibly Related to Therapy or Causality Unknown†

	All Therapeutic Studies	**Studies 307/602 and 608 (IV/ oral therapy)**			**Study 305 (oral therapy)**	
	Voriconazole N = 1655	Voriconazole N = 468	Ampho B* N=185	Ampho B→ Fluconazole N= 131	Voriconazole N = 200	Fluconazole N =191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Special Senses**						
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0	31 (15.5)	8 (4.2)
Photophobia	37 (2.2)	8 (1.7)	0	0	5 (2.5)	2 (1.0)
Chromatopsia	20 (1.2)	2 (0.4)	0	0	2 (1.0)	0
Body as a Whole						
Fever	94 (5.7)	8 (1.7)	25 (13.5)	5 (3.8)	0	0
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)	1 (0.5)	0
Headache	49 (3.0)	9 (1.9)	8 (4.3)	1 (0.8)	0	1 (0.5)
Cardiovascular System						
Tachycardia	39 (2.4)	6 (1.3)	5 (2.7)	0	0	0
Digestive System						
Nausea	89 (5.4)	18 (3.8)	29 (15.7)	2 (1.5)	2 (1.0)	3 (1.6)
Vomiting	72 (4.4)	15 (3.2)	18 (9.7)	1 (0.8)	2 (1.0)	1 (0.5)
Liver function tests abnormal	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)	6 (3.0)	2 (1.0)
Cholestatic jaundice	17 (1.0)	8 (1.7)	0	1 (0.8)	3 (1.5)	0
Metabolic and Nutritional Systems						
Alkaline phosphatase increased	59 (3.6)	19 (4.1)	4 (2.2)	3 (2.3)	10 (5.0)	3 (1.6)
Hepatic enzymes increased	30 (1.8)	11 (2.4)	5 (2.7)	1 (0.8)	3 (1.5)	0
SGOT increased	31 (1.9)	9 (1.9)	0	1 (0.8)	8 (4.0)	2 (1.0)
SGPT increased	29 (1.8)	9 (1.9)	1 (0.5)	2 (1.5)	6 (3.0)	2 (1.0)
Hypokalemia	26 (1.6)	3 (0.6)	36 (19.5)	16 (12.2)	0	0
Bilirubinemia	15 (0.9)	5 (1.1)	3 (1.6)	2 (1.5)	1 (0.5)	0
Creatinine increased	4 (0.2)	0	59 (31.9)	10 (7.6)	1 (0.5)	0
Nervous System						

	All Therapeutic Studies	**Studies 307/602 and 608 (IV/ oral therapy)**			**Study 305 (oral therapy)**	
	Voriconazole N = 1655	Voriconazole N = 468	Ampho B* N=185	Ampho B→ Fluconazole N= 131	Voriconazole N = 200	Fluconazole N =191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hallucinations	39 (2.4)	13 (2.8)	1 (0.5)	0	0	0
Skin and Appendages						
Rash	88 (5.3)	20 (4.3)	7 (3.8)	1 (0.8)	3 (1.5)	1 (0.5)
Urogenital						
Kidney function abnormal	10 (0.6)	6 (1.3)	40 (21.6)	9 (6.9)	1 (0.5)	1 (0.5)
Acute kidney failure	7 (0.4)	2 (0.4)	11 (5.9)	7 (5.3)	0	0

† Study 307/602: invasive aspergillosis; Study 608: candidemia; Study 305: esophageal candidiasis
*Amphotericin B followed by other licensed antifungal therapy
** See WARNINGS – Visual Disturbances, PRECAUTIONS – Information For Patients

4. The following statements in the **ADVERSE REACTIONS** section were revised to read "***VISUAL DISTURBANCES***: Voriconazole treatment-related visual disturbances are common. In therapeutic trials, approximately 21% of patients experienced abnormal vision, color vision change and/or photophobia."

We 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 the FPL electronically 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, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "**FPL for approved supplement NDA 21-266/S-012, NDA 21-267/S-011, and NDA 21-630/S-005**." Approval of these submissions by FDA is not required before the labeling is used.

In addition, as required by 21 CFR 314.550, 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 proposed package inserts directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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) 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

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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