DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-016
NDA 21-267/S-016
NDA 21-630/S-009

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

Dear Mr. Clark:

Please refer to your supplemental new drug applications dated September 16, 2005, received on September 19, 2005, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-016
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-016
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-009

We acknowledge receipt of your submissions dated:

January 30, 2006
February 8, 2006
March 9, 2006
October 23, 2006
November 22, 2006
August 15, 2007
October 19, 2007
December 3, 2007
January 22, 2008
January 25, 2008

These supplemental new drug applications provide for the addition of breakpoint and zone diameter interpretive criteria for *Candida* species in the **MICROBIOLOGY** section of the package insert of the labeling for VFEND®.

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 revisions to the package insert were as follows (additions noted with underline and deletions noted with ~~strikethrough~~):

1. The **MICROBIOLOGY** section was modified as follows:

MICROBIOLOGY

Mechanism of Action
Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Activity In Vitro ~~and In Vivo~~
~~Voriconazole has demonstrated *in vitro* activity against *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. niger* and *A. terreus*), *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis*), *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*(see INDICATIONS AND USAGE, CLINICAL STUDIES).~~

Voriconazole has been shown to be active against most strains of the following microorganisms, **both *in vitro* and in clinical infections.**

Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus
Candida albicans
Candida glabrata (In clinical studies, the voriconazole MIC_{90} was 4 µg/mL)*
Candida krusei
Candida parapsilosis
Candida tropicalis
Fusarium spp. including *Fusarium solani*
Scedosporium apiospermum

*In clinical studies, voriconazole MIC_{90} for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥ 4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC_{90} was 1 µg/mL (see table 4).

The following data are available, **but their clinical significance is unknown.**

Voriconazole exhibits *in vitro* minimal inhibitory concentrations (MICs) of 1 µg/mL or less against most (>90%) isolates of the following microorganisms; however, the safety and effectiveness of voriconazole in treating clinical infections due to these *Candida* species have not been established in adequate and well-controlled clinical trials:

Candida lusitaniae
Candida guilliermondii

~~*In vitro* susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) methods (M38-P for moulds and M27-A for yeasts). Voriconazole breakpoints have not been established for any fungi. The relationship between clinical outcome and *in vitro* susceptibility results remains to be elucidated.~~

Susceptibility Testing Methods[2,3]
***Aspergillus* species and other filamentous fungi**

No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

***Candida* species**
The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours.[2,3]

***Broth Microdilution Techniques*:** Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours.[2] Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in Table 4.

***Diffusion Techniques*:** Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* spp. to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations.[3] This procedure uses paper disks impregnated with 1 μg of voriconazole to test the susceptibility of yeasts to voriconazole at 24 hours. Disk diffusion interpretive criteria are also provided in Table 4.

Table 4: Susceptibility Interpretive Criteria for Voriconazole[2,3]

	Broth Microdilution at 48 hours (MIC in μg/mL)			Disk Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	Intermediate (I)	Resistant (R)	Susceptible (S)	Intermediate (I)	Resistant (R)
Voriconazole	≤1.0	2.0	≥4.0	≥17	14-16	≤13

NOTE: Shown are the breakpoints (μg/mL) for voriconazole against *Candida* species.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used for the site of infection. The intermediate category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a

high dosage of drug is used. The resistant category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard voriconazole powder and 1 µg disks should provide the following range of values noted in Table 5.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Table 5
Acceptable Quality Control Ranges for Voriconazole to be used in Validation of Susceptibility Test Results

QC Strain	**Broth Microdilution (MIC in µg/mL) @ 48-hour**	**Disk Diffusion (Zone diameter in mm) @ 24- hour**
Candida parapsilosis ATCC 22019	0.03-0.25	28-37
Candida krusei ATCC 6258	0.12-1.0	16-25
Candida albicans ATCC 90028	*	31-42

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

ATCC is a registered trademark of the American Type Culture Collection.

Activity *In Vivo*

Voriconazole was active in normal and/or immunocompromised guinea pigs with systemic and/or pulmonary infections due to *A. fumigatus* (including an isolate with reduced susceptibility to itraconazole) or *Candida* species *[C.albicans* (including an isolate with reduced susceptibility to fluconazole), *C. krusei and C. glabrata]* in which the endpoints were prolonged survival of infected animals and/or reduction of mycological burden from target organs. In one experiment, voriconazole exhibited activity against *Scedosporium apiospermum* infections in immune competent guinea pigs.

2. The **REFERENCES** section of the package insert was modified as follows:

REFERENCES

1. ~~National Committee for~~ Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Approved Standard M38-P. ~~National Committee for~~ Clinical Laboratory Standards Institute, Villanova, Pa.

2. ~~National Committee for~~ Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved Standard M27-A. ~~National Committee for~~ Clinical Laboratory Standards Institute, Villanova, Pa.

3. Clinical Laboratory Standards Institute. Method for antifungal disk diffusion susceptibility testing of yeasts. Approved guideline M44-A. Clinical Laboratory Standards Institute, Villanova, Pa.

3. Minor editorial corrections were made throughout the package insert.

CONTENT OF LABELING

As soon as possible, please submit the 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 to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "**SPL for approved NDA 21-266/S-016, NDA 21-267/S-016, and NDA 21-630/S-009**."

LETTERS TO HEALTH CARE PROFESSIONALS

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
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

REPORTING REQUIREMENTS

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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