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:

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

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

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.

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. 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. 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

<table>
<thead>
<tr>
<th></th>
<th>Broth Microdilution at 48 hours (MIC in μg/mL)</th>
<th>Disk Diffusion at 24 hours (Zone diameters in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (S)</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>≤1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

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.

### Quality Control Microorganisms

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

* 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**


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](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/
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Renata Albrecht
2/5/2008 09:09:02 AM