



NDA 19-949/S-041
NDA 19-950/S-043
NDA 20-090/S-022

Pfizer, Inc.
Attention: Ms. Beatrice Curran
Associate Director, Worldwide Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Curran:

Please refer to your supplemental new drug applications dated September 30, 2005, received on October 3, 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
DIFLUCAN [®] (fluconazole) Tablets, 50 mg, 100 mg and 200 mg	19-949	S-041
DIFLUCAN [®] (fluconazole) I.V., 2 mg/mL	19-950	S-043
DIFLUCAN [®] (fluconazole) for Oral Suspension, 10 mg/mL and 40 mg/mL	20-090	S-022

We acknowledge receipt of your submissions dated:

December 3, 2007	March 7, 2008
January 22, 2008	March 25, 2008
February 12, 2008	

These supplemental new drug applications provide for the addition of minimum inhibitory concentrations and zone diameter interpretive criteria/breakpoints for *Candida* species in the **MICROBIOLOGY** section of the package insert of the labeling for DIFLUCAN[®].

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 **Mode of Action** subsection in the **CLINICAL PHARMACOLOGY** section of the package insert was revised and moved to the **MICROBIOLOGY** section. The **MICROBIOLOGY** section was modified as follows:

Microbiology

Mode~~Mode~~Mechanism of Action

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 ~~sterol C-14~~ alpha-demethylation dependent enzyme lanosterol 14- α -demethylase. This enzyme functions to convert lanosterol to ergosterol. The subsequent loss of normal sterols correlates with the accumulation of 14- α -methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Mammalian cell demethylation is much less sensitive to fluconazole inhibition.

Activity In Vitro and In Clinical Infections

~~Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp.~~
Fluconazole has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections.

Candida albicans

Candida glabrata (Many strains are intermediately susceptible)*

Candida parapsilosis

Candida tropicalis

Cryptococcus neoformans

* In a majority of the studies, fluconazole MIC₉₀ values against *C. glabrata* were above the susceptible breakpoint ($\geq 16 \mu\text{g/ml}$). Resistance in *Candida glabrata* usually includes upregulation of CDR genes resulting in resistance to multiple azoles. For an isolate where the MIC is categorized as intermediate (16 to 32 $\mu\text{g/ml}$, see Table 1), the highest dose is recommended (see Dosage and Administration). For resistant isolates alternative therapy is recommended.

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

Fluconazole exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 8 $\mu\text{g/mL}$ or less against most ($\geq 90\%$) strains of the following microorganisms, however, the safety and effectiveness of fluconazole in treating clinical infections due to these microorganisms have not been established in adequate and well controlled trials.

Candida dubliniensis

Candida guilliermondii

Candida kefyr

Candida lusitaniae

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to DIFLUCAN (e.g., *Candida krusei*). Such cases may require alternative antifungal therapy.

Susceptibility Testing Methods

***Cryptococcus neoformans* and filamentous fungi:**

No interpretive criteria have been established for *Cryptococcus neoformans* and filamentous fungi.

***Candida* species:**

Broth Dilution 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. Standardized procedures are based on a dilution method (broth)¹ with standardized inoculum concentrations of fluconazole powder. The MIC values should be interpreted according to the criteria provided in Table 1.

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 procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 25 µg of fluconazole to test the susceptibility of yeasts to fluconazole. Disk diffusion interpretive criteria are also provided in Table 1.

Table 1: Susceptibility Interpretive Criteria for Fluconazole

<u>Antifungal agent</u>	<u>Broth Dilution at 48 hours (MIC in µg/mL)</u>			<u>Disk Diffusion at 24 hours (Zone Diameters in mm)</u>		
	<u>Susceptible (S)</u>	<u>Intermediate (I)**</u>	<u>Resistant (R)</u>	<u>Susceptible (S)</u>	<u>Intermediate (I)**</u>	<u>Resistant (R)</u>
<u>Fluconazole*</u>	<u>≤ 8.0</u>	<u>16-32</u>	<u>≥64</u>	<u>≥19</u>	<u>15-18</u>	<u>≤14</u>

* Isolates of *C. krusei* are assumed to be intrinsically resistant to fluconazole and their MICs and/or zone diameters should not be interpreted using this scale.

** The intermediate category is sometimes called Susceptible-Dose Dependent (SDD) and both categories are equivalent for fluconazole.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used. 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. Standardized fluconazole powder and 25 µg disks should provide the following range of values noted in Table 2. 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 2: Acceptable Quality Control Ranges for Fluconazole to be Used in Validation of Susceptibility Test Results

<u>QC Strain</u>	<u>Macrodilution (MIC in µg/mL) @ 48 hours</u>	<u>Microdilution (MIC in µg/mL) @ 48 hours</u>	<u>Disk Diffusion (Zone Diameter in mm) @ 24 hours</u>
<u><i>Candida parapsilosis</i> ATCC 22019</u>	<u>2.0-8.0</u>	<u>1.0-4.0</u>	<u>22-33</u>
<u><i>Candida krusei</i> ATCC 6258</u>	<u>16-64</u>	<u>16-128</u>	<u>---*</u>
<u><i>Candida albicans</i> ATCC 90028</u>	<u>---*</u>	<u>---*</u>	<u>28-39</u>
<u><i>Candida tropicalis</i> ATCC 750</u>	<u>---*</u>	<u>---*</u>	<u>26-37</u>

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

Activity In Vivo

Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*.

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. Fluconazole administered orally and/or intravenously was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies is unknown.

Oral fluconazole has been shown to be active in an animal model of vaginal candidiasis.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with ~~*Cr. Cryptococcus neoformans*~~, and antagonism of the two drugs in systemic infection with *Asp. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Drug Resistance

Fluconazole resistance may arise from a modification in the quality or quantity of the target enzyme (lanosterol 14- α -demethylase), reduced access to the drug target, or some combination of these mechanisms.

Point mutations in the gene (*ERG11*) encoding for the target enzyme lead to an altered target with decreased affinity for azoles. Overexpression of *ERG11* results in the production of high concentrations of the target enzyme, creating the need for higher intracellular drug concentrations to inhibit all of the enzyme molecules in the cell.

The second major mechanism of drug resistance involves active efflux of fluconazole out of the cell through the activation of two types of multidrug efflux transporters; the major facilitators (encoded by *MDR* genes) and those of the ATP-binding cassette superfamily (encoded by *CDR* genes). Upregulation of the *MDR* gene leads to fluconazole resistance, whereas, upregulation of *CDR* genes may lead to resistance to multiple azoles.

Resistance in *Candida glabrata* usually includes upregulation of *CDR* genes resulting in resistance to multiple azoles. For an isolate where the MIC is categorized as Intermediate (16 to 32 $\mu\text{g}/\text{mL}$), the highest fluconazole dose is recommended.

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to DIFLUCAN (e.g., *Candida krusei*). Such cases may require alternative antifungal therapy.

2. A **REFERENCES** section was added to the package insert as follows:

REFERENCES

1. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Second Edition. CLSI Document M27-A2, 2002 Volume 22, No 15, CLSI, Wayne, PA, August 2002.
2. Clinical and Laboratory Standards Institute. Methods for Antifungal Disk Diffusion Susceptibility Testing of Yeasts; Approved Guideline. CLSI Document M44-A, 2004 Volume 24, No. 15 CLSI, Wayne, PA, May 2004.
3. Pfaller, M. A., Messer, S. A., Boyken, L., Rice, C., Tendolkar, S., Hollis, R. J., and Diekema, D. J. Use of Fluconazole as a Surrogate Marker To Predict Susceptibility and Resistance to Voriconazole among 13,338 Clinical Isolates of *Candida* spp. Tested by Clinical and Laboratory Standard Institute-Recommended Broth Microdilution Methods. 2007. Journal of Clinical Microbiology. 45:70–75.

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 19-949/S-041, NDA 19-950/S-043, NDA 20-090/S-022.”**

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
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/s/

Renata Albrecht
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