



NDA 19-949/S-030, S-032, S-035  
NDA 19-950/S-031, S-033, S-037  
NDA 20-090/S-012, S-014, S-017

Pfizer, Inc.  
Attention: Corinne Gamper  
Director, Worldwide Regulatory Strategy  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Dear Ms. Gamper:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act as follows:

Drug Product	NDA #	Supplement #	Date Submitted	Date Received
Diflucan® (fluconazole) Tablets, 150 mg	19-949	030	July 27, 2000	July 28, 2000
		032	February 28, 2001	March 1, 2001
		035	August 14, 2003	August 19, 2003
Diflucan® (fluconazole) Injection, 200	19-950	031	July 27, 2000	July 28, 2000
		033	February 28, 2001	March 1, 2001
		037	August 14, 2003	August 19, 2003
Diflucan® (fluconazole) Powder for Oral	20-090	012	July 27, 2000	July 28, 2000
		014	February 28, 2001	March 1, 2001
		017	August 14, 2003	August 19, 2003

We acknowledge receipt of your submissions to each NDA dated March 5, 2003.

Your submission of September 16, 2004 constituted a complete response to our February 5, 2003 action letter.

Your submission of July 20, 2004 constituted a complete response to our February 13, 2004 action letter.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are in ~~strikethrough~~):

**1. CLINICAL PHARMACOLOGY**

- A new **Pharmacokinetics in Elderly** subsection was added to read:

**Pharmacokinetics in Elderly**

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54 mcg/mL and occurred at 1.3 hours post dose. The mean AUC was 76.4+ 20.3 mcg-h/mL, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter

AUC or C<sub>max</sub>. In addition, creatinine clearance (74 mL/min), the percent of drug recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 mL/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared with the predicted half-life – creatinine clearance curve derived from normal subjects and subjects with varying degrees of renal insufficiency indicated that 21 of 22 subjects fell within the 95% confidence limit of the predicted half-life – creatinine clearance curves. These results are consistent with the hypothesis that higher values for the pharmacokinetic parameters observed in the elderly subjects compared with normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

- A third paragraph was added to the **Drug Interaction Studies, Oral Contraceptives** subsection to read:

A third study evaluated the potential interaction of once weekly dosing of fluconazole 300 mg to 21 normal females taking an oral contraceptive containing ethinyl estradiol and norethindrone. In this placebo-controlled, double-blind, randomized, two-way crossover study carried out over three cycles of oral contraceptive treatment, fluconazole dosing resulted in small increases in the mean AUCs of ethinyl estradiol and norethindrone compared to similar placebo dosing. The mean AUCs of ethinyl estradiol and norethindrone increased by 24% (95% C.I. range 18-31%) and 13% (95% C.I. range 8-18%), respectively relative to placebo. Fluconazole treatment did not cause a decrease in the ethinyl estradiol AUC of any individual subject in this study compared to placebo dosing. The individual AUC individual values of norethindrone decreased very slightly (<5%) in 3 of the 21 subjects after fluconazole treatment.

- The **Drug Interactions Studies, Cisapride** subsection was revised to read:

*Cisapride:*

~~A preliminary report from a placebo-controlled, randomized multiple-dose study in subjects given fluconazole 200 mg daily and cisapride 20 mg four times daily starting after 7 days of fluconazole dosing found that fluconazole significantly increased the AUC and C<sub>max</sub> of cisapride both after single (AUC 102% and C<sub>max</sub> 92% increases) and multiple (AUC 192% and C<sub>max</sub> 153% increases) dosing of cisapride. Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 5 days.~~

A placebo-controlled, randomized, multiple-dose study examined the potential interaction of fluconazole with cisapride. Two groups of 10 normal subjects were administered fluconazole 200 mg daily or placebo. Cisapride 20 mg four times daily was started after 7 days of fluconazole or placebo dosing. Following a single dose of fluconazole, there was a 101% increase in the cisapride AUC and a 91% increase in the cisapride C<sub>max</sub>. Following multiple doses of fluconazole, there was a 192% increase in the cisapride AUC and a 154% increase in the cisapride C<sub>max</sub>. Fluconazole significantly increased the QTc interval

in subjects receiving cisapride 20 mg four times daily for 5 days. (See **CONTRAINDICATIONS** and **PRECAUTIONS**.)

- A **Drug Interactions Studies**, *Midazolam* subsection was added to read:

*Midazolam*: The effect of fluconazole on the pharmacokinetics and pharmacodynamics of midazolam was examined in a randomized, cross-over study in 12 volunteers. In the study, subjects ingested placebo or 400 mg fluconazole on Day 1 followed by 200 mg daily from Day 2 to Day 6. In addition, a 7.5 mg dose of midazolam was orally ingested on the first day, 0.05 mg/kg was administered intravenously on the fourth day, and 7.5 mg orally on the sixth day. Fluconazole reduced the clearance of IV midazolam by 51%. On the first day of dosing, fluconazole increased the midazolam AUC and C<sub>max</sub> by 259% and 150%, respectively. On the sixth day of dosing, fluconazole increased the midazolam AUC and C<sub>max</sub> by 259% and 74%, respectively. The psychomotor effects of midazolam were significantly increased after oral administration of midazolam but not significantly affected following intravenous midazolam.

A second randomized, double-dummy, placebo-controlled, cross-over study in three phases was performed to determine the effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. In each phase the subjects were given oral fluconazole 400 mg and intravenous saline; oral placebo and intravenous fluconazole 400 mg; and oral placebo and IV saline. An oral dose of 7.5 mg of midazolam was ingested after fluconazole/placebo. The AUC and C<sub>max</sub> of midazolam were significantly higher after oral than IV administration of fluconazole. Oral fluconazole increased the midazolam AUC and C<sub>max</sub> by 272% and 129%, respectively. IV fluconazole increased the midazolam AUC and C<sub>max</sub> by 244% and 79%, respectively. Both oral and IV fluconazole increased the pharmacodynamic effects of midazolam. (See **PRECAUTIONS**.)

- A **Drug Interactions Studies**, *Azithromycin* subsection was added to read:

*Azithromycin*: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 800 mg oral dose of fluconazole on the pharmacokinetics of a single 1200 mg oral dose of azithromycin as well as the effects of azithromycin on the pharmacokinetics of fluconazole. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

## 2. PRECAUTIONS

- The following paragraphs were added to the beginning of the **General** subsection:

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Most of these reports involved seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

- “Short-acting benzodiazepines” was added to the list of **Drug Interactions**.
- The **Drug Interactions**, *Coumarin-type anticoagulants* subsection was revised to read:

*Coumarin-type anticoagulants:* Prothrombin time may be increased in patients receiving concomitant DIFLUCAN and coumarin-type anticoagulants. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

- The **Drug Interactions**, *Cisapride* subsection was revised to read:

*Cisapride:* There have been reports of cardiac events, including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. The combined use of fluconazole with cisapride is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

- A new **Drug Interactions**, *Short-acting Benzodiazepines* subsection was added to read:

*Short-acting Benzodiazepines:* Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If short-acting benzodiazepines, which are metabolized by the cytochrome P450 system, are concomitantly administered with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

- A new **Geriatric Use** subsection was added to read:

#### **Geriatric Use**

In non-AIDS patients, side effects possibly related to fluconazole treatment were reported in fewer patients aged 65 and older (9%, n=339) than for younger patients (14%, n=2240). However, there was no consistent difference between the older and younger patients with respect to individual side effects. Of the most frequently reported (>1%) side effects, rash, vomiting and diarrhea occurred in greater proportions of older patients. Similar proportions of older patients (2.4%) and younger patients (1.5%) discontinued fluconazole therapy

because of side effects. In post-marketing experience, spontaneous reports of anemia and acute renal failure were more frequent among patients 65 years of age or older than in those between 12 and 65 years of age. Because of the voluntary nature of the reports and the natural increase in the incidence of anemia and renal failure in the elderly, it is however not possible to establish a casual relationship to drug exposure.

Controlled clinical trials of fluconazole did not include sufficient numbers of patients aged 65 and older to evaluate whether they respond differently from younger patients in each indication. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Fluconazole is primarily cleared by renal excretion as unchanged drug. Because elderly patients are more likely to have decreased renal function, care should be taken to adjust dose based on creatinine clearance. It may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

### 3. ADVERSE REACTIONS

- The following sentence was deleted immediately before the *Hepatobiliary* subsection:

~~The following adverse events have occurred under conditions where a causal association is probable:~~

- A new **Post-Marketing Experience** header and the following sentence were added to read:

#### **Post-Marketing Experience**

In addition, the following adverse events have occurred during post-marketing experience.

- The **Post-Marketing Experience**, *Immunologic* subsection was revised to read:

*Immunologic:* In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.

- The following sentence was deleted following the **Post-Marketing Experience**, *Immunologic* subsection:

~~The following adverse events have occurred under conditions where a causal association is uncertain:~~

- A new **Post-Marketing Experience**, *Cardiovascular* subsection was added following the *Immunologic* subsection to read:

*Cardiovascular:* QT prolongation, torsades de pointes. (see PRECAUTIONS)

- Dizziness was added to the **Post-Marketing Experience**, *Central Nervous System* subsection to read:

*Central Nervous System:* Seizures, dizziness.

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#### 4. OVERDOSAGE

- The first sentence in this section was revised to read:

There ~~has been one reported case~~ have been reports of overdosage with DIFLUCAN (fluconazole).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon labeling text for the package insert submitted September 16, 2004 (enclosed).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 19-949/S-S-030, S-032, 035, NDA 19-950/S-031, S-033, S-037, NDA 20-090/S-012, S-014, S-017.**" Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, call Robin Anderson, R.N., M.B.A., Labeling Reviewer, 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

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/s/

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Renata Albrecht  
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