

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***  
**ANDA 76-837**

***Name:*** Fluconazole Injection, 2 mg/mL  
(in 0.9% Sodium Chloride Injection)

Packaged in 200 mg/100 mL and  
400 mg/200 mL single-dose flexible  
plastic containers

***Sponsor:*** SICOR Pharmaceuticals, Inc.

***Approval Date:*** January 13, 2005

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***  
**ANDA 76-837**

## CONTENTS

|  |
|--|
| <b>Reviews / Information Included in this Review</b> |
|--|

|                                  |          |
|----------------------------------|----------|
| <b>Approval Letter</b>           | <b>X</b> |
| <b>Tentative Approval Letter</b> |          |
| <b>Labeling</b>                  | <b>X</b> |
| <b>Labeling Reviews</b>          | <b>X</b> |
| <b>Medical Review(s)</b>         |          |
| <b>Chemistry Reviews</b>         | <b>X</b> |
| <b>Bioequivalence Review</b>     | <b>X</b> |
| <b>Statistical Review</b>        |          |
| <b>Microbiology Review</b>       | <b>X</b> |
| <b>Administrative Documents</b>  | <b>X</b> |
| <b>Correspondence</b>            | <b>X</b> |
|                                  |          |

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 76-837**

**APPROVAL LETTER**

ANDA 76-837

JAN 13 2005

SICOR Pharmaceuticals, Inc.  
Attention: Rosalie A. Lowe  
19 Hughes  
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 29, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection), packaged in 200 mg/100 mL and 400 mg/200 mL single-dose flexible plastic containers.

Reference is also made to your amendments dated July 14, August 17, August 27, October 19, and December 3, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diflucan<sup>®</sup> Injection, 2 mg/mL (in 0.9% Sodium Chloride) of Pfizer Central Research).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed

launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 1/13/05  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 76-837  
Division File  
Field Copy  
HFD-610/R. West  
HFD-205  
HFD-610/Orange Book Staff

\\CDSE\SUB PGDI\N76837\N-000\2004-10-19

Approved Electronic Labeling Located at: ~~XXXXXXXX~~

Endorsements:

HFD-640/Z. Getahun/ *Zellaka Getahun* 12/23/04  
HFD-643/R.Adams/ *RAF* 12/23/04  
HFD-617/T.Palat/12/20/04 *TPU* 12/27/04  
HFD-613/C.Park/ *Chad* 12/29/04  
HFD-613/L.Golson/ *L.Golson* 1/3/05

*CMC OK  
1/11/05 RCH*

*Robert West  
1/13/2005*

V:\FIRMSNZ\SICOR\LTRS&REV\76837.AP.DOC

F/T by rad12/22/04

APPROVAL

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**LABELING**

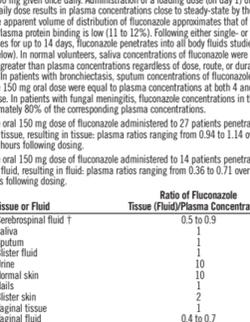
# Fluconazole Injection

## For Intravenous Infusion Only

### DESCRIPTION

Fluconazole, the first of a new subclass of synthetic triazole antifungal agents, is available as a sterile solution for intravenous use in glass containers and in plastic containers.

Fluconazole is designated chemically as 2-(4-difluoro-oxo-1,1-bis[1H-1,2,4-triazol-1-ylmethyl] benzyl alcohol with a molecular formula of  $C_{12}H_{12}F_4N_6O$  and molecular weight 366.3. The structural formula is:



Fluconazole is a white crystalline solid which is slightly soluble in water and saline. Fluconazole injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in sodium chloride diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride. The pH ranges from 4.0 to 8.0 in the sodium chloride diluent. Injection volumes of 100 mL and 200 mL are packaged in glass vials and plastic containers. The plastic container is composed of sterilizable medical grade film (Cryovac® M312 Pharmaceutical Solution Film). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the dose significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

### CLINICAL PHARMACOLOGY

#### Mode of Action

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha-demethylase. Mammalian cell demethylase is much less sensitive to fluconazole inhibition. Subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

#### Pharmacokinetics and Metabolism

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration.

Peak plasma concentrations ( $C_{max}$ ) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20 to 50 hours) after oral administration.

In fasted normal volunteers, administration of a single oral 400 mg dose of fluconazole leads to a mean  $C_{max}$  of 6.72 mcg/mL (range: 4.12 to 8.08 mcg/mL) and after single oral doses of 50 to 400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.

Administration of a single oral 150 mg tablet of fluconazole to ten lactating women resulted in a mean  $C_{max}$  of 2.61 mcg/mL (range: 1.57 to 3.65 mcg/mL).

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water since protein binding is low (11 to 12%). Following either single- or multiple-dose for up to 14 days, fluconazole penetrates into all body fluids studied (see table below). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchitis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the CSF are approximately 80% of the corresponding plasma concentrations.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue: plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid: plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

| Tissue or Fluid       | Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration* |
|-----------------------|---|
| Cerebrospinal fluid † | 0.5 to 0.9  |
| Saliva                | 1   |
| Serum                 | 1   |
| Blester fluid         | 1   |
| Urine                 | 10  |
| Normal skin           | 10  |
| Nails                 | 1   |
| Blester skin          | 2   |
| Vaginal tissue        | 1   |
| Vaginal fluid         | 0.4 to 0.7  |

\* Relative to concurrent concentrations in plasma in subjects with normal renal function. † Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of fluconazole may need to be reduced in patients with impaired renal function. (See **DOSE AND ADMINISTRATION**) A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

In normal volunteers, fluconazole administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the adrenocortical axis.

#### Pharmacokinetics in Children

In children, the following pharmacokinetic data (Mean (%CV)) have been reported:

| Age Studied       | Dose (mg/kg)             | Clearance (mL/min/kg) | Half-life (Hours) | $C_{max}$ (mcg/mL) | $V_{dss}$ (L/kg) |
|-------------------|--------------------------|-----------------------|-------------------|--------------------|------------------|
| 9 months-13 years | Single-Oral 2 mg/kg N=14 | 0.40 (38%)            | 25.0              | 2.9 (22%)          | —                |
| 9 months-13 years | Single-Oral 8 mg/kg N=15 | 0.51 (60%)            | 19.5              | 9.8 (20%)          | —                |
| 5-15 years        | Multiple IV 2 mg/kg N=4  | 0.49 (40%)            | 17.4              | 5.5 (25%)          | 0.722 (36%)      |
| 5-15 years        | Multiple IV 4 mg/kg N=5  | 0.59 (64%)            | 15.2              | 11.4 (44%)         | 0.729 (33%)      |
| 5-15 years        | Multiple IV 8 mg/kg N=7  | 0.66 (31%)            | 17.6              | 14.1 (22%)         | 1.069 (37%)      |

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 (17%) mL/min/kg.

In premature newborns (gestational age 26 to 29 weeks), the mean (%CV) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.219 (31%, N=5) mL/min/kg 6 days later and 0.53 (55%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

#### 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  $C_{max}$  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. Co-administration of diuretics did not significantly alter AUC or  $C_{max}$ . In addition, creatinine clearance (74 mL/min) the percent of drug recovered unchanged in urine (0-24 hr, 2%) 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.

#### Drug Interaction Studies

**Oral contraceptives:** Oral contraceptives were administered as a single oral dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of 50 mg of fluconazole. The mean increase in ethinyl estradiol AUC was 5% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

In a second study, twenty-five normal females received daily doses of both 200 mg fluconazole tablets or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 36% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.

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 25% (95% C.I. range 15-31%) and 15% (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.

**Cimetidine:** Fluconazole 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC.  $C_{max}$  There was a mean ± SD decrease in fluconazole AUC of 13% ± 11% (range: -3.4 to -31%) and  $C_{max}$  decreased 15% ± 14% (range: -5 to -40%). However, the dose interaction study demonstrated that fluconazole 100 mg administered over a four-hour period (one hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers.

**Antacid:** Administration of Maalox® (20 mL) to 14 normal male volunteers immediately prior to a single dose of fluconazole 100 mg had no effect on the absorption or elimination of fluconazole.

**Hydrochlorothiazide:** Concurrent oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and  $C_{max}$  compared to fluconazole given alone. There was a mean ± SD increase in fluconazole AUC and  $C_{max}$  of 45% ± 31% (range: 13 to 114%) and 43% ± 31% (range: 13 to 122%), respectively. These changes corresponded to a mean ± SD reduction in renal clearance of 30% ± 12% (range: -10 to -50%).

**Rifampin:** Administration of a single oral 200 mg dose of fluconazole after 15 days of rifampin administered as 600 mg daily in eight healthy male volunteers resulted in a significant decrease in fluconazole AUC and a significant increase in apparent oral clearance of fluconazole. There was a mean ± SD reduction in fluconazole AUC of 23% ± 9% (range: -13 to -42%). Apparent oral clearance of fluconazole increased 32% ± 17% (range: 16 to 72%). Fluconazole half-life decreased from 33.4 ± 4.4 hours to 26.8 ± 3.9 hours. (See **PRECAUTIONS**.)

**Warfarin:** There was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15 mg) administered to 13 normal male volunteers following oral fluconazole 200 mg administered daily for 14 days as compared to the administration of warfarin alone. There was a mean ± SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 4% (range: -2 to 13%). (See **PRECAUTIONS**.) Mean is based on data from 12 subjects as one of 13 subjects experienced a 2-fold increase in his prothrombin time response.

**Phenytoin:** Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days followed by 250 mg intravenously for one dose) both with and without the administration of oral fluconazole 200 mg daily for 16 days in 10 normal male volunteers. There was a significant increase in phenytoin AUC. The mean ± SD increase in phenytoin AUC was 85% ± 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear disposition of phenytoin. (See **PRECAUTIONS**.)

**Cyclosporine:** Cyclosporine AUC and  $C_{min}$  were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 5 weeks. There was a significant increase in cyclosporine AUC,  $C_{min}$ ,  $C_{24}$  (24-hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ± SD increase in AUC was 92% ± 43% (range: 18 to 147%). The  $C_{min}$  increased 60% ± 48% (range: -5 to 133%). The  $C_{24}$  increased 157% ± 95% (range: 31 to 302%). The apparent oral clearance decreased 45% ± 15% (range: -15 to -60%). (See **PRECAUTIONS**.)

**Zidovudine:** Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least two weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean ± SD increase in AUC was 20% ± 32% (range: -27 to 104%). The metabolite, ZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2.

**Theophylline:** The pharmacokinetics of theophylline were determined from a single intravenous dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC,  $C_{max}$ , and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range: -1 to 48%). The  $C_{max}$  increased 13% ± 17% (range: -15 to 46%). Theophylline clearance decreased 16% ± 11% (range: -32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours. (See **PRECAUTIONS**.)

**Terfenadine:** Six healthy volunteers received terfenadine 50 mg BID for 15 days. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 36% (range: 7 to 102%) from day 8 to day 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as measured by Holter QTc intervals. Another study at a 400-mg and 800-mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. (See **CONTRAINDICATIONS AND PRECAUTIONS**.)

**Oral hypoglycemics:** The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo-controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of fluconazole 100 mg daily for 7 days. In these three studies 22/46 (47.8%) of fluconazole treated patients and 9/22 (40.9%) of placebo treated patients experienced symptoms consistent with hypoglycemia. (See **PRECAUTIONS**.)

**Tolbutamide:** In 13 normal male volunteers, there was significant increase in tolbutamide (500 mg single dose) AUC and  $C_{max}$  following the administration of fluconazole. There was a mean ± SD increase in tolbutamide AUC of 28% ± 9% (range: 12 to 39%). Tolbutamide  $C_{max}$  increased 11% ± 9% (range: -6 to 27%). (See **PRECAUTIONS**.)

**Glipizide:** The AUC and  $C_{min}$  of glipizide (2.5 mg single dose) were significantly increased following the administration of fluconazole in 13 normal male volunteers. There was a mean ± SD increase in AUC of 49% ± 13% (range: 27 to 73%) and an increase in  $C_{min}$  of 19% ± 23% (range: -11 to 79%). (See **PRECAUTIONS**.)

**Glyburide:** The AUC and  $C_{min}$  of glyburide (5 mg single dose) were significantly increased following the administration of fluconazole in 20 normal male volunteers. There was a mean ± SD increase in AUC of 44% ± 25% (range: -13 to 115%) and  $C_{min}$  increased 19% ± 19% (range: -23 to 62%). Five subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration. (See **PRECAUTIONS**.)

**Rifabutin:** There have been published reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. (See **PRECAUTIONS**.)

**Tacrolimus:** There have been published reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. (See **PRECAUTIONS**.)

**Cisapride:** 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  $C_{max}$ . Following multiple doses of fluconazole, there was a 152% increase in the cisapride AUC and a 154% increase in the cisapride  $C_{max}$ . Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 7 days. (See **CONTRAINDICATIONS AND PRECAUTIONS**.)

**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  $C_{max}$  by 259% and 150%, respectively. On the sixth day of dosing, fluconazole increased the midazolam AUC and  $C_{max}$  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 treatment. The AUC and  $C_{max}$  of midazolam were significantly higher after oral than IV administration of fluconazole. Oral fluconazole increased the midazolam AUC and  $C_{max}$  by 272% and 129%, respectively. IV fluconazole increased the midazolam AUC and  $C_{max}$  by 244% and 79%, respectively. Both oral and IV fluconazole increased the pharmacodynamic effects of midazolam. (See **PRECAUTIONS**.)

**Azithromycin:** An open-label, randomized, three-way crossover study of 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.

### Microbiology

Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. 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 fumigatus* and *Aspergillus terreus* 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 severely 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 *C. neoformans*; and antagonism of the two drugs in systemic infection with *Asp. fumigatus*. The clinical significance of results obtained in these studies is unknown.

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

### INDICATIONS AND USAGE

Fluconazole injection is indicated for the treatment of:

- Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.
- Cryptococcal meningitis. Before prescribing fluconazole for AIDS patients with cryptococcal meningitis, please see **CLINICAL STUDIES**.

Studies comparing fluconazole to amphotericin B in non-HIV-infected patients have not been conducted.

**Prophylaxis:** Fluconazole is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

### CLINICAL STUDIES

**Cryptococcal meningitis:** In a multicenter study comparing fluconazole (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/mm<sup>3</sup>. Mortality among high risk patients was 33% and 40% for amphotericin B and fluconazole patients, respectively ( $p=0.50$ ), with overall death rates of 14% of 63 subjects and 15% (14 of 131 subjects) for the 2 arms of study (40/48).

Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined (Saag, *et al.* N Engl J Med 1992; 326: 83-9).

### Pediatric Studies

**Oropharyngeal candidiasis:** An open-label, comparative study of the efficacy and safety of fluconazole (2 to 3 mg/kg/day) and oral nystatin (400,000 IU, 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and microbiological response rates were higher in the children treated with fluconazole. Clinical cure at the end of treatment was reported for 86% of fluconazole treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.

|                          | Fluconazole | Nystatin    |
|--------------------------|-------------|-------------|
| Enrolled                 | 96          | 90          |
| Clinical Cure            | 76/88 (86%) | 36/78 (46%) |
| Mycological eradication* | 55/72 (76%) | 6/54 (11%)  |

\*Subjects without follow-up cultures for any reason were considered nonevaluable for mycological response.

The proportion of patients with clinical relapse 2 weeks after the end of treatment was 14% for subjects receiving fluconazole and 16% for subjects receiving nystatin. At 4 weeks after the end of treatment the percentages of patients with clinical relapse were 22% for fluconazole and 23% for nystatin.

### CONTRAINDICATIONS

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles. Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See **CLINICAL PHARMACOLOGY, Drug Interactions and PRECAUTIONS**.)

### WARNINGS

(1) **Hepatic injury:** Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.

Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.

- (2) Anaphylaxis. In rare cases, anaphylaxis has been reported.
- (3) Dermatologic. Patients have rarely developed exfoliative skin disorders during treatment with fluconazole. In patients with serious underlying diseases (predominantly AIDS and malignancy), these have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if rashes progress.

**PRECAUTIONS**

**General**

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.

**Drug Interactions**

See **CLINICAL PHARMACOLOGY, Drug Interaction Studies** and **CONTRAINDICATIONS**. Clinically or potentially significant drug interactions between fluconazole and the following agent/class(es) have been observed. These are described in greater detail below:

|                              |                              |
|------------------------------|------------------------------|
| Oral hypoglycemics           | Terfenadine                  |
| Coumarin-type anticoagulants | Cisapride                    |
| Phenytoin                    | Azolemole                    |
| Cyclosporine                 | Rifabutin                    |
| Rifampin                     | Tacrolimus                   |
| Theophylline                 | Short-acting benzodiazepines |

**Oral hypoglycemics:** Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Coumarin-type anticoagulants:** Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. In post-marketing experience, as with other azole antifungals, bleeding events (including 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 fluconazole and coumarin-type anticoagulants is recommended. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Phenytoin:** Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Cyclosporine:** Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Rifampin:** Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Theophylline:** Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving fluconazole and theophylline is recommended. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Terfenadine:** Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200-mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400-mg and 800-mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.) The coadministration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored.

**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**.)

**Azolemole:** The use of fluconazole in patients concurrently taking azolemole or other drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when coadministering fluconazole. Patients should be carefully monitored.

**Rifabutin:** There have been reports of rashes in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**Tacrolimus:** There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.)

**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**.)

Fluconazole tablets coadministered with ethinyl estradiol- and levonorgestrel-containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels, however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels. (See **CLINICAL PHARMACOLOGY, Drug Interaction Studies**.) The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Physicians should be aware that interaction studies with medications other than those listed in the **CLINICAL PHARMACOLOGY** section have not been conducted, but such interactions may occur.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2 to 7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in strains of *S. typhimurium* and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 mcg/ml) showed no evidence of chromosomal mutations. Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats, 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See **CLINICAL PHARMACOLOGY**.)

**Pregnancy**

**Teratogenic Effects. Pregnancy Category C:** Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25 and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels and abortions occurred at 75 mg/kg (approximately 20 to 60 times the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20 to 60 times the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 to 800 mg/day) fluconazole therapy for cryptococcosis (an unindicated use). The relationship between fluconazole use and these events is unclear. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

**Nursing Mothers**

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of fluconazole in nursing mothers is not recommended.

**Pediatric Use**

An open-label, randomized, controlled trial has shown fluconazole to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age. (See **CLINICAL STUDIES**.)

The use of fluconazole in children with cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children (see **CLINICAL PHARMACOLOGY**) have established a dose proportionality between children and adults. (See **DOSE AND ADMINISTRATION**.)

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 or 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 12 (71%) of the evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of fluconazole for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children. The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days. (See **ADVERSE REACTIONS**.)

Efficacy of fluconazole has not been established in infants less than 6 months of age. (See **CLINICAL PHARMACOLOGY**.) A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with fluconazole.

**Geriatric Use**

In non-AIDS patients, side effects possibly related to fluconazole treatment were reported in fewer patients aged 65 and older (9%, n=33) than for younger patients (14%, n=224). 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 causal 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 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 **DOSE AND ADMINISTRATION**.)

**ADVERSE REACTIONS**

**In Patients Receiving Multiple Doses for Other Infections Than Vaginal Candidiasis**  
Sixteen percent of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%). The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

**Hepatobiliary:** In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. (See **WARNINGS**.) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression or relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonamide hypoglycemic agents.

**Post-Marketing Experience**

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

- Immunologic:** In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.
- Cardiovascular:** QT prolongation, torsade de pointes. (See **PRECAUTIONS**.)
- Central Nervous System:** Seizures, dizziness.

**Dermatologic:** Exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see **WARNINGS**), alopecia.

**Hematopoietic and Lymphatic:** Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

**Metabolic:** Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

**Gastrointestinal:** Dyspepsia, vomiting.

**Other Senses:** Taste perversion.

**Adverse Reactions in Children**

In Phase I/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatment related adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment related laboratory test abnormalities were elevations of transaminases or alkaline phosphatase.

| Percentage of Patients With Treatment-Related Side Effects |                     |                            |
|--|---------------------|----------------------------|
|  | Fluconazole (N=577) | Comparative Agents (N=451) |
| With any side effect                                       | 13.0                | 9.3                        |
| Vomiting   | 5.4                 | 5.1                        |
| Abdominal pain   | 2.8                 | 1.6                        |
| Nausea   | 2.3                 | 1.6                        |
| Diarrhea   | 2.1                 | 2.2                        |

**OVERDOSAGE**

There have been reports of overdose with fluconazole. A 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours without sequelae. In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted. Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis; death was sometimes preceded by tonic convulsions.

**DOSE AND ADMINISTRATION**

**Dosage and Administration in Adults**  
SINCE ORAL ADMINISTRATION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy. The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until patients with parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

**Oropharyngeal candidiasis:** The recommended dosage of fluconazole for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

**Esophageal candidiasis:** The recommended dosage of fluconazole for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

**Systemic Candida infections:** For systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

**Urinary tract infections and peritonitis:** For the treatment of *Candida* urinary tract infections and peritonitis, daily doses of 50 to 200 mg have been used in open, noncomparative studies of small numbers of patients.

**Cryptococcal meningitis:** The recommended dosage of fluconazole for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of fluconazole for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

**Prophylaxis in patients undergoing bone marrow transplantation:** The recommended fluconazole daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per cu mm.

**Dosage and Administration in Children**

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

|                           |               |
|---------------------------|---------------|
| <b>Pediatric Patients</b> | <b>Adults</b> |
| 3 mg/kg                   | 100 mg        |
| 6 mg/kg                   | 200 mg        |
| 12 mg/kg                  | 400 mg        |

Some older children may have clearances similar to that of adults. Absolute doses exceeding 500 mg/day are not recommended.

Experience with fluconazole in neonates is limited by pharmacokinetic studies in premature newborns. (See **CLINICAL PHARMACOLOGY**.) Based on the prolonged half-life seen in premature newborns (gestational age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first two weeks, these children should be dosed once daily. No information regarding fluconazole pharmacokinetics in full-term newborns is available.

**Oropharyngeal candidiasis:** The recommended dosage of fluconazole for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

**Esophageal candidiasis:** For the treatment of esophageal candidiasis, the recommended dosage of fluconazole in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.

**Systemic Candida infections:** For the treatment of candidemia and disseminated *Candida* infections, daily doses of 6 to 12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

**Cryptococcal meningitis:** For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of fluconazole is 6 mg/kg once daily.

**Dosage in Patients With Impaired Renal Function**

Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose should be indicated should be based on the following table:

| Creatinine Clearance (mL/min) | Percent of Recommended Dose |
|-------------------------------|-----------------------------|
| >50 (no dialysis)             | 100%                        |
| 25-50 (on dialysis)           | 50%                         |
| Regular dialysis              | 100% after each dialysis    |

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

$$\text{Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

For females, 0.85 x above value

Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The following formula may be used to estimate creatinine clearance in children:

$$\text{K} \times \frac{\text{linear length or height (cm)}}{\text{serum creatinine (mg/100 mL)}}$$

(Where K=0.55 for children older than 1 year and 0.45 for infants.)

**Minimum Infection Dose**

Fluconazole injection may be administered by intravenous infusion. Fluconazole injection has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of fluconazole should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

Fluconazole injections in glass vials and plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if the solution is cloudy or precipitated or if the seal is not intact.

**Directions for IV Use of Fluconazole Injection in Plastic Containers**

Do not remove fluid from overwrap until ready for use. The inner bag maintains the sterility of the product.

**CAUTION:** Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

**To Open**

Tear overwrap at the silt and remove solution container. Some spiciness of the plastic due to moisture and sterilization process may be observed. This is not harmful. If the seal is not intact, do not use. The solution is cloudy or precipitated or if the seal is not intact. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

**DO NOT ADD SUPPLEMENTARY MEDICATION.**

**HOW SUPPLIED**

Fluconazole injection for intravenous infusion administration are formulated as sterile solution in iso-osmotic sodium chloride diluent containing 2 mg/mL of fluconazole. They are supplied in glass vials and plastic containers containing volumes of 100 mL and 200 mL affording doses of 200 mg and 400 mg of fluconazole, respectively.

| NDC Number   | Contents | Package Size                                       |
|--------------|----------|--|
| 0703-1019-09 | 200 mg   | 100 mL glass vial packaged 6 per shelf pack        |
| 0703-1010-09 | 400 mg   | 200 mL glass vial packaged 6 per shelf pack        |
| 0703-1020-30 | 200 mg   | 100 mL plastic container packaged 6 per shelf pack |
| 0703-1020-30 | 400 mg   | 200 mL plastic container packaged 6 per shelf pack |

**Glass Vial Storage:** Store between 5° to 30°C (41° to 86°F). Protect from freezing.

**Plastic Container Storage:** Store between 5° to 25°C (41° to 77°F). Protect from freezing. Brief exposure up to 40°C (104°F) does not adversely affect the product.

Maxalt® is a registered trademark of Novartis Consumer Health, Inc.



SICOR Pharmaceuticals, Inc.  
Irvine, CA 92618

100 mL

By only

Each 100 mL contains: 200 mg of fluconazole and 900 mg of sodium chloride, USP in water for injection, USP.

NDC 0703-1029-31

**Fluconazole  
Injection**

Iso-Osmotic SODIUM  
CHLORIDE Diluent

**200 mg**  
(2 mg/mL)

Osmolarity is 315 mOsm/L (calc).

**Usual Dosage:** See Package Insert.

**CAUTIONS:** Do not add supplementary medication. Must not be used in series connections. Do not use unless solution is clear.

Single Dose Container

Sterile Nonpyrogenic

FOR INTRAVENOUS  
INFUSION ONLY

**STORAGE:** STORE UNITS IN OVERWRAP BETWEEN 5° TO 25°C (41° TO 77°F) UNTIL READY TO USE. AVOID EXCESSIVE HEAT. PROTECT FROM FREEZING.

**APPROVED**

**sicor™**

SICOR Pharmaceuticals, Inc.  
Irvine, CA 92618

**JAN 13 2005**

102001

200 mL

R<sub>x</sub>only

NDC 0703-1020-31

# Fluconazole Injection

Iso-Osmotic SODIUM  
CHLORIDE Diluent

**400 mg**  
(2 mg/mL)

Single Dose Container

Sterile Nonpyrogenic

FOR INTRAVENOUS  
INFUSION ONLY

**sicor**<sup>TM</sup>

SICOR Pharmaceuticals, Inc.  
Irvine, CA 92618

104001

Each 200 mL contains: 400 mg of  
fluconazole and 1.8 g of sodium  
chloride, USP in water for injection,  
USP.

Osmolarity is 315 mOsmol/L (calc).

**Usual Dosage:** See Package Insert.

**CAUTIONS:** Do not add supplementary  
medication. Must not be used in series  
connections. Do not use unless solution  
is clear.

**STORAGE:** STORE UNITS IN OVERWRAP  
BETWEEN 5° TO 25°C (41° TO 77°F)  
UNTIL READY TO USE. AVOID EXCESSIVE  
HEAT. PROTECT FROM FREEZING.

**APPROVED**

**JAN 13 2005**

**SICOR Pharmaceuticals, Inc.**  
**FLUCONAZOLE INJECTION**  
**ANDA 76-837**

**Response to Deficiency Letter of July 14, 2004**

**SHELFPACK LABEL**  
**200 mg**

**CAUTIONS:** Squeeze and inspect inner container which maintains product sterility. Discard if leaks are found. Do not add supplementary medication. Must not be used in series connections. Do not use unless solution is clear.

**STORAGE:** STORE UNITS IN OVERWRAP BETWEEN 5° TO 25°C (41° TO 77°F) UNTIL READY TO USE. AVOID EXCESSIVE HEAT.

**PROTECT FROM FREEZING.**

**Fluconazole Injection**  
Iso-Osmotic SODIUM CHLORIDE Diluent  
**200 mg (2 mg/mL)**

**Each 100 mL contains 200 mg of fluconazole and 900 mg of sodium chloride, USP in water for injection, USP.**

Osmolarity is 315 mOsmol/L (calc).

**Usual Dosage:** See Package Insert.

**APPROVED** <sup>80358A</sup>

JAN 13 2005

**sicor™**  
SICOR Pharmaceuticals, Inc.  
Irvine, CA 92618

NDC 0703-1029-30

only

Sterile Nonpyrogenic  
**6 Single-dose plastic containers x 100 mL**

  
3 07031 02930 8

SHELFPAK LABEL  
400 mg

**CAUTIONS:** Squeeze and inspect inner container which maintains product sterility. Discard if leaks are found. Do not add supplementary medication. Must not be used in series connections. Do not use unless solution is clear.

**STORAGE:** STORE UNITS IN OVERWRAP BETWEEN 5° TO 25°C (41° TO 77°F) UNTIL READY TO USE. AVOID EXCESSIVE HEAT.

**PROTECT FROM FREEZING.**

**Fluconazole Injection**  
Iso-Osmotic SODIUM CHLORIDE Diluent

NDC 0703-1020-30 Rx only

**400 mg**  
(2 mg/mL)

Sterile Nonpyrogenic  
**6 Single-dose plastic containers x 200 mL**

Each 200 mL contains 400 mg of fluconazole and 1.8 g of sodium chloride, USP in water for injection, USP.

Osmolarity is 315 mOsmol/L (calc).

**Usual Dosage:** See Package Insert.

00259A  
**APPROVED**

**EXP. 13 2005**

**sicor™**  
SICOR Pharmaceuticals, Inc.  
Irvine, CA 92618

N 3 07031 02030 5

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**LABELING REVIEWS**

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

---

ANDA Number: 76-837

Date of Submission: August 29, 2003

Applicant's Name: Sicor Pharmaceuticals, Inc.

Established Name: Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection)

1. GENERAL

Delete the term  in association with "Plastic Container" from the labels and labeling.

2. CONTAINER - 200 mg/100 mL & 400 mg/200 mL

- a. We encourage you to differentiate your drug product strengths (200 mg & 400 mg) by using boxing, contrasting colors, and/or some other means.
- b. Include the total volume (*i.e.*, 100 ml or 200 mL), preferably at the upper left corner of the container labels.
- c. Include the text "FOR INTRAVENOUS INFUSION ONLY", preferably beneath the text "Sterile Nonpyrogenic".
- d. Revise to read "CAUTIONS: ..." [plural]
- e. Increase the prominence of the term "Rx Only".
- f. Revise your storage temperature statement to be the same as the one proposed for your Shelf Pack Label.
- g. We note that you included information regarding your unapproved drug product in glass vial (ANDA 76-653) throughout the insert labeling. Please note that ANDA 76-653 must be approved prior to the approval of this application or these applications must be approved at the same time. Otherwise, further revisions will be necessary prior to approval of this application.

3. OVERWRAP

We note that you did not submit overwrap labeling. Please submit and/or comment.

4. SHELF PACK CARTON

- a. See comments 1(d) & 1(g) above.
- b. Revise the net quantity statement to read "6 Single-dose plastic containers x 100 mL (or 200 mL)".

5. INSERT

a. General

Delete the term  in association with "plastic containers" throughout the insert labeling.

b. TITLE

We encourage the inclusion of the text "For Intravenous Infusion Only" beneath the established name.

c. DESCRIPTION

i. Second paragraph:

"molecular formula" rather than \_\_\_\_\_ formula"

ii. Include information specific to your proposed plastic container as the last paragraph and/or comment. We refer you to the innovator's labeling in this regard.

d. CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism

Delete the last sentence of the first paragraph.

e. ADVERSE REACTIONS - In Patients Receiving Multiple Doses for other infections:

Revise this subsection heading to read "In Patients Receiving Multiple Doses for Other Than Vaginal Candidiasis".

f. DOSAGE AND ADMINISTRATION (Second paragraph, first sentence) - Revise to read:

The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis should be...

g. HOW SUPPLIED

i. First sentence - Revise to read:

...as sterile solution in Iso-osmotic Sodium Chloride Diluent containing...

ii. See comment 1(g) above.

iii. ...mL glass vial packaged... [add "glass"]

iv. ...mL plastic container packaged... ["plastic container" rather than \_\_\_\_ ]

v. Revise "\_\_\_\_\_" to read "200 mL"

vi. Revise to read "Glass Vial Storage:". [add "Glass"]

vii. Revise to read "Plastic Container Storage:". [delete \_\_\_\_\_]

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "W. Peter Rickman", written over a horizontal line.

William Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

**FOR THE RECORD:**

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-034 approved 8/7/02 is specifically related to the approval of PPI for the 150 mg tablets.
2. This drug product is **not** the subject of a USP monograph
3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1054 (Volume 1.1).
4. Patent Data

| App No. | Prod No. | Patent No.  | Patent Expiration | Drug Substance Claim | Drug Product Claim | Use Code |
|---------|----------|-------------|-------------------|----------------------|--------------------|----------|
| 019950  | 001      | 4404216     | JAN 29,2004       |                      |                    |          |
| 019950  | 001      | 4404216*PED | JUL 29,2004       |                      |                    |          |

**Exclusivity Data**

There is no unexpired exclusivity for this product.

The sponsor has filed Patent Certification III.

**5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

Plastic container - RLD - Store between 77oF (25oC) and 41oF (5oC). Brief exposure up to 104oF (40oC) does not adversely affect this product. Protect from freezing. Avoid excessive heat.

ANDA: Same as the RLD.

Glass vial - Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

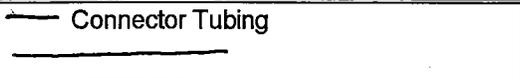
**6. PACKAGING CONFIGURATIONS**

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)  
 ANDA – 200 mg/100 mL & 200 mg/200 mL (in both plastic container and glass vial in Sodium Chloride ) However, see comment 1(g) above.

**7. CONTAINER/CLOSURE -** The following is from the chemist's review. There is no information submitted on the glass vial.

The summary of Container Closure System (CCS) for Fluconazole Infusion bags for Lot #s: X03C501 and X03C501F1 (100 mL and 200 mL Fill Bags):

| Component | Description   | Certificate of Compliance |
|-----------|---|---------------------------|
| Container | MC312 Infusion bag 100 mL bag/ 250 mL bag<br>Cryovac Sealed Corp. | p. 2025                   |
| Port      |   | p. 2121                   |

|              |  |         |
|--------------|--|---------|
| Tubing       | <br>Connector Tubing  | p. 2161 |
| Labeling Ink | The ink is applied  it does not come in contact with the drug product |         |
| Over wrap    | This is secondary packaging; it is not intended to be a sterility or moisture barrier  |         |

The results for USP systemic toxicity study for the CCS are on pp. 2026 – 2046. The USP <661> test results are on pp. 2049 -2052. The container meets the JPXIII test for resistance to water vapor permeation. (p. 2055).

The Certificate of Compliance for the Spike Ports and for the Connector Tubing state that the extracts from each meet the requirements of a USP Plastic Class VI. The details of the biological, physicochemical and toxicology tests methods and results are provided (pp. 2122 – 2159, pp. 2162 - 2190).

**8. The following was determined at the time of ANDA 76-087 in the past.**

**The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads “The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration.” Also, the D&A section reads that “Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. The majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for “Vaginal Candidiasis” only. Therefore, we will have the generic sponsors silent on all information specifically associated with “Vaginal Candidiasis”**

9. The proposed labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.
10. The following e-mail was sent to PM in the new drug division on 1/24/02 and answer form the division on 1/29/02. (See file folder for detail)

**Question:**

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal candidiasis. We have a generic application for the injection only. Would you please let us know that fluconazole injection is also indicated for these symptoms. If only oral suspension is indicated for the treatment of these, then we have to direct the generic sponsor to carve out the information associated with these from the insert labeling. Your help would be appreciated. Thanks,

Chan

**Answer:**

As far as I can tell all three formulations are indicated for OPC and EC. I am not aware of any reasons barring applicants from applying separately for those indications using each formulation.

Imo (Ibia, Ekopino)

11. The review for the container labels and overwrap was done using RLD labeling for the same packaging configuration. **It appears that the RLD labeling for the glass bottle and plastic bags are not identical to each other.**
12. This drug product is manufactured by Sicor Pharmaceutical, Inc. (p.1103, vol.1.2)

---

Date of Review: 2/18/04

Date of Submission: 8/29/03

Primary Reviewer: Chan Park

Date:

3/3/04

Team Leader:

Date:

3/3/04

---

cc:

ANDA: 76-837

DUP/DIVISION FILE

HFD-613/Cpark/LGolson (no cc)

V:\FIRMS\NZ\SICOR\LTRS&REV\76837na1.LABELING.doc

Review

APPEARS THIS WAY  
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

---

ANDA Number: 76-837

Date of Submission: July 14, 2004

Applicant's Name: Sicor Pharmaceuticals, Inc.

Established Name: Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection)

1. GENERAL

We note that you included information regarding your unapproved drug product in a glass vial (ANDA 76-653) throughout the insert labeling. Please note that ANDA 76-653 must be approved prior to the approval of this application or these applications must be approved at the same time. Otherwise, further revisions will be necessary prior to approval of this application.

2. CONTAINER - 200 mg/100 mL & 400 mg/200 mL

Add the statement "Protect from freezing." to the storage temperature statement and/or comment.

3. OVERWRAP

We acknowledge that you will employ clear overwrap without text. Please verify that your proposed overwrap is sufficiently clear so that all text appearing on the containers is sufficiently legible through the overwrap. Please comment.

4. INSERT

a. DESCRIPTION:

As discussed between Chan Park of the Agency and Sonya Hernandez of your firm via a tele-conference on July 20, 2004, the following statement specific to your container system should be found acceptable based on your response to the chemistry deficiencies regarding this issue. We defer the comment pending review of your chemistry response.

*The plastic container is composed of sterilizable medical grade film. (Cryovac M312 Pharmaceutical Solution Film). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.*

b. HOW SUPPLIED

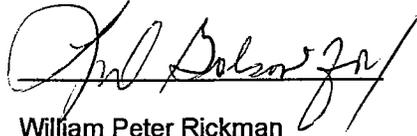
See GENERAL COMMENT above.

Please revise your labels and labeling, as instructed above. Please note that the electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. (Refer to Final Rule [Docket No. 2000N-1652] <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-30641.htm>). To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



William Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

**QUESTIONS/NOTES TO THE CHEMIST - The following e-mail was sent to the chemist on 7/20/04. Also refer to the comment under insert above.**

Hi Zelleka,

Please do me a favor. The sponsor included the following language in the insert labeling regarding their container. I was informed that they do not have other approved applications which used the same packaging and the same language in the labeling. Please review the language to see this is accurate and acceptable in terms of chemistry view point. Thank you for your help,

Chan

The plastic container is composed of sterilizable medical grade film. (Cryovac M312 Pharmaceutical Solution Film). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

---

**FOR THE RECORD:**

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.
2. This drug product is **not** the subject of a USP monograph.
3. SHELF PACK CARTON - Satisfactory in FPL as of 7/14/04 submission (vol. 2.1)
4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1054 (Volume1.1).
5. Patent Data

| App'l No. | Prod No. | Patent No.  | Patent Expiration | Drug Substance Claim | Drug Product Claim | Use Code |
|-----------|----------|-------------|-------------------|----------------------|--------------------|----------|
| 019950    | 001      | 4404216     | JAN 29,2004       |                      |                    |          |
| 019950    | 001      | 4404216*PED | JUL 29,2004       |                      |                    |          |

---

**Exclusivity Data**

There is no unexpired exclusivity for this product.

The sponsor has filed Patent Certification III.

**6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

Plastic container - RLD - Store between 77oF (25oC) and 41oF (5oC). Brief exposure up to 104oF (40oC) does not adversely affect this product. Protect from freezing. Avoid excessive heat.

ANDA: Same as the RLD.

Glass vial - Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)  
 ANDA – 200 mg/100 mL & 200 mg/200 mL (in both plastic container and glass vial in Sodium Chloride ) However, see GENERAL COMMENT above.

8. CONTAINER/CLOSURE - The following is from the chemist's review. There is no information submitted on the glass vial.

The summary of Container Closure System (CCS) for Fluconazole Infusion bags for Lot #s: X03C501 and X03C501F1 (100 mL and 200 mL Fill Bags):

| Component    | Description   | Certificate of Compliance |
|--------------|---|---------------------------|
| Container    | MC312 Infusion bag 100 mL bag/ 250 mL bag<br>Cryovac Sealed Corp.                     | p. 2025                   |
| Port         | _____   | p. 2121                   |
| Tubing       | _____ Connector Tubing  | p. 2161                   |
| Labeling Ink | The ink is applied _____ it does not come in contact with the drug product            |                           |
| Over wrap    | This is secondary packaging; it is not intended to be a sterility or moisture barrier |                           |

The results for USP systemic toxicity study for the CCS are on pp. 2026 – 2046. The USP <661> test results are on pp. 2049 -2052. The container meets the JPXIII test for resistance to water vapor permeation. (p. 2055).

The Certificate of Compliance for the Spike Ports and for the Connector Tubing state that the extracts from each meet the requirements of a USP Plastic Class VI. The details of the biological, physicochemical and toxicology tests methods and results are provided (pp. 2122 – 2159, pp. 2162 - 2190).

9. The following was determined at the time of ANDA 76-087 in the past.

**The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." Also, the D&A section reads that "Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. The majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will have the generic sponsors silent on all information specifically associated with "Vaginal Candidiasis"**

10. The proposed labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

11. The following e-mail was sent to PM in the new drug division on 1/24/02 and answer from the division on 1/29/02. (See file folder for detail)

**Question:**

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal candidiasis. We have a generic application for the **injection** only. Would you please let us know that fluconazole injection is also indicated for these symptoms. If only oral suspension is indicated for the treatment of these, then we

have to direct the generic sponsor to carve out the information associated with these from the insert labeling. Your help would be appreciated. Thanks,

Chan

**Answer:**

As far as I can tell all three formulations are indicated for OPC and EC. I am not aware of any reasons barring applicants from applying separately for those indications using each formulation.

lmo (Ibia, Ekopino)

11. The review for the container labels and overwrap was done using RLD labeling for the same packaging configuration. **It appears that the RLD labeling for the glass bottle and plastic bags are not identical to each other.**
12. This drug product is manufactured by Sicor Pharmaceutical, Inc. (p.1103, vol.1.2)

---

Date of Review: 7/20/04

Date of Submission: 7/14/04

Primary Reviewer: Chan Park

Date:

*Chan*  
7/28/04

Team Leader:

Date:

*Jul Sue*

7/30/04

---

cc:

ANDA: 76-837  
DUP/DIVISION FILE  
HFD-613/Cpark/LGolson (no cc)  
V:\FIRMSNZ\SICOR\LTRS&REV\76837na2.LABELING.doc  
Review

**APPEARS THIS WAY  
ON ORIGINAL**

*This AP Summary is superseded by  
the AP Summary #2 prepared on 4/19/04.*

(APPROVAL SUMMARY)  
**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

---

ANDA Number: 76-837

Date of Submission: August 27, 2004

Applicant's Name: Sicor Pharmaceuticals, Inc.

Established Name: Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection)

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

**CONTAINER LABELS - 200 mg/100 mL & 400 mg/200 mL**

Satisfactory in FPL as of 8/27/04 submission (vol. 3.1)

**SHELFPACK LABEL - 6 x 100 mL or 6 x 200 mL**

Satisfactory in FPL as of 8/27/04 submission (vol. 3.1)

**OVERWRAP POUCH**

The sponsor proposed a clear pouch. Pouch is clear enough so that the text on the labels is sufficiently legible per the sponsor's statement submitted 8/27/04.

**PROFESSIONAL PACKAGE INSERT LABELING**

Satisfactory in FPL as of 8/27/04 submission (vol. 3.1, Rev. March 2004)

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan® Injection

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

PI - 19-950/S-028, approved February 22, 1999

PPI - 19-950/S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.

Has this been verified by the MIS system for the NDA?

Yes

Was this approval based upon an OGD labeling guidance? No

**QUESTIONS/NOTES TO THE CHEMIST - The following e-mail was to/from the chemist on the packaging material.**

**Question - Hi Zelleka,**

Please do me a favor. The sponsor included the following language in the insert labeling regarding their container. I was informed that they do not have other approved applications which used the same packaging and the same language in the labeling. Please review the language to see this is accurate and acceptable in terms of chemistry view point. Thank you for your help, Chan

The plastic container is composed of sterilizable medical grade film. (Cryovac M312 Pharmaceutical Solution Film). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

**Answer from the chemist:**

I read the statement that you e-mailed, and I think that it is fine, as long as the RLD also uses the same Cryovac M312 Pharmaceutical Solution Film. I have seen such a statement on an innovator's label. Although the statement is vague and does not spell out exactly how much water or what chemicals leach out of the container. I believe if something is good enough for the RLD it is fine for the ANDA. Please let me know if I may be of further help.  
Zelleka

---

**FOR THE RECORD:**

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.
2. The sponsor proposed a combined package insert labeling with ANDA 76-653 (Fluconazole injection in glass vial). 76-653 has been approved on July 29, 2004.
3. Pertaining the description of plastic container used for this drug product, please refer to the answer from the chemist above. The sponsor's description appears accurate per the chemist.
4. This drug product is **not** the subject of a USP monograph.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1054 (Volume 1.1).
6. Patent Data/Exclusivities  
None
7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON  
Plastic container - RLD - Store between 77oF (25oC) and 41oF (5oC). Brief exposure up to 104oF (40oC) does not adversely affect this product. Protect from freezing.  
Avoid excessive heat.

ANDA: Same as the RLD.

Glass vial - Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from

freezing.

8. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)  
ANDA – 200 mg/100 mL & 200 mg/200 mL (in both plastic container and glass vial in Sodium Chloride)

9. CONTAINER/CLOSURE - The following is from the chemist's review.

The summary of Container Closure System (CCS) for Fluconazole Infusion bags for Lot #s: X03C501 and X03C501F1 (100 mL and 200 mL Fill Bags):

| Component    | Description   | Certificate of Compliance |
|--------------|---|---------------------------|
| Container    | MC312 Infusion bag 100 mL bag/ 250 mL bag<br>Cryovac Sealed Corp.                     | p. 2025                   |
| Port         | _____   | p. 2121                   |
| Tubing       | _____ Connector Tubing  | p. 2161                   |
| Labeling Ink | The ink is applied _____ it does not come in contact with the drug product            |                           |
| Over wrap    | This is secondary packaging; it is not intended to be a sterility or moisture barrier |                           |

The results for USP systemic toxicity study for the CCS are on pp. 2026 – 2046. The USP <661> test results are on pp. 2049 -2052. The container meets the JPXIII test for resistance to water vapor permeation. (p. 2055).

The Certificate of Compliance for the Spike Ports and for the Connector Tubing state that the extracts from each meet the requirements of a USP Plastic Class VI. The details of the biological, physicochemical and toxicology tests methods and results are provided (pp. 2122 – 2159, pp. 2162 - 2190).

10. The following was determined at the time of ANDA 76-087 in the past.

The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." Also, the D&A section reads that "Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. The majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will have the generic sponsors silent on all information specifically associated with "Vaginal Candidiasis"

11. The proposed labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

12. The following e-mail was sent to PM in the new drug division on 1/24/02 and answer form the division on 1/29/02. (See file folder for detail)

**Question:**

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal candidiasis. We have a generic application for the **injection** only. Would you please let us know that fluconazole injection is also indicated for these symptoms. If only oral suspension is indicated for the treatment of these, then we

have to direct the generic sponsor to carve out the information associated with these from the insert labeling. Your help would be appreciated. Thanks,

Chan

**Answer:**

As far as I can tell all three formulations are indicated for OPC and EC. I am not aware of any reasons barring applicants from applying separately for those indications using each formulation.

Imo (Ibia, Ekopino)

13. The review for the container labels and shelfpack labels was done using RLD labeling for the same packaging configuration. **It appears that the RLD labeling for the glass bottle and plastic bags are not identical to each other.**
14. This drug product is manufactured by Sicor Pharmaceutical, Inc. (p.1103, vol.1.2)

---

**Date of Review:** 9/27/04

**Date of Submission:** 8/27/04

**Primary Reviewer:** Chan Park

**Date:**

9/30/04

**Team Leader:**

**Date:**

9/30/04

---

cc:

ANDA: 76-837  
DUP/DIVISION FILE  
HFD-613/Cpark/LGolson (no cc)  
V:\FIRMSNZ\SICOR\LTRS&REV\76837AP.LABELING.doc  
Review

**APPEARS THIS WAY  
ON ORIGINAL**

This AP summary#2 supersedes the AP summary prepared 9/27/04  
(APPROVAL SUMMARY #2)  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

---

ANDA Number: 76-837

Date of Submission: October 19, 2004

Applicant's Name: Sicor Pharmaceuticals, Inc.

Established Name: Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection)

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

**CONTAINER LABELS - 200 mg/100 mL & 400 mg/200 mL**

Satisfactory in FPL as of 8/27/04 submission (vol. 3.1)

**SHELFPACK LABEL - 6 x 100 mL or 6 x 200 mL**

Satisfactory in FPL as of 8/27/04 submission (vol. 3.1)

**OVERWRAP POUCH**

The sponsor proposed a clear pouch. Pouch is clear enough so that the text on the labels is sufficiently legible per the sponsor's statement submitted 8/27/04.

**PROFESSIONAL PACKAGE INSERT LABELING**

Satisfactory in FPL as of 10/19/04 submission (vol. 4.1, Rev. October, 2004)

\\CDSESUBPGD1\N76837\N\_000\2004-10-19

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan® Injection

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

PI - 19-950/S-031, 033, & 037, approved October 7, 2004

PPI - 19-950/S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.

Has this been verified by the MIS system for the NDA?

Yes

Was this approval based upon an OGD labeling guidance? No

**QUESTIONS/NOTES TO THE CHEMIST - The following e-mail was to/from the chemist on the packaging material.**

**Question - Hi Zelleka,**

Please do me a favor. The sponsor included the following language in the insert labeling regarding their container. I was informed that they do not have other approved applications which used the same packaging and the same language in the labeling. Please review the language to see this is accurate and acceptable in terms of chemistry view point. Thank you for your help, Chan

The plastic container is composed of sterilizable medical grade film. (Cryovac M312 Pharmaceutical Solution Film). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

**Answer from the chemist:**

I read the statement that you e-mailed, and I think that it is fine, as long as the RLD also uses the same Cryovac M312 Pharmaceutical Solution Film. I have seen such a statement on an innovator's label. Although the statement is vague and does not spell out exactly how much water or what chemicals leach out of the container. I believe if something is good enough for the RLD it is fine for the ANDA. Please let me know if I may be of further help.  
Zelleka

---

**FOR THE RECORD:**

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-31, 33, & 37) labeling approved October 7, 2004. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.
2. The sponsor proposed a combined package insert labeling with ANDA 76-653 (Fluconazole injection in glass vial). 76-653 has been approved on July 29, 2004.
3. Pertaining the description of plastic container used for this drug product, please refer to the answer from the chemist above. The sponsor's description appears accurate per the chemist.
4. This drug product is **not** the subject of a USP monograph.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1054 (Volume 1.1).
6. Patent Data/Exclusivities  
None
7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Plastic container - RLD - Store between 77oF (25oC) and 41oF (5oC). Brief exposure up to 104oF (40oC) does not adversely affect this product. Protect from freezing.  
Avoid excessive heat.

ANDA: Same as the RLD.

Glass vial - Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

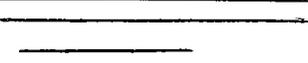
*Still current as of 12/29/04*  
*Chan*

8. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)  
 ANDA – 200 mg/100 mL & 200 mg/200 mL (in both plastic container and glass vial in Sodium Chloride)

9. CONTAINER/CLOSURE - The following is from the chemist's review.

The summary of Container Closure System (CCS) for Fluconazole Infusion bags for Lot #s: X03C501 and X03C501F1 (100 mL and 200 mL Fill Bags):

| Component    | Description  | Certificate of Compliance |
|--------------|--|---------------------------|
| Container    | MC312 Infusion bag 100 mL bag/ 250 mL bag<br>Cryovac Sealed Corp.                                  | p. 2025                   |
| Port         |                   | p. 2121                   |
| Tubing       |  Connector Tubing | p. 2161                   |
| Labeling Ink | The ink is applied _____; it does not come in contact with the drug product                        |                           |
| Over wrap    | This is secondary packaging; it is not intended to be a sterility or moisture barrier              |                           |

The results for USP systemic toxicity study for the CCS are on pp. 2026 – 2046. The USP <661> test results are on pp. 2049 -2052. The container meets the JPXIII test for resistance to water vapor permeation. (p. 2055).

The Certificate of Compliance for the Spike Ports and for the Connector Tubing state that the extracts from each meet the requirements of a USP Plastic Class VI. The details of the biological, physicochemical and toxicology tests methods and results are provided (pp. 2122 – 2159, pp. 2162 - 2190).

10. The following was determined at the time of ANDA 76-087 in the past.

The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." Also, the D&A section reads that "Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. The majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will have the generic sponsors silent on all information specifically associated with "Vaginal Candidiasis"

11. The proposed labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

12. The following e-mail was sent to PM in the new drug division on 1/24/02 and answer from the division on 1/29/02. (See file folder for detail)

**Question:**

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal candidiasis. We have a generic application for the injection only. Would you please let us know that fluconazole injection is also indicated for these symptoms. If only oral suspension is indicated for the treatment of these, then we have to direct the generic sponsor to carve out the information associated with these from the insert labeling. Your help would be appreciated. Thanks,

Chan

**Answer:**

As far as I can tell all three formulations are indicated for OPC and EC. I am not aware of any reasons barring applicants from applying separately for those indications using each formulation.

lmo (lbia, Ekopino)

13. The review for the container labels and shelfpack labels was done using RLD labeling for the same packaging configuration. **It appears that the RLD labeling for the glass bottle and plastic bags are not identical to each other.**
14. This drug product is manufactured by Sicor Pharmaceutical, Inc. (p.1103, vol.1.2)
15. The submission of 10/19/04 is for the package insert labeling reflecting the update innovator's labeling. The sponsor submitted only pdf format electronically while submitted the side-by-side statements in MS Word in hard copy.

---

**Date of Review: 11/10/04**

**Date of Submission: 10/19/04**

**Primary Reviewer: Chan Park**

**Date:** 11/10/04

**Team Leader: Golson Lillie**

**Date:** 11/17/04

---

cc:

ANDA: 76-837  
DUP/DIVISION FILE  
HFD-613/Cpark/LGolson (no cc)  
V:\FIRMSNZ\SICOR\LTRS&REV\76837AP#2.LABELING.doc  
Review

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**CHEMISTRY REVIEWS**



**ANDA 76-837**

**Fluconazole Injection in Plastic Container  
2 mg/mL**

**SICOR Pharmaceuticals, Inc.**

**Zelleka Getahun, Ph. D.  
OGD - Division of Chemistry II**



# Table of Contents

|  |          |
|--|----------|
| <b>Table of Contents .....</b>   | <b>2</b> |
| <b>Chemistry Review Data Sheet.....</b>  | <b>3</b> |
| <b>The Executive Summary.....</b>  | <b>7</b> |
| I. Recommendations.....  | 7        |
| A. Recommendation and Conclusion on Approvability.....   | 7        |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ..... | 7        |
| II. Summary of Chemistry Assessments.....  | 7        |
| A. Description of the Drug Product(s) and Drug Substance(s).....   | 7        |
| B. Description of How the Drug Product is Intended to be Used .....  | 8        |
| C. Basis for Approvability or Not-Approval Recommendation .....  | 8        |
| III. Administrative.....   | 8        |
| A. Reviewer's Signature .....  | 8        |
| B. Endorsement Block .....   | 8        |
| C. CC Block.....   | 8        |
| <b>Chemistry Assessment .....</b>  | <b>9</b> |



# Chemistry Review Data Sheet

1. ANDA 76-837
2. REVIEW #: 1
3. REVIEW DATE: 24-DEC-2003
4. REVIEWER: Zelleka Getahun, Ph.D.
5. PREVIOUS DOCUMENTS:  
N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Original

Document Date  
August 8, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: SICOR Pharmaceuticals, Inc.  
19 Hughes  
Address: Irvine, CA 92618 – 1902  
Representative: Rosalie A. Lowe  
Telephone: (949)-457-2808

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fluconazole Injection in 0.9% Sodium Chloride



## Chemistry Review Data Sheet

**9. LEGAL BASIS FOR SUBMISSION:**

Diflucan<sup>®</sup> in Sodium Chloride 0.9% in Plastic Container; NDA # 19-950 (001), Pfizer, Inc.

Patent no. 4,404,216 expires on January 29, 2004. Paragraph III certification is appended (p. 1012). The product is not covered by any exclusivity (a copy from the Orange Book is appended, p.1011).

**10. PHARMACOL. CATEGORY:** Antifungal

**11. DOSAGE FORM:** Infusion solution

**12. STRENGTH/POTENCY:** 2 mg/mL in 100mL and 200 mL fill infusion bags

**13. ROUTE OF ADMINISTRATION:** Intravenous

**14. Rx/OTC DISPENSED:**  Rx  OTC

**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

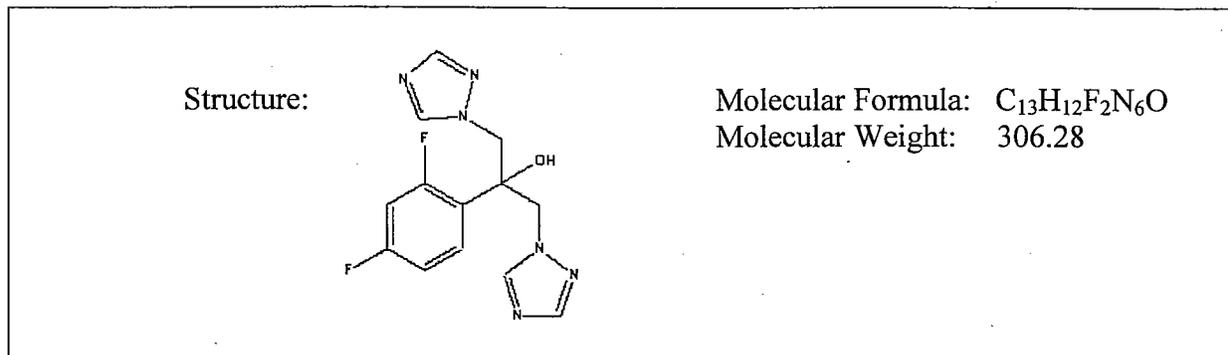
SPOTS product – Form Completed

Not a SPOTS product

**APPEARS THIS WAY  
ON ORIGINAL**

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Fluconazole; 2,4-Difluoro- $\alpha,\alpha$ -bis(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

| DMF # | TYPE | HOLDER  | ITEM REFERENCED        | CODE <sup>1</sup> | STATUS <sup>2</sup> | REVIEW DATE | COMMENTS           |
|-------|------|---------|------------------------|-------------------|---------------------|-------------|--------------------|
| —     | II   | —       | —                      | 3                 | Adequate*           | 29-AUG-003  | LOA pp. 1058, 1059 |
| 9705  | III  | Cryovac | M312/plastic packaging | 4                 | N/A                 |             | LOA p. 2023        |
| —     | III  | —       | —                      | 4                 | N/A                 |             | LOA p. 2023        |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed\*

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate or N/A

(There is enough data in the application; therefore the DMF did not need to be reviewed)

\* DMF # — was reviewed by R. Rajagopalan.



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                              |
|----------|--------------------|--|
| ANDA     | 76-653             | Cross referenced by SICOR on FDA 356 (h) |

SICOR has listed ANDA 76-653 in the list of cross references on its current application. ANDA 76-653 and the current application are similar; the major difference is in the container of the drug product. In ANDA 76-653 the drug product is supplied in 100 mL and 200 mL glass vials, in the current application the drug product is supplied in plastic infusion bags.

### 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                   | DATE        | REVIEWER         |
|-------------------------------|----------------------------------|-------------|------------------|
| Microbiology                  | Review Pending                   |             |                  |
| EES                           | Acceptable                       | 15-OCT-2003 | OC /J.D Ambrogio |
| Methods Validation            | Acceptable<br>SOPs pp.2260 -2570 | 24-DEC-2003 | Z. Getahun       |
| Labeling                      | Review Pending                   |             |                  |
| Bioequivalence                | Review Pending                   |             |                  |
| EA                            | N/A                              |             |                  |
| Radiopharmaceutical           | N/A                              |             |                  |

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  
 Yes     No    If no, explain reason(s) below:

# The Chemistry Review for ANDA 76-837

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is **not approvable**; there are pending chemistry issues.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Fluconazole is a synthetic broad spectrum antifungal agent. Fluconazole Injection (Infusion) in Sodium Chloride 0.9% in plastic containers is supplied as a 2 mg /mL solution in volumes of 100 mL and 200 mL.

The drug substance is manufactured by \_\_\_\_\_ . The drug substance is non-compendial; the manufacturer has provided the structures of the identified impurities and has also set tight specifications for total impurities. The applicant has verified that impurities in the drug substance are either non-detectable or constitute less than — % of the bulk of the drug substance.



Stability indicating method for the drug product is non-compendial. The firm has established in-house methods and methods validations. Through the forced degradation studies the drug product, is shown to be very stable; and it is also shown that the degradation profile of the drug product is identical to the RLD.

The label storage condition for the product is 5° - 25° C. The proposed expiration dating is 24 months.



Executive Summary Section

**B. Description of How the Drug Product is intended to be used**

N/A

**C. Basis for Approvability or Not-Approval Recommendation**

The application is **not approvable**, pending satisfactory response to the chemistry issues that are raised: \_\_\_\_\_

\_\_\_\_\_ is not provided.

Labeling, Microbiology and Bioequivalence review are pending.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ZGetahun/1/23/04  
GJSmith/1/28/04  
TPalat/2/2/04

**C. CC Block**

**APPEARS THIS WAY  
ON ORIGINAL**

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

---

CHEMISTRY REVIEW #1

---



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-837  
ANDA DUP  
DIV FILE  
Field Copy

### Endorsements (Draft and Final with Dates):

HFD-640/ZGetahun/1/23/04 *ZGetahun 2/4/04*

HFD-647/GJSmith/1/28/04 *GJSmith 2/4/04*

HFD-615/TPalat/2/2/04 *TPalat 2/5/04*

F/T by rad2/3/04

V:\FIRMSAM\SICOR\LTRS&REV\76837Ncr1.ZG

**TYPE OF LETTER:** NOT APPROVABLE - MINOR

**APPEARS THIS WAY  
ON ORIGINAL**

**ANDA 76-837**

**Fluconazole Injection in Plastic Container  
2 mg/mL**

**SICOR Pharmaceuticals, Inc.**

**Zelleka Getahun, Ph. D.  
OGD - Division of Chemistry II**



# Table of Contents

|  |          |
|--|----------|
| <b>Table of Contents .....</b>   | <b>2</b> |
| <b>Chemistry Review Data Sheet.....</b>  | <b>3</b> |
| <b>The Executive Summary.....</b>  | <b>7</b> |
| I. Recommendations.....  | 7        |
| A. Recommendation and Conclusion on Approvability.....   | 7        |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ..... | 7        |
| II. Summary of Chemistry Assessments.....  | 7        |
| A. Description of the Drug Product(s) and Drug Substance(s).....   | 7        |
| B. Description of How the Drug Product is Intended to be Used .....  | 7        |
| C. Basis for Approvability or Not-Approval Recommendation .....  | 8        |
| III. Administrative.....   | 8        |
| A. Reviewer's Signature .....  | 8        |
| B. Endorsement Block .....   | 8        |
| C. CC Block.....   | 8        |
| <b>Chemistry Assessment .....</b>  | <b>9</b> |



# Chemistry Review Data Sheet

1. ANDA 76-837

2. REVIEW # 2

3. REVIEW DATE: September 23, 2004

4. REVIEWER: Zelleka Getahun, Ph.D.

5. PREVIOUS DOCUMENTS:

Original Application Document Date: August 8, 2003

6. SUBMISSION(S) BEING REVIEWED:

Minor Amendment Document Date: August 17, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: SICOR Pharmaceuticals, Inc.

Address: 19 Hughes

Irvine, CA 92618 - 1902

Representative: Rosalie A. Lowe

Telephone: (949)-457-2808

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Fluconazole Injection in 0.9% Sodium Chloride

9. LEGAL BASIS FOR SUBMISSION:

Diflucan® in Sodium Chloride 0.9% in Plastic Container; NDA # 19-950 (001), Pfizer, Inc.

Patent no. 4,404,216 expiration date: January 29, 2004. Paragraph III certification is appended (p. 1012).

Patent no. 4404216\*PED expiration date: July 29, 2004



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Infusion solution

12. STRENGTH/POTENCY: 2 mg/mL in 100mL and 200 mL fill infusion bags

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON LINE TRACKING SYSTEM)

SPOTS product – Form Completed

Not a SPOTS product

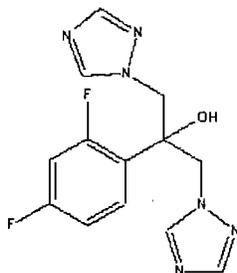
**APPEARS THIS WAY  
ON ORIGINAL**

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Fluconazole; 2,4-Difluoro- $\alpha,\alpha$ -bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol

Structure:

Molecular Formula:  $C_{13}H_{12}F_2N_6O$ 

Molecular Weight: 306.28

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

| DMF # | TYPE | HOLDER  | ITEM REFERENCED        | CODE <sup>1</sup> | STATUS <sup>2</sup> | REVIEW DATE | COMMENTS           |
|-------|------|---------|------------------------|-------------------|---------------------|-------------|--------------------|
| _____ | II   | _____   | _____                  | 3                 | Adequate*           | 12/15/04    | LOA pp. 1058, 1059 |
| 9705  | III  | Cryovac | M312/plastic packaging | 4                 | N/A                 |             | LOA p. 2023        |
| _____ | III  | _____   | _____                  | 4                 | N/A                 |             | LOA p. 2023        |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review\*

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate or N/A

(There is enough data in the application; therefore the DMF did not need to be reviewed)

\* DMF # \_\_\_\_\_ was reviewed by R. Rajagopalan.

Annual report submitted by the DMF holder on 5-MAR-2004, not reviewed.

Chemistry Review Data Sheet

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                              |
|----------|--------------------|--|
| ANDA     | 76-653             | Cross referenced by SICOR on FDA 356 (h) |

SICOR has listed ANDA 76-653 in the list of cross references on its current application. ANDA 76-653 and the current application are similar; the major difference is in the container of the drug product. In ANDA 76-653 the drug product is supplied in 100 mL and 200 mL glass vials, in the current application the drug product is supplied in plastic infusion bags.

**18. STATUS:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                   | DATE        | REVIEWER         |
|-------------------------------|----------------------------------|-------------|------------------|
| Microbiology                  | Acceptable                       | 14-OCT-2004 |                  |
| EES                           | Acceptable                       | 15-OCT-2003 | OC /J.D Ambrogio |
| Methods Validation            | Acceptable<br>SOPs pp.2260 -2570 | 24-DEC-2003 | Z. Getahun       |
| Labeling                      | Acceptable                       | 17-NOV-2004 |                  |
| Bioequivalence                | Acceptable                       | 18-JUN-2004 |                  |
| EA                            | N/A                              |             |                  |
| Radiopharmaceutical           | N/A                              |             |                  |

**19. ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt.  
 Yes     No    If no, explain reason(s) below:

# The Chemistry Review for ANDA 76-837

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Approvable. There are no pending chemistry issues.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

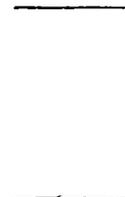
N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Fluconazole is a synthetic broad spectrum antifungal agent. Fluconazole Injection (Infusion) in Sodium Chloride 0.9% in plastic containers is supplied as a 2 mg/mL solution in volumes of 100 mL and 200 mL.

The drug substance is manufactured by \_\_\_\_\_. The drug substance is non-compendial; the manufacturer has provided the structures of the identified impurities and has also set tight specifications for total impurities. The applicant has verified that the impurities in the drug substance are either non-detectable or constitute less than —% of the bulk of the drug substance.



The firm has established in-house analytical methods that are stability indicating. Satisfactory methods validation data are included. The forced degradation studies of the drug product show that it is very stable. Forced degradations of the DP and the RLD show that the degradation profile of the DP is identical to that of the RLD. The label storage condition for the product is 5° - 25° C. The proposed expiration dating is 24 months.

#### B. Description of How the Drug Product is intended to be used

N/A



## CHEMISTRY REVIEW



### Executive Summary Section

#### C. Basis for Approvability or Not-Approval Recommendation

The application is **approvable**. Sicor has submitted fairly satisfactory responses to all the comments made by Review # 1. The specifications limits for total impurities

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_ (expiration dating is 24 months). The analytical methods used are satisfactory.

### III. Administrative

#### A. Reviewer's Signature

Zelleka Getahun 12/23/04

#### B. Endorsement Block

ZGetahun/9/28/04

GJSmith/12/15/04

TPalat/12/20/04

#### C. CC Block

APPEARS THIS WAY  
ON ORIGINAL

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

---

CHEMISTRY REVIEW # 2

---



- 33. ESTABLISHMENT INSPECTION** **Acceptable**  
Overall EER is Acceptable as of 15-Oct-2003.

**34. BIOEQUIVALENCE**

Acceptable 18-Jun-04

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

The firm seeks categorical exclusion under 21 CFR § 25.31 (a). The RLD for the same indications, level of dosage and duration of administration is on the market; and the data available establish that at the level of exposure the substance does not pose a toxicity risk to organisms in the environment. The firm also states that it is in compliance with all applicable Federal, State and local environmental rules and regulations (p. 2637).

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-837  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/ZGetahun/ Zelleka Getahun 12/23/04

HFD-647/GJSmith/ *GJ* 12/23/04

HFD-615/TPalat/ *TP* 12/27/04

F/T by

V:\FIRMSAM\SICOR \LTRS&REV\76837Ncr2.ZG

**TYPE OF LETTER:** APPROVABLE

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**BIOEQUIVALENCE REVIEW**

JUN 17 2004

7/97

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-837

SPONSOR : SICOR Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM: Fluconazole Injection in Sodium Chloride 0.9% in plastic containers

STRENGTH(S): 2 mg/mL, 100 mL and 200 mL

STUDY SUMMARY: The test drug product is a parental solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as the approved reference listed product. A waiver of the in-vivo bioavailability/bioequivalence study requirements is granted [21 CFR 320.22(b)(1)]

**DSI INSPECTION STATUS**

|                          |                              |                     |
|--------------------------|------------------------------|---------------------|
| Inspection needed:<br>No | Inspection status:           | Inspection results: |
| First Generic _____      | Inspection requested: (date) |                     |
| New facility _____       | Inspection completed: (date) |                     |
| For cause _____          |                              |                     |
| Other _____              |                              |                     |

PROJECT MANAGER: Aaron Sigler, Pharm.D.

BRANCH: I

INITIAL: AS

DATE: 17 JUN 04

SPECIAL ASSISTANT TO THE DIRECTOR: Lizzie Sanchez, Pharm.D.

INITIAL: LS

DATE: 6/19/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: DC

DATE: 6/17/04

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-837

APPLICANT: SICOR Pharmaceuticals, Inc.

DRUG PRODUCT: Fluconazole for Injection in Sodium Chloride in plastic containers,  
2 mg/mL, 100 mL and 200 mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director,

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**MICROBIOLOGY REVIEW**

# Product Quality Microbiology Review

## Review for HFD-640

October 8, 2004

ANDA: 76-837

### Drug Product Name

**Proprietary:** N/A

**Non-proprietary:** Fluconazole Injection 2 mg/mL

**Drug Product Classification:** N/A

**Review Number:** #1

### Subject of this Review

**Submission Date:** August 29, 2003

**Receipt Date:** September 2, 2003

**Consult Date:** N/A

**Date Assigned for Review:** June 25, 2004

### Submission History (for amendments only)

**Date(s) of Previous Submission(s):** N/A

**Date(s) of Previous Micro Review(s):** N/A

### Applicant/Sponsor

**Name:** SICOR Pharmaceuticals, Inc.

**Address:** 19 Hughes, Irvine CA 92618-1902

**Representative:** Rosalie Lowe, Director, Regulatory Affairs

**Telephone:** 949-457-2808

**Name of Reviewer:** Lisa S.G. Shelton

**Conclusion:** The submission is **recommended** for approval on the basis of sterility assurance.

## Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUPPLEMENT:** N/A
  2. **SUPPLEMENT PROVIDES FOR:** N/A
  3. **MANUFACTURING SITE:**  
SICOR Pharmaceuticals, Inc.  
19 Hughes  
Irvine, CA 92618-1902
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile liquid, intravenous, 2 mg/mL packaged as 200 mg/ 100 mL in a 100 mL infusion bag and 400 mg/ 200 mL in a 250 mL infusion bag, single dose containers
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** Antifungal

- B. SUPPORTING/RELATED DOCUMENTS:**
- DMF \_\_\_\_\_  
DMF 9705 – Cryovac  
DMF \_\_\_\_\_  
ANDA 76-653 – Fluconazole Injection 2 mg/mL in 100 mL and 200 mL vials.

- C. REMARKS:**
- Parts of this review are similar to that of N.Nath (Microbiology Review #1, 8/28/03) for ANDA 76-653 Fluconazole Injection 2 mg/mL in 100 and 200 mL vials.
- The applicant was contacted by telephone to clarify if the units used for the \_\_\_\_\_ validation were overwrapped and \_\_\_\_\_ (10/7/04). Their response is incorporated into the subject review.

**filename:** V:\MICROREV\76-837.doc

**Executive Summary**

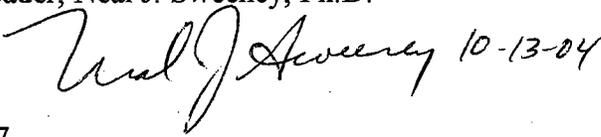
**I. Recommendations**

- A. Recommendation on Approvability –**  
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" section.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –**
- B. Brief Description of Microbiology Deficiencies – N/A**
- C. Assessment of Risk Due to Microbiology Deficiencies –**  
The safety risk on the basis of sterility assurance is considered minimal.

**III. Administrative**

- A. Reviewer's Signature** *Lisa S.G. Shelton*
  - B. Endorsement Block**  
Microbiologist, Lisa S.G. Shelton, Ph.D. *10/8/04 Lgs*  
Microbiology Team Leader, Neal J. Sweeney, Ph.D.
  - C. CC Block**  
cc:  
Original ANDA 76-837  
Division File  
Field Copy
- 

*Neal J. Sweeney 10-13-04*

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

---

MICROBIOLOGY REVIEW #1

---

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**ADMINISTRATIVE DOCUMENTS**

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-837 Applicant SICOR Pharmaceuticals Inc.
Drug Fluconazole Injection Strength(s) 2 mg/ml

APPROVAL [X] TENTATIVE APPROVAL [ ] SUPPLEMENTAL APPROVAL (NEW STRENGTH) [ ] OTHER [ ]

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 21 Dec 2004
Initials MAS

Date 1/13/05
Initials [Signature]

Contains GDEA certification: Yes [X] No [ ] Determ. of Involvement? Yes [ ] No [X]
Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes [X] No [ ]
If Para. IV Certification- did applicant

RLD =
NDA# 19-956
Date Checked Prevalently granted

Notify patent holder/NDA holder Yes [ ] No [ ]

Nothing Submitted

Was applicant sued w/in 45 days: Yes [ ] No [ ]

Written request issued [ ]
Study Submitted [ ]

Has case been settled: Yes [ ] No [ ]

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes [ ] No [ ]

Date of latest Labeling Review/Approval Summary 11/17/2004

Any filing status changes requiring addition Labeling Review Yes [ ] No [X]

Type of Letter:

Comments:

PII to '06, no patent exclusivity issues barring approval
... eligible for full approval

2. Project Manager, Tel Plot Team 9
Review Support Branch

Date 12/20/04
Initials GP

Date
Initials

Original Rec'd date 8-29-03
Date Acceptable for Filing 9-2-03
Patent Certification (type) II
Date Patent/Exclus. expires N/A

EER Status Pending [ ] Acceptable [X] OAI [ ]
Date of EER Status 10-15-03
Date of Office Bio Review 6-16-04
Date of Labeling Approv. Sum 11-17-04

Citizens' Petition/Legal Case Yes [ ] No [X] Labeling Acceptable Email Rec'd Yes [ ] No [X]
Labeling Acceptable Email filed Yes [ ] No [X]

First Generic Yes [ ] No [X] Date of Sterility Assur. App. 11-14-04
Methods Val. Samples Pending Yes [ ] No [X]
MV Commitment Rcd. from Firm Yes [ ] No [X]

Acceptable Bio reviews tabbed Yes [ ] No [ ] Modified-release dosage form: Yes [ ] No [X]
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes [ ]

Pediatric Waiver Request Accepted [ ] Rejected [ ] Pending [ ]

Previously reviewed and tentatively approved [ ] Date

Previously reviewed and CGMP def. /NA Minor issued [ ] Date

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included [ ]
OGD Regulatory Counsel, Post-MMA Language Included [ ]

Date
Initials

Comments:

N/A

4. Div. Dir /Deputy Dir
Chemistry Div. I II OR III

Date 1/11/05
Initials RCA

Comments:

One OK See attached
table for impurity comparison
approval letter being revised
to state plastic containers

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only  
Assoc. Dir. For Chemistry  
Comments: (First generic drug review)

Date \_\_\_\_\_  
Initials \_\_\_\_\_

N/A. Multiple ANDAs have been approved for this drug product.

6. Vacant Deputy Dir., DLPS

RCD = Diflucan Injection (in Sodium Chloride 0.9%)  
in Plastic Container 200mg/100 ml  
Prizer Central Research NDA 19-950 (002)

Date \_\_\_\_\_  
Initials \_\_\_\_\_

7. Peter Rickman  
Director, DLPS

Date 1/13/05  
Initials [Signature]

Para. IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No

Comments: Microbiology/sterility assurance found acceptable 10/13/04. Bioequivalence waiver granted under 21 CFR 320.22 (b)(1). Office-level bioequivalence 6/11/04. CMC found acceptable for approval 12/23/04. Methods validation was not requested.

8. Robert L. West  
Deputy Director, OGD

Date 1/13/2005  
Initials [Signature]

Para. IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No

Comments: Acceptable EES dated 10/15/03 (verified 1/13/05). No O.A.I. alerts noted. There are no unexpired patents or exclusivity concerns listed up the Orange Book for this drug product. Sinc has provided a paragraph II patent certification.

This ANDA is recommended for approval.

9. Gary Buehler  
Director, OGD  
Comments:

Date 1/13/05  
Initials GB

First Generic Approval  PD or Clinical for BE  Special Scientific or Reg. Issue

10. Project Manager, Team Ted Palat  
Review Support Branch

Date CK 1/13/05  
Initials \_\_\_\_\_

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

4/1 Time notified of approval by phone Y05 Time approval letter faxed

FDA Notification:

1/13 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

1/13 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-837**

**CORRESPONDENCE**



PHARMACEUTICALS, INC.



19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

*55 (12) 100.K  
Mortimer  
3 October 2003*

August 29, 2003

Mr. Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

*76-837  
N-000*

RE: Fluconazole Injection  
2 mg/mL  
ANDA: Number to be Assigned

Dear Mr. Buehler:

In accordance with Section 314.92 of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Fluconazole Injection, 2 mg/mL, a parenteral preparation supplied as:

| Strength | Total Drug Content      | How Supplied                                  |
|----------|-------------------------|---|
| 2 mg/mL  | 200 mg per infusion bag | 100 mL infusion bag packaged 6 per shelf pack |
|          | 400 mg per infusion bag | 250 mL infusion bag packaged 6 per shelf pack |

On July 2, 2003, we notified the Agency that Gensia Sicor Pharmaceuticals, Inc. changed the corporate company name to SICOR Pharmaceuticals, Inc. Please note that this submission reflects the new corporate company name, SICOR Pharmaceuticals, Inc. Although we have initiated changes to documents revising the corporate company name to SICOR Pharmaceuticals, Inc, there are still some documents in this submission with the previous company name, Gensia Sicor Pharmaceuticals, Inc.

SICOR's proposed drug product is the generic version of Pfizer's Diflucan® in Sodium Chloride 0.9% in Plastic Container, pursuant to NDA No. 19-950 (002). Pfizer's drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 23<sup>rd</sup> Edition*. The approved drug product marketed by Pfizer is available in a 100 mL and 200 mL Viaflex® Plus plastic container.

Our proposed drug product, Fluconazole Injection, has the same active and inactive ingredients, dosage form, strength, route of administration, and conditions of use as Pfizer's listed drug product.

RECEIVED

SEP 02 2003

OGD/CDER

Mr. Gary Buehler  
August 29, 2003  
Page 2

Fluconazole Injection will be packaged in a 100 mL and 250-mL flexible, \_\_\_\_\_ polymer bag with a single port fitting (combination filling port and twist-off connector spike port). The infusion bags are composed of sterilizable medical grade film (Cryovac® M312 Pharmaceutical Solutions Film). Cryovac Sealed Air Corporation manufactures this \_\_\_\_\_ film. The information for the M312 film is provided in **Drug Master File (DMF) No. 9705**. The \_\_\_\_\_ spike port is manufactured by \_\_\_\_\_. The \_\_\_\_\_ connector tubing is manufactured by \_\_\_\_\_ (DMF No. \_\_\_\_\_).

Two (2) stability lots of Fluconazole Injection were manufactured and data are presented in **Section XVII** of this application.

Four (4) copies of the proposed labeling have also been provided in **Section V** of the application in both the archival and review copies.

The application consists of three (3) volumes and has been formatted in accordance with the Office of Generic Drug's Guidance for Industry, Organization of an ANDA, OGD #1, issued February 1999. Copies are provided as follows:

- 1) One (1) Archival Copy bound in Blue Jackets
- 2) One (1) Review Copy bound in Red Jackets

A true copy of this application, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration of Irvine, California, District Office.

Since the stability indicating method for the product is non-compendial, three (3) additional methods validation packages have been included and are marked "Analytical Methods". These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 457-2808. I can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Rosalie A. Lowe  
Director, Regulatory Affairs

cc: Mr. Alonza Cruse  
District Director  
U.S. Food and Drug Administration, Los Angeles District  
19900 MacArthur Blvd., Suite 300  
Irvine, CA 92615



PHARMACEUTICALS, INC.



19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

December 8, 2003

Mr. Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

**RE: Fluconazole Injection**  
**2 mg/mL**  
**ANDA: 76-837**

**AMENDMENT-Chemistry**

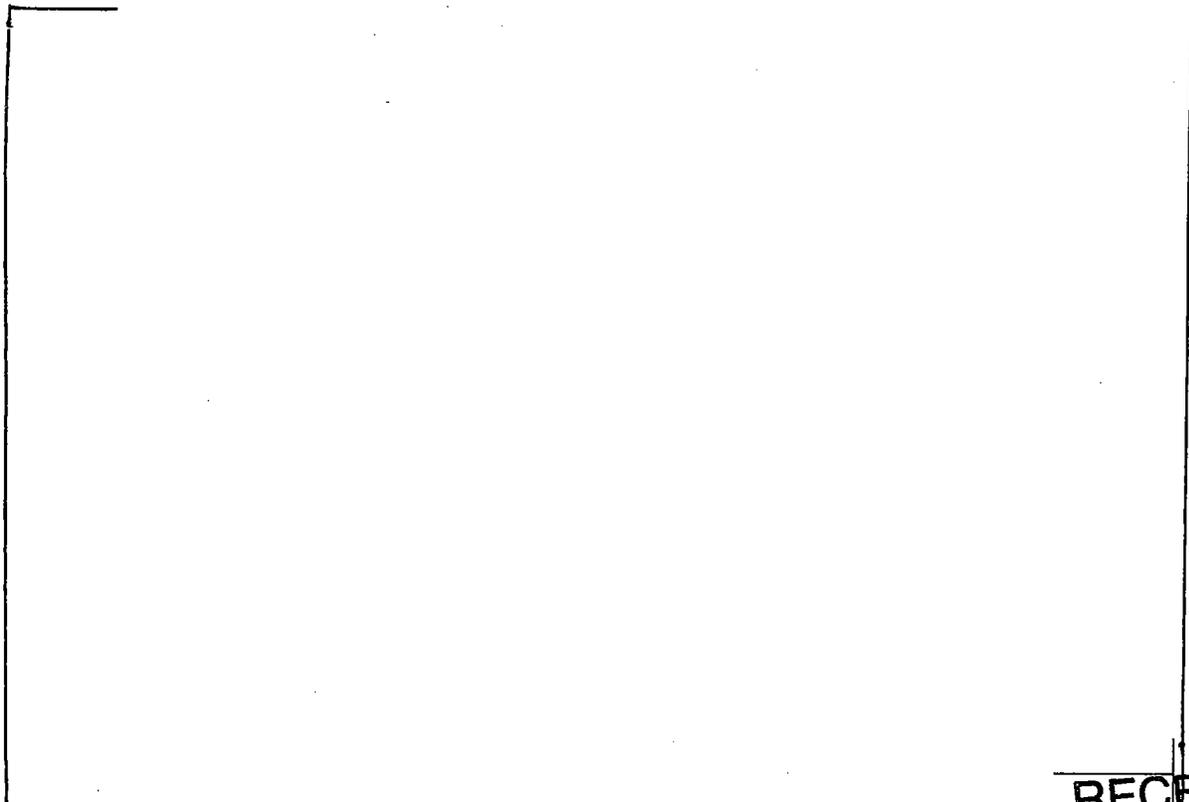
**ORIG AMENDMENT**

*N/A/C*

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole Injection, 2 mg/mL, submitted on August 29, 2003.

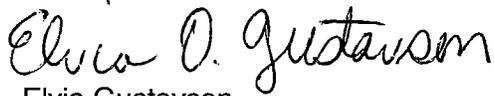
We hereby amend this application, in accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*. Specifically, we wish to include an alternate



**RECEIVED**  
**DEC 09 2003**  
**OGD/CDER**

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Elvia Gustavson

Director, Regulatory Affairs

S:\Fluconazole Bags\Amends\Amend1.doc

cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300  
Irvine, CA 92612

**APPEARS THIS WAY  
ON ORIGINAL**

2.1



PHARMACEUTICALS, INC.

ORIGINAL



19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

July 14, 2004

Mr. Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

ORIG AMENDMENT  
N/AF

RE: Fluconazole for Injection in Plastic Container  
ANDA: 76-837

MINOR AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole for Injection in Plastic Container, 2 mg/mL, submitted on August 29, 2003. Reference is also made to the deficiency letter dated March 3, 2004.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the **labeling** information. Twelve (12) samples of the final printed labels and labeling are provided in **Attachment 1** for your review. Additionally, a side-by-side labeling comparison of our proposed labeling with our previous submission is provided for your review in **Attachment 2**, with all differences annotated and explained.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe  
Director, Regulatory Affairs

S:\Fluconazole\Amends\Amend3.doc  
cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED  
JUL 15 2004  
OGD / CDER

RECEIVED  
004  
OGD / CDER



19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

ORIG AMENDMENT

N/A/M

August 17, 2004

Mr. Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

RE: Fluconazole for Injection in Plastic Container  
ANDA: 76-837

**MINOR AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole for Injection in Plastic Container, 2 mg/mL, submitted on August 29, 2003. Reference is also made to the deficiency letter dated February 5, 2004.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the **chemistry** information.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe  
Director, Regulatory Affairs

S:\Fluconazole\Amends\Amend3.doc

cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED  
AUG 18 2004  
OGD/CDER



August 27, 2004

Mr. Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AE

19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

RE: **Fluconazole for Injection in Plastic Container**  
ANDA: 76-837

**MINOR AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole for Injection in Plastic Container, 2 mg/mL, submitted on August 29, 2003. Reference is also made to the deficiency letter dated July 14, 2004.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the **labeling** information. Twelve (12) samples of the final printed labels and labeling are provided in **Attachment 1** for your review. Additionally, a side-by-side labeling comparison of our proposed labeling with our previous submission is provided for your review in **Attachment 2**, with all differences annotated and explained.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mirabelle Pao, Project Specialist at (949) 457-2848. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe  
Director, Regulatory Affairs

S:\Fluconazole Bags\Amends\Amend5.doc

cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED

AUG 30 2004

OGD/CDER

19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

October 19, 2004

Mr. Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

**ORIG AMENDMENT**

N/AF

**RE: Fluconazole for Injection in Plastic Container  
ANDA: 76-837**

**MINOR AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole for Injection in Plastic Container, 2 mg/mL, submitted on August 29, 2003. Reference is also made to the minor amendment submitted on August 27, 2004.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide our most current **labeling** information. The package insert labeling was revised to incorporate the Safety-Related Change from the RLD labeling, Diflucan®, approved on October 7, 2004.

A CD copy of the final printed labeling is provided for your review. Additionally, a side-by-side labeling comparison of our proposed labeling with our previous submission is provided for your review in **Attachment 1**, with all differences annotated and explained.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mirabelle Pao, Project Specialist at (949) 457-2848. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Rosalie A. Lowe  
Director, Regulatory Affairs

S:\Fluconazole Bags\Amends\Amend6.doc  
cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

**RECEIVED**

**OCT 20 2004**

**OGD/CDER**



PHARMACEUTICALS, INC.

SICOR Pharmaceuticals, Inc.

19 Hughes  
Irvine, CA 92618  
Toll Free: 800.729.9991  
Telephone: 949.455.4700  
Fax: 949.855.8210  
www.sicor.com

December 3, 2004

Mr. Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, HFD-600  
Attention: Documentation and Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

**NEW CORRESP**  
XP

**RE: Fluconazole for Injection in Plastic Container  
ANDA: 76-837**

**PATENT AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-837, for Fluconazole for Injection in Plastic Container, 2 mg/mL, submitted on August 29, 2003.

In accordance with the provisions of Section 314.94 (a)(12)(viii)(C) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide a revised patent certification due to the expiration of U.S. Patent No. 4,404,216. Enclosed is the requisite Paragraph II Certification.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Tania Hoffman, Manager at (949) 455-4728. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe  
Director, Regulatory Affairs

S:\Fluconazole Bags 76-837\Amends\Amend7.doc  
cc: Mr. Alonza Cruse  
District Director  
FDA, Los Angeles District  
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

**RECEIVED**  
DEC 06 2004  
OGD / CDER