CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-617

***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 plastic containers

***Sponsor*:** Mayne Pharma (USA), Inc.

***Approval Date*:** July 29, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

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Microbiology Review	X
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Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

APPROVAL LETTER

ANDA 76-617

JUL 29 2004

Mayne Pharma (USA) Inc.
Attention: Steve Richardson
Mack Cali Centre II
650 From Road, Second Floor
Paramus, NJ 07652

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2002, 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 plastic containers.

Reference is also made to the Tentative Approval letter issued by this office on October 30, 2003, and to your amendments dated December 17, 2003, and July 19, 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 Injection®, 2 mg/mL, (in 0.9% Sodium Chloride Injection) of Pfizer, Inc).

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,

/for/ 1/29/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-617
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/R.Rajagopalan/R. Rajagopalan 7/21/04
HFD-645/B.Arnwine/ 7/21/04
HFD-617/N.Lee/ 7/22/04
HFD-613/C.Park/7/20/04 7/21/04
HFD-613/L.Golson/ 7/21/04

CMC OK
7/26/04
RAR

Robert A. West
7/26/2004

\\CDSNAS\OGDS11\FIRMSam/faulding/ltrs&rev/76617ap
F/T by: rad7/20/04

APPROVAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

TENTATIVE APPROVAL LETTER

ANDA 76-617

OCT 30 2003

Faulding Pharmaceutical Co.
Attention: Heather A. Bradley
Mack Cali Center II
650 From Roadm 2nd Floor
Paramus, NJ 07652

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2002, 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 plastic containers.

Reference is also made to your amendments dated July 7, July 24, August 20, and August 27, 2003.

We have completed the review of this abbreviated application and based upon the information you have presented to date, we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due to the patent discussed below, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Diflucan® Injection (in 0.9% Sodium Chloride Injection) of Pfizer Inc., is currently subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book, U.S. patent 4,404,216 (the '216 patent) is scheduled to expire on January 29, 2004). Your application contains a paragraph III certification to the

'216 patent under Section 505(j)(2) (A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of the '216 patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '216 patent has expired, i.e., January 29, 2004.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will <u>not</u> be deemed approved for marketing under

21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to January 29, 2004, you should amend your application accordingly.

For further information on the status of this application, or upon submitting an amendment to the application, please contact Nicole Park, Project Manager, (301) 827-5849.

Sincerely yours,

Gary Buehler 10/30/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-617
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/R.Rajagopalan/R Rajagopalan 10/17/03
HFD-645/B.Arnwine/10/16/03 B Arnwine 10/23/03
HFD-617/N.Park/ for 10/23/03
HFD-600/L.Ensor/ L. Ensor 10/21/03
HFD-600/N.Sweeney/ 10/21/03
HFD-613/C.Park/ C Park 10/17/03
HFD-613/L.Golson/ 10/20/03

Robert Rest
10/30/2003

v:\firmsam\faulding\ltrs&rev\76617ta.doc
F/T by: EW 10/16/03

TENTATIVE APPROVAL

Comm satisfactory
Wayne Hayes
10/30/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

LABELING

FLUCONAZOLE INJECTION

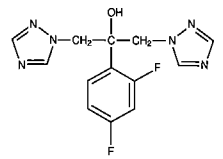
Iso-Osmotic Sodium Chloride Dilution
For Intravenous Infusion Only **℞only**

Faulding

DESCRIPTION

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

Fluconazole is designated chemically as 2,4-difluoro-α,α¹-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with a molecular formula of $C_{13}H_{12}F_2N_6O$ and molecular weight 306.3. The structural formula is:



JUL 29

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 a sodium chloride diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride. The pH ranges from 4.5 to 7.5. Injection volumes of 100 mL and 200 mL are packaged in plastic containers.

The plastic container is fabricated from polyvinyl chloride with a polypropylene overwrap. 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, e.g. di-2-ethylhexylphthalate (DEHP), up to 5 parts per million. 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-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The 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 (Cmax) 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 Cmax 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 Cmax 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. Plasma protein binding is low (11 to 12%). Following either single- or multiple-oral doses 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 bronchiectasis, 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
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister 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 **DOSAGE 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 ACTH-stimulated cortisol response.

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)	Cmax (mcg/mL)	Vdss (L/kg)
9 Months to 13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	--
9 Months to 13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	--
5 to 15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5 to 15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5 to 15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

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 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, 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.

Drug Interaction Studies

Oral contraceptives: Oral contraceptives were administered as a single 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 6% (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 on 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 38% (range: –11 to 101%). Both of these increases were statistically significantly different from placebo.

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 and Cmax. There was a mean ± SD decrease in fluconazole AUC of 13% ± 11% (range: –3.4 to –31%) and Cmax decreased 19% ± 14% (range: –5 to –40%). However, the administration of cimetidine 600 mg to 900 mg intravenously over a four-hour period (from 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. Maalox® is a registered trademark of Novartis.

Hydrochlorothiazide: Concomitant 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 Cmax compared to fluconazole given alone. There was a mean ± SD increase in fluconazole AUC and Cmax of 45% ± 31% (range: 19 to 114%) and 43% ± 31% (range: 19 to 122%), respectively. These changes are attributed 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 88% ± 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 Cmax 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 6 weeks. There was a significant increase in cyclosporine AUC, Cmax, Cmin (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 Cmax increased 60% ± 48% (range: –5 to 133%). The Cmin increased 157% ± 96% (range: 33 to 360%). 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, GZDV, 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, Cmax, and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range: –5 to 48%). The Cmax increased 13% ± 17% (range: –13 to 40%). 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 60 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 (40.1%) 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 Cmax following the administration of fluconazole. There was a mean ± SD increase in tolbutamide AUC of 26% ± 9% (range: 12 to 39%). Tolbutamide Cmax increased 11% ± 9% (range: –6 to 27%). (See **PRECAUTIONS.**)

Glipizide: The AUC and Cmax 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 Cmax of 19% ± 23% (range: –11 to 79%). (See **PRECAUTIONS.**)

Glyburide: The AUC and Cmax 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% ± 29% (range: –13 to 115%) and Cmax 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 preliminary report from a placebo-controlled, randomized multiple-dose study in subjects given fluconazole 200 mg daily and cisapride 20 mg four times daily starting after 7 days of fluconazole dosing found that fluconazole significantly increased the AUC and Cmax of cisapride both after single (AUC 102% and Cmax 92% increases) and multiple (AUC 192% and Cmax 153% increases) dosing of cisapride. Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 5 days. (See **CONTRAINDICATIONS** and **PRECAUTIONS.**)

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 flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies is unknown.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cr. 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:
1. 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.

2. Cryptococcal meningitis. Before prescribing fluconazole for AIDS patients with cryptococcal meningitis, please see **CLINICAL STUDIES** section. 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/mm³. Mortality among high risk patients was 33% and 40% for amphotericin B and fluconazole patients, respectively (p=0.58), with overall deaths 14% (9 of 63 subjects) and 18% (24 of 131 subjects) for the 2 arms of the study (p=0.48). 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 I.U. 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and mycological 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	98	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 injection 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. Coadministration 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. Coadministration of cisapride is contraindicated in patients receiving fluconazole. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies** 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 lesions progress.

PRECAUTIONS

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

Oral hypoglycemics
Coumarin-type anticoagulants
Phenytoin
Cyclosporine
Rifampin
Theophylline
Terfenadine
Cisapride
Astemizole
Rifabutin
Tacrolimus

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. 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. The combined use of fluconazole with cisapride is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interaction Studies.**)

Astemizole: The use of fluconazole in patients concurrently taking astemizole 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 uveitis 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.**)

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 4 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 at 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 coccidioidomycosis (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 **DOSAGE 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 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of 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.

ADVERSE REACTIONS

In Patients Receiving Multiple Doses
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%.

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

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 of 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 sulfonylurea hypoglycemic agents.

Immunologic: In rare cases, anaphylaxis has been reported.

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

Central Nervous System: Seizures.

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.

Adverse Reactions in Children
In Phase II/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 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 has been one reported case of overdosage 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 the hospital, and his condition resolved within 48 hours.

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 clonic convulsions.

DOSAGE AND ADMINISTRATION

Dosage and Administration in Adults

SINCE ORAL ABSORPTION 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 should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical 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 judgement 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 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 judgement 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:

Pediatric Patients	Adults
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 600 mg/day are not recommended.

Experience with fluconazole in neonates is limited to 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 (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	Percent of Recommended Dose
>50	100%
≤ 50 (no 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:

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

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:

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

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

Administration
Fluconazole injection is 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 injection in plastic containers is 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 in Plastic Containers
Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. 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
Grasp the end of the overwrap at the serrated edge with both hands and tear on one of the precut perforations. At this point, the Fluconazole Injection in Sodium Chloride Diluent plastic container can be removed from the protective overwrap. **NOTE: The overwrap is not designed to be opened by pulling apart the two sheets of the overwrap.** After removing the overwrap, check the inner bag for minute leaks by squeezing firmly. If leaks are found, discard solution as sterility may be impaired.

DO NOT ADD SUPPLEMENTARY MEDICATION.

Preparation for Administration
1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

WARNING: Must not be used in series connections.

HOW SUPPLIED

Fluconazole Injection, an iso-osmotic sodium chloride dilution, is available as follows:
200 mg/100 mL (2 mg/mL) plastic container x 10 (NDC 61703-414-63)
400 mg/200 mL (2 mg/mL) plastic container x 10 (NDC 61703-414-64)

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

Manufactured for:
Faulding Pharmaceutical Co.
a Mayne Group Company
Paramus, NJ 07652
by Haemonetics Corporation
Union, SC

Rev. September 2003

L422, Rev.–

10 **SINGLE DOSE** 100 mL PLASTIC CONTAINERS NDC 61703-414-63

FLUCONAZOLE INJECTION

200 mg (2 mg/mL)

Iso-Osmotic Sodium Chloride Dilution

STERILE, NONPYROGENIC
FOR INTRAVENOUS INFUSION ONLY
Rx only

Each 100 mL contains 200 mg of Fluconazole and 900 mg of Sodium Chloride, USP in Water for Injection, USP. Osmolarity 315 mOsmol/L (CALC).
USUAL DOSAGE: Intravenously as directed by a physician. See package insert.
CAUTIONS: **Do not remove unit from overwrap until ready for use.** 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. Discard Unused Portion.
STORAGE: STORE UNITS IN MOISTURE BARRIER OVERWRAP BETWEEN 77°F (25°C) AND 41°F (5°C) UNTIL READY TO USE. AVOID EXCESSIVE HEAT. **PROTECT FROM FREEZING**.

Manufactured for **Faulding Pharmaceutical Co.** Paramus, NJ 07652
by Haemonetics Corporation, Union, SC

L393, Rev. A

10 **SINGLE DOSE** 200 mL PLASTIC CONTAINERS NDC 61703-414-64

FLUCONAZOLE INJECTION

400 mg (2 mg/mL)

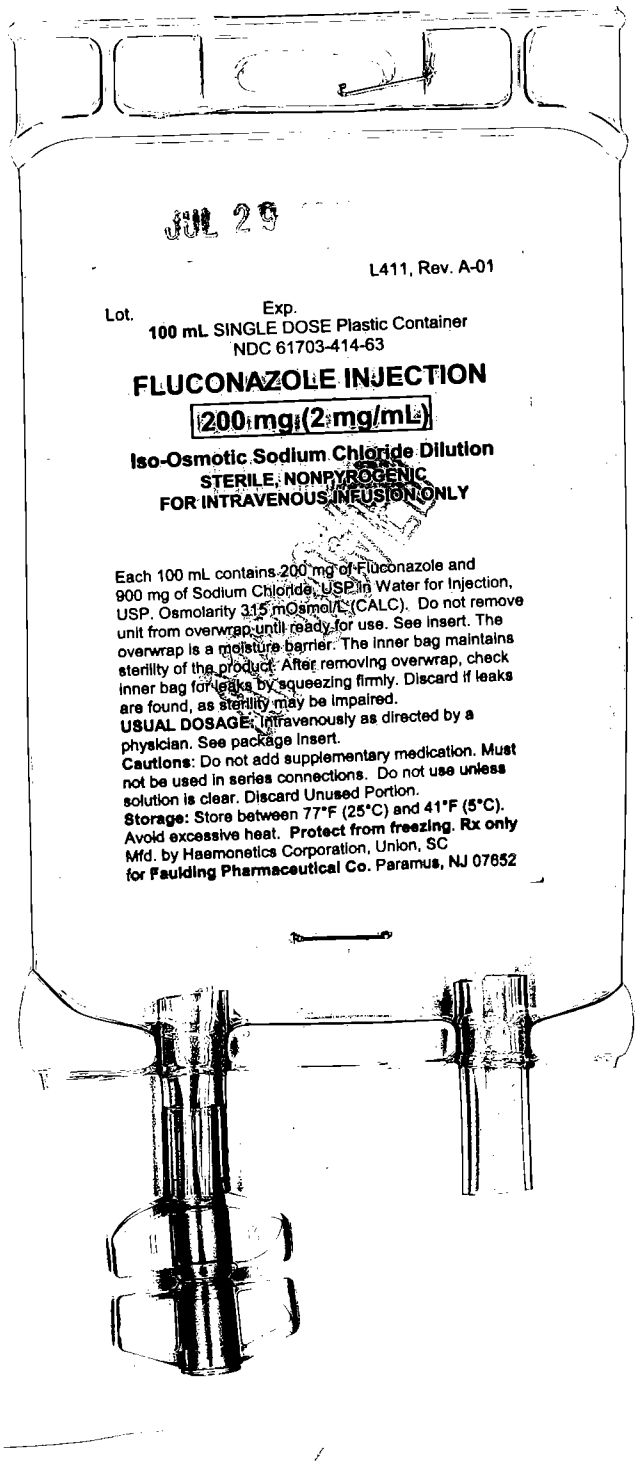
Iso-Osmotic Sodium Chloride Dilution

STERILE, NONPYROGENIC
FOR INTRAVENOUS INFUSION ONLY
Rx only

Each 200 mL contains 400 mg of Fluconazole and 1.8 g of Sodium Chloride, USP in Water for Injection, USP. Osmolarity 315 mOsmol/L (CALC).
USUAL DOSAGE: Intravenously as directed by a physician. See package insert.
CAUTIONS: **Do not remove unit from overwrap until ready for use.** 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. Discard Unused Portion.
STORAGE: STORE UNITS IN MOISTURE BARRIER OVERWRAP BETWEEN 77°F (25°C) AND 41°F (5°C) UNTIL READY TO USE. AVOID EXCESSIVE HEAT. **PROTECT FROM FREEZING**.

Manufactured for **Faulding Pharmaceutical Co.** Paramus, NJ 07652
by Haemonetics Corporation, Union, SC

L394, Rev. A



JUL 29

L411, Rev. A-01

Lot. Exp.

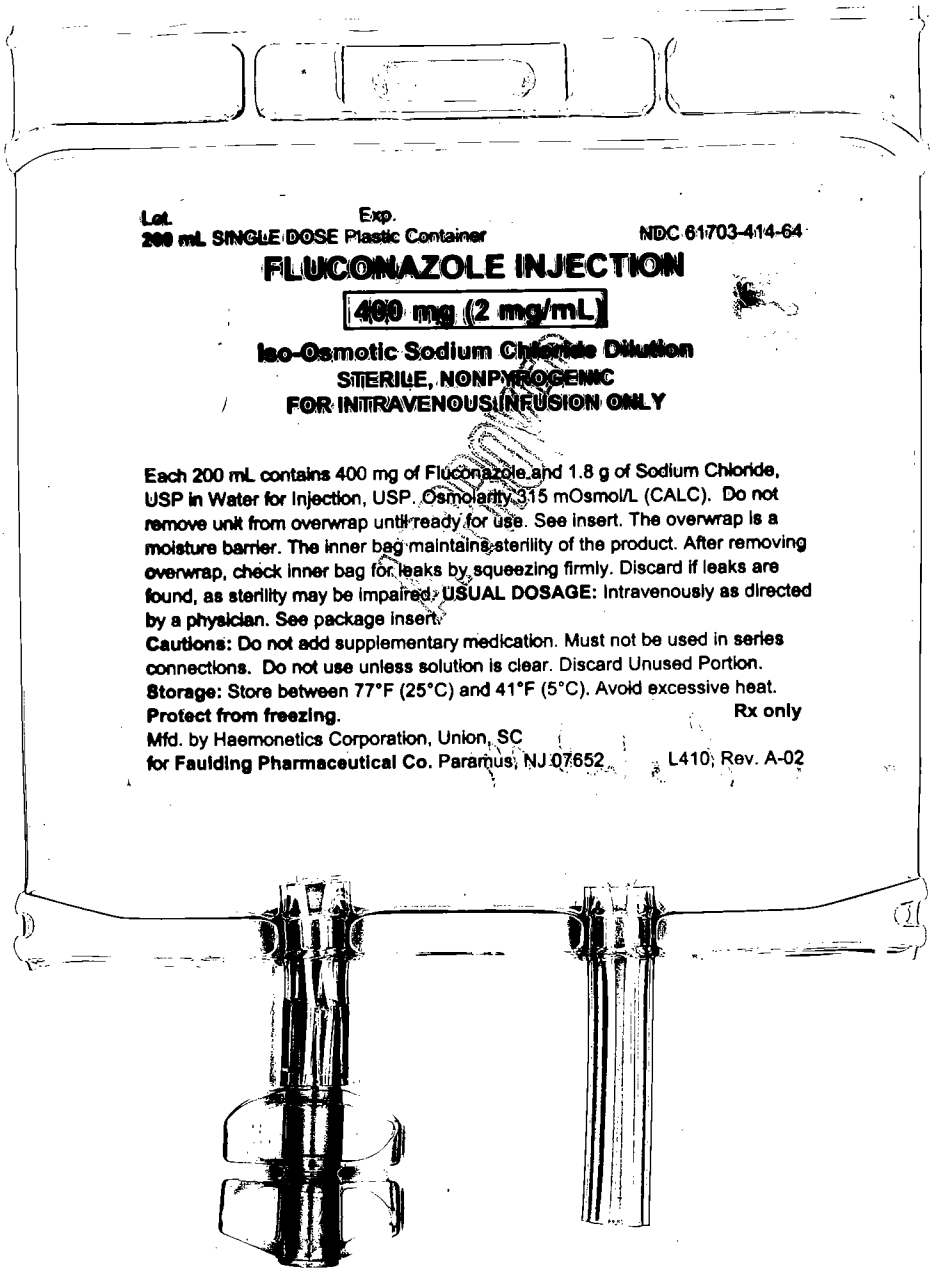
100 mL SINGLE DOSE Plastic Container
NDC 61703-414-63

FLUCONAZOLE INJECTION

200 mg (2 mg/mL)

Iso-Osmotic Sodium Chloride Dilution
STERILE, NONPYROGENIC
FOR INTRAVENOUS INFUSION ONLY

Each 100 mL contains 200 mg of Fluconazole and 900 mg of Sodium Chloride, USP in Water for Injection, USP. Osmolarity 315 mOsmol/L (CALC). Do not remove unit from overwrap until ready for use. See insert. The overwrap is a moisture barrier. The inner bag maintains sterility of the product. After removing overwrap, check inner bag for leaks by squeezing firmly. Discard if leaks are found, as sterility may be impaired.
USUAL DOSAGE: Intravenously as directed by a physician. See package insert.
Cautions: Do not add supplementary medication. Must not be used in series connections. Do not use unless solution is clear. Discard Unused Portion.
Storage: Store between 77°F (25°C) and 41°F (5°C). Avoid excessive heat. **Protect from freezing. Rx only**
Mfd. by Haemonetics Corporation, Union, SC
for **Faulding Pharmaceutical Co.** Paramus, NJ 07652



Lot. Exp.
200 mL SINGLE DOSE Plastic Container NDC 61703-414-64

FLUCONAZOLE INJECTION

400 mg (2 mg/mL)

Iso-Osmotic Sodium Chloride Dilution
STERILE, NONPYROGENIC
FOR INTRAVENOUS INFUSION ONLY

Each 200 mL contains 400 mg of Fluconazole and 1.8 g of Sodium Chloride, USP in Water for Injection, USP. Osmolarity 315 mOsmol/L (CALC). Do not remove unit from overwrap until ready for use. See insert. The overwrap is a moisture barrier. The inner bag maintains sterility of the product. After removing overwrap, check inner bag for leaks by squeezing firmly. Discard if leaks are found, as sterility may be impaired. **USUAL DOSAGE:** Intravenously as directed by a physician. See package insert.

Cautions: Do not add supplementary medication. Must not be used in series connections. Do not use unless solution is clear. Discard Unused Portion.

Storage: Store between 77°F (25°C) and 41°F (5°C). Avoid excessive heat.

Protect from freezing. **Rx only**

Mfd. by Haemonetics Corporation, Union, SC
for **Fauiding Pharmaceutical Co.** Paramus, NJ 07652 L410; Rev. A-02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

LABELING REVIEWS

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

ANDA Number: 76-617 Date of Submission: December 30, 2002

Applicant's Name: Faulding Pharmaceutical Co.

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

1. GENERAL COMMENT

   We acknowledge that this application was transferred from ESI Lederle to Baxter Healthcare Corporation on December 20, 2002. We also acknowledge that Baxter Healthcare Corporation is divesting the rights of this application to Faulding Pharmaceuticals Co. Please revise your labels and labeling to reflect these changes.

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

   a. See GENERAL COMMENT above.

   b. We encourage you to differentiate your drug product strengths by using boxing, contrasting colors, and/or some other means. In addition, we recommend that you use the same color for the established name and expression of strength of one drug product for all labeling pieces except the insert labeling.

   c. Revise the expression of strength to read "200 mg (2 mg/mL)"" as the total volume appears on the labels. Since the unit strength (2 mg/mL) is also included, we believe that it is not necessary to express as "200 mg/100 mL (2 mg/mL)". This comment also applies to the 400 mg strength.

   d. Revise the text "[redacted]' to read "Iso-Osmotic Sodium Chloride Dilution" and delete the term "Iso-Osmotic" appearing in association with "Sterile, Nonpyrogenic".

   e. Add the text "FOR INTRAVENOUS INFUSION ONLY" immediately after the text "ISO-OSMOTIC, STERILE, NONPYROGENIC".

   f. Add the text "Discard Unused Portion" at the end of the Cautions statement.

   g. Revise to read:

      After removing...leaks by squeezing firmly.

2. OVERWRAP

   We acknowledge that you proposed a clear and unprinted overwrap. Hence, the text on the overwrap is represented by the text on the container labels. We find this proposal acceptable only if the text on the container labels is sufficiently legible through the clear plastic overwrap. Please comment.

3. CARTON

   a. See GENERAL COMMENT above.

   b. See comments under CONTAINER, where applicable.

   c. We encourage the Inclusion of the text "Do not remove unit from overwrap until ready for use." in a prominent manner as the first sentence under 'CAUTIONS:".

4. INSERT

a. GNERAL

i. It is preferable to use the term "to" rather than a hyphen to express a numerical range.

ii. It is preferable to use the term "mcg" rather than ""μg" throughout the text..

b. DESCRIPTION - Second paragraph:

"chemical formula" rather than " [redacted] formula"

c. CLINICAL PHARMACOLOGY (Drug Interaction Studies) -

i. Antacid:

Please include a disclaimer for Maalox®.

ii. Phenytoin - First sentence:

...the administration of oral fluconazole 200 mg daily...

iii. Microbiology

Delete the third paragraph as this information is specific to the 150 mg tablet.

d. INDICATIONS AND USAGE

i. Revise to read "Fluconazole injection is ...

ii. Prophylaxis

Delete the [redacted] as this does not appear in the innovator's labeling.

e. CONTRAINIDICATIONS

See comment e(i) above.

f. PRECAUTIONS

It is preferable to use the term "times" rather than the symbol "x". [e.g. "2 to 7 times" rather than "2-7 x" in 3 instances]

g. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults:

A) Delete the subsection heading " [redacted]".

B) Include the following as the new first sentence of the first paragraph:

SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION.

C) Second paragraph, first sentence - Revise to read:

The daily dose of fluconazole for the treatment of infections should...

ii. Administration

A) First paragraph:

Fluconazole injection is administered... [rather than ' [redacted] "]

B) Second paragraph:

Fluconazole injection in plastic containers is intended...

iii. [redacted]

Revise this subsection heading to read "Directions for IV Use of Fluconazole in Plastic Containers".

iv. To Open - Last sentence:

Revise to read "After removing overwrap, check the inner...

v. Preparation for Administration - Add the following as the end:

WARNING: Must not be used in series connections.

h. HOW SUPPLIED

a. See GENERAL COMMENT above.

b. Include the text "Avoid excessive heat" in your storage temperature statement as it appears on your labels and carton labeling.

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.

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

QUESTION/COMMENT TO THE CHEMIST

1. **It is stated that the pH of this drug product is 3.5 to 7.5. Is this accurate?**

2. **The storage temperature proposed is identical to the innovator's. It states that "brief exposure up to 104°F (40°C) does not adversely affect the product.". Is this accurate statement based on their stability protocol?**

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

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 176 (Volume B 1.1).

4. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	001	4404216	JAN 29,2004	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification **III.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

   ANDA: Same as RLD. See comment #2 for the chemist above. Post-approval stability test will be performed at 25°C ± 2°C/40% ± 5% RH & 5°C±3°C up to 24 months. (p.1678 & 1679, B. 1.4)

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 (Plastic container; in o.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.823, B. 1.3)

   Primary container - Polyvinyl chloride
   Overwrap - Polypropylene

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. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product when reviewing ANDA 76-087. The e-mail correspondences can be found in the file folder. Until the innovator changes the name or USP lists this as "fluconazole in sodium chloride injection", the generics will be the same as the innovator regarding established name (i.e., fluconazole injection). This is not the subject of a USP monograph, yet.

folks,

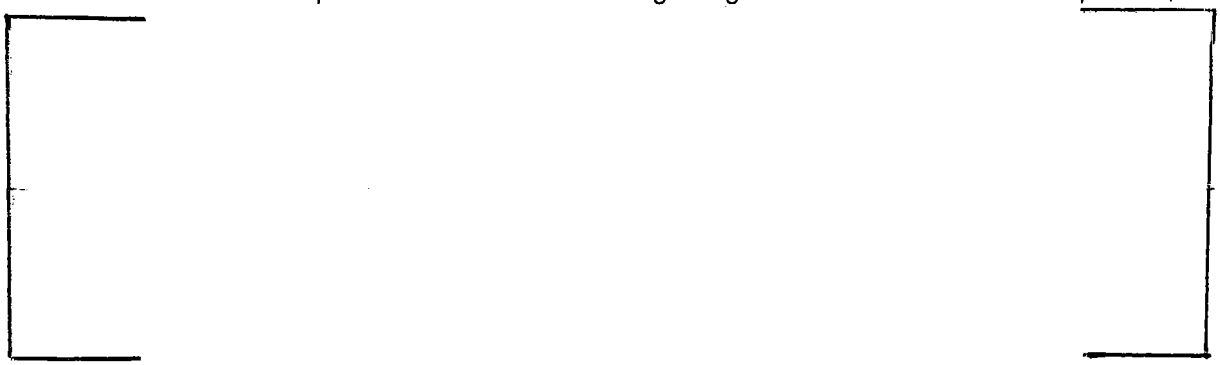
This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (19-950). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

10. We decided to revisit the name issue and sent the following e-mail to the PM for Diflucan Injection on 9/10/11.

Hi Matthew:

As I checked the old correspondence from Yana Mille regarding the established name of this product, her



Chan

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.

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by Haemonetics Corporation, Union, SC (p.285a, vol.B.1.1). This is Baxter's contract manufacturing facility.

Date of Review: 5/30/03 **Date of Submission: 12/20/02**

Primary Reviewer: Chan Park C Park **Date:** 6/21/03

Team Leader: T.W. Baker **Date:** 6/30/03

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cc:

ANDA: 76-617
DUP/DIVISION FILE
HFD-613/Cpark/Lgolson

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Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 76-617 Date of Submission: August 20, 2003 and August 27, 2003

Applicant's Name: Faulding Pharmaceutical Co.

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

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

Do you have 12 Final Printed Labels and Labeling? No

Submitted in draft labeling

CONTAINER LABELS - 200 mg (2 mg/mL) & 400 mg (2 mg/mL)

Satisfactory in draft as of 8/20/03 submission

CARTON LABELING - 10 Single Dose

200 mg - Satisfactory in draft as of **8/20/03** submission

400 mg - Satisfactory in draft as of **8/27/03** submission

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in draft as of 8/20/03 submission

REVISIONS NEEDED POST-APPROVAL:

1. CARTON - Shelf carton

   a. Increase the prominence of the text "Use no sharp...carton.".

   b. Please assure that the requirements of 21 CFR 201.15(a)(2) are met. (information on 2 or more panels)

2. INSERT

   a. DESCRIPTION - Second paragraph:

      Upon further review, revise to read "molecular formula" rather than "chemical formula".

   b. HOW SUPPLIED (First sentence) - Revise to read:

      Fluconazole Injection in Iso-Osmotic Sodium Chloride Dilution is available as follows:

Above comments were forwarded to Ms. Heather Bradley of the firm via tele-conference on 9/17/03. She was requested that the revisions should be made to the labeling prior to the submission of the FPL. She stated that she will do as directed.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan® Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:
S-028, approved February 22, 1999

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparisons
Basis of Approval for the Carton Labeling: Side-by-side comparisons

Other comments:

After much deliberation, we decided to accept the sponsor's proposal for the container and carton labels pertaining the distinction of these two different strengths (i.e., 200 mg vs. 400 mg) after considering the justification forwarded by the sponsor in the amendment of 8/20/03 (vol. 3.1)

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

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 176 (Volume B 1.1).

4. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	001	4404216	JAN 29,2004	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification **III.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Same as RLD. See comment #2 for the chemist above. Post-approval stability test will be performed at 25°C ± 2°C/40% ± 5% RH & 5°C±3°C up to 24 months. (p.1678 & 1679, B. 1.4)

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 (Plastic container; in o.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.823, B. 1.3)

Primary container - Polyvinyl chloride
Overwrap - Polypropylene

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. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product when reviewing ANDA 76-087. The e-mail correspondences can be found in the file folder. Until the innovator changes the name or USP lists this as "fluconazole in sodium chloride injection", the generics will be the same as the innovator regarding established name (i.e., fluconazole injection). This is not the subject of a USP monograph, yet.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (19-950). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

10. We decided to revisit the name issue and sent the following e-mail to the PM for Diflucan Injection on 9/10/11.

Hi Matthew:

As I checked the old correspondence from Yana Mille regarding the established name of this product, her

[ ]

Chan

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.

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by Haemonetics Corporation, Union, SC (p.285a, vol.B.1.1). This is Baxter's contract manufacturing facility.

13. The sponsor proposed a clear and unprinted overwrap. The sponsor stated that only clearly legible and sufficiently overwrapped plastic containers will be released. Hence, the text on the overwrap is represented on the proposed container labels.

Date of Review: 9/17/03 **Date of Submission: 8/20/03 & 8/27/03**

Primary Reviewer: Chan Park **Date:** 9/26/03.

Team Leader: **Date:** 9/29/03

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cc:

ANDA: 76-617
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HFD-613/Cpark/Lgolson

Review

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

ANDA Number: 76-617 Date of Submission: December 17, 2003

Applicant's Name: Mayne Pharma (USA) Inc. (formerly "Faulding Pharmaceutical Inc.)

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

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 (2 mg/mL) & 400 mg (2 mg/mL)

Satisfactory in FPL as of 12/17/03 submission (vol.3.1)

CARTON LABELING - 10 Single Dose x 100 mL; 10 Single Dose x 200 mL

Satisfactory in FPL as of 12/17/03 submission (vol. 3.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 12/17/03 submission (vol. 3.1, Rev. 9/03, Code - L422)

POST-APPRVOAL REVISION NEDDED:

The sponsor (Ms. Heather Bradley) committed via a tele-conference with Chan Park on 1/14/04 that the sponsor will revise all labeling reflecting the new company name (Mayne Pharma(USA) Inc.) and submit in an annual report. She will submit a written commitment regarding this. The sponsor informed to the Agency that the name "Faulding Pharmaceutical Co." has been changed to "Mayne Pharma (USA) Inc." in a letter dated November 14, 2003.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan® Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:
S-028, approved February 22, 1999

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparisons
Basis of Approval for the Carton Labeling: Side-by-side comparisons

Other comments:

1. After much deliberation, we decided to accept the sponsor's proposal for the container and carton labels pertaining the distinction of these two different strengths (i.e., 200 mg vs. 400 mg) after considering the justification forwarded by the sponsor in the amendment of 8/20/03 (vol. 3.1)

2. The sponsor proposed a clear and unprinted overwrap. The sponsor stated that only clearly legible and sufficiently overwrapped plastic containers will be released. Hence, the text on the overwrap is represented on the proposed container labels.

3. The sponsor will affix the carton label on two panels of the blank, universal carton box.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

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 176 (Volume B 1.1).

4. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Patent Certification	Labeling Impact
019950	001	4404216	JAN 29,2004		III	No

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification **III.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

   ANDA: Same as RLD. See comment #2 for the chemist above. Post-approval stability test will be performed at 25°C ± 2°C/40% ± 5% RH & 5°C±3°C up to 24 months. (p.1678 & 1679, B. 1.4)

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 (Plastic container; in o.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.823, B. 1.3)

   Primary container - Polyvinyl chloride
   Overwrap - Polypropylene

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"

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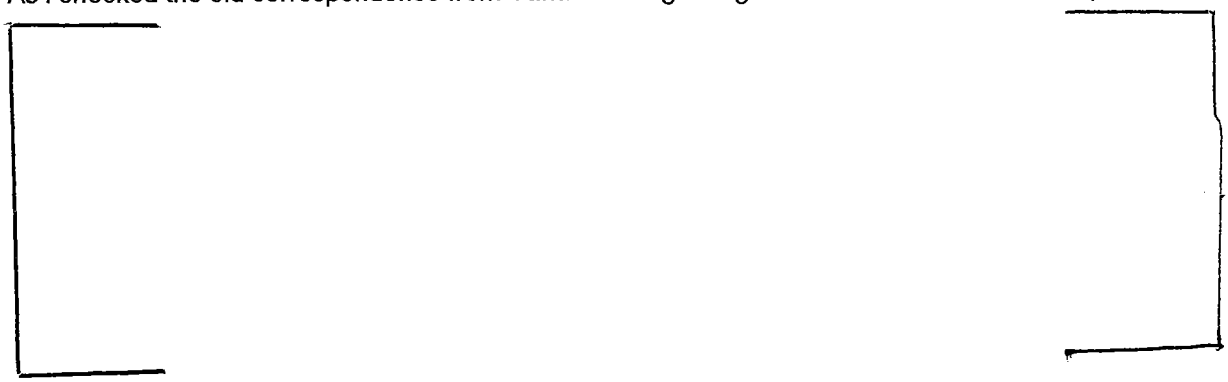

Chan

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:

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Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by Haemonetics Corporation, Union, SC (p.285a, vol.B.1.1). This is Baxter's contract manufacturing facility.

13. The sponsor proposed a clear and unprinted overwrap. The sponsor stated that only clearly legible and sufficiently overwrapped plastic containers will be released. Hence, the text on the overwrap is represented on the proposed container labels.

Date of Review: 1/14/03 **Date of Submission: 12/17/03**

Primary Reviewer: Chan Park C Park **Date:** 1/20/04

Team Leader: [signature] **Date:** 1/20/04

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cc:

ANDA: 76-617
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HFD-613/Cpark/Lgolson

Review

APPEARS THIS WAY
ON ORIGINAL

(This AP summary #2 supersedes the AP summary prepared on 1/14/04)
(APPROVAL SUMMARY#2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-617 Date of Submission: December 17, 2003

Applicant's Name: Mayne Pharma (USA) Inc. (formerly "Faulding Pharmaceutical Inc.)

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

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 (2 mg/mL) & 400 mg (2 mg/mL)

Satisfactory in FPL as of 12/17/03 submission (vol.3.1)

CARTON LABELING - 10 Single Dose x 100 mL; 10 Single Dose x 200 mL

Satisfactory in FPL as of 12/17/03 submission (vol. 3.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 12/17/03 submission (vol. 3.1, Rev. 9/03, Code - L422)

POST-APPRVOAL REVISION NEDDED:

The sponsor (Ms. Heather Bradley) committed via a tele-conference with Chan Park on 1/14/04 that the sponsor will revise all labeling reflecting the new company name (Mayne Pharma(USA) Inc.) and submit in an annual report. She will submit a written commitment regarding this. The sponsor informed to the Agency that the name "Faulding Pharmaceutical Co." has been changed to "Mayne Pharma (USA) Inc." in a letter dated November 14, 2003.

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 #:
S-028, approved February 22, 1999
S-039, approved on March 24, 2004 is for the revised patient information leaflet 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

Basis of Approval for the Container Labels: Side-by-side comparisons
Basis of Approval for the Carton Labeling: Side-by-side comparisons

Other comments:

1. After much deliberation, we decided to accept the sponsor's proposal for the container and carton labels pertaining the distinction of these two different strengths (i.e., 200 mg vs. 400 mg) after considering the justification forwarded by the sponsor in the amendment of 8/20/03 (vol. 3.1)

2. The sponsor proposed a clear and unprinted overwrap. The sponsor stated that only clearly legible and sufficiently overwrapped plastic containers will be released. Hence, the text on the overwrap is represented on the proposed container labels.

3. The sponsor will affix the carton label on two panels of the blank, universal carton box.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. S-039 approved on March 24, 2004 is for the revised patient information leaflet 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 176 (Volume B 1.1).

4. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Patent Certification	Labeling Impact
019950	001	4404216	JAN 29,2004		III	None
019950	001	4404216*PED	JUL 29,2004		III	None

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification **III.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

   ANDA: Same as RLD. See comment #2 for the chemist above. Post-approval stability test will be performed at 25°C ± 2°C/40% ± 5% RH & 5°C±3°C up to 24 months. (p.1678 & 1679, B. 1.4)

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 (Plastic container; in o.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.823, B. 1.3)

Primary container - Polyvinyl chloride
Overwrap - Polypropylene

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. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product when reviewing ANDA 76-087. The e-mail correspondences can be found in the file folder. Until the innovator changes the name or USP lists this as "fluconazole in sodium chloride injection", the generics will be the same as the innovator regarding established name (i.e., fluconazole injection). This is not the subject of a USP monograph, yet.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (19-950). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

10. We decided to revisit the name issue and sent the following e-mail to the PM for Diflucan Injection on 9/10/11.

Hi Matthew:

As I checked the old correspondence from Yana Mille regarding the established name of this product, her

Chan

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.

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by Haemonetics Corporation, Union, SC (p.285a, vol.B.1.1). This is Baxter's contract manufacturing facility.

13. The sponsor proposed a clear and unprinted overwrap. The sponsor stated that only clearly legible and sufficiently overwrapped plastic containers will be released. Hence, the text on the overwrap is represented on the proposed container labels.

Date of Review: 7/20/04 **Date of Submission: 12/17/03**

Primary Reviewer: Chan Park **Date:** 7/20/04

Team Leader: **Date:** 7/21/04

---

cc:

ANDA: 76-617
V:\FIRMSAM\MAYNEPharma\LTRS&REV\76617AP#2.LABELING.doc
HFD-613/Cpark/Lgolson

Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

CHEMISTRY REVIEWS

ANDA #76-617

Fluconazole Injection in Sodium chloride Diluent

Faulding Pharmaceutical Company

Radhika Rajagopalan, Ph.D.,
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-617

2. REVIEW #: 1

3. REVIEW DATE: 5/20/03

4. REVIEWER: Radhika Rajagopalan

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12/30/02
Amendment	1/17/03
Amendment	5/2/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Faulding pharmaceutical Co.
Address:	650 Farm Road Mack-Cali Center II, 2nd Floor Main lobby Paramas, NJ 07652
Representative:	Mr. Stephen Richardson

Chemistry Review Data Sheet

Telephone: 201-225-5514

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Roerig/Diflucan®
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:
U.S. Patent 4,404,216 will expire on 1/29/2004. A Paragraph III certification is enclosed on page 8. Page 11 indicates that there is no market exclusivity identified in the 22nd edition of Orange Book.

10. PHARMACOL. CATEGORY:
Antifungal; Indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis.

10. DOSAGE FORM:
Injectable solution

11. STRENGTH/POTENCY:
200 mg/100 mL and 400 mg/200 mL

12. ROUTE OF ADMINISTRATION:
Intravenous infusion

14. Rx/OTC DISPENSED: __x_Rx ___OTC

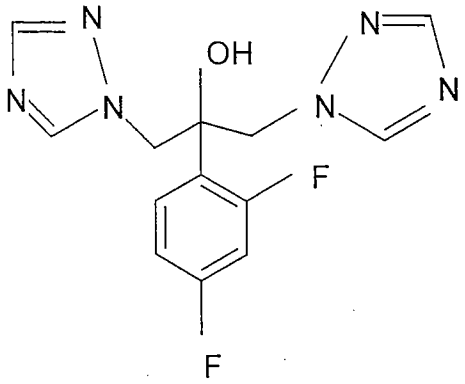
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

_____x_Not a SPOTS product

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

APPEARS THIS WAY
ON ORIGINAL



NAME:	Fluconazole
CHEMICAL NAME:	2-(2,4-difluorphenyl)-1,3-bis(1H-1,24-triazol-1-yl)2propanol
CAS NUMBER	86386-73-4
MOLECULAR WEIGHT:	306.3
CHEMICAL FORMULA:	$C_{13}H_{12}N_6OF_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	5/23/03	
	III			4			
	III			4			
	III			4			

[1] 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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-950	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Initiated	2/13/03	
Methods Validation	To be initiated		
Labeling	Pending		
Bioequivalence	Pending		
EA			
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Inter-branch assignment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA #76-617

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable in this review cycle.

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

NA

II. Summary of Chemistry Assessments

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

Drug Product: Fluconazole and Sodium chloride are formulated in Water for Injection. The solution is non-buffered, and [redacted]. It is packaged in ready to administer flexible bags with ports. The flexible bags are protected by overwrap. Fluconazole is administered intravenously.

Drug Substance: Fluconazole is readily soluble in water and exhibits polymorphism. Since the drug substance is dissolved in Water for Injection, polymorph concerns do not exist for this ANDA. It has reasonable chemical and physical stability.

B. Description of How the Drug Product is Intended to be Used

IV

C. Basis for Approvability or Not-Approval Recommendation

Due to deficiencies in the DMF, and control of drug product, the ANDA is not recommended for approval in this cycle.

III. Administrative

A. Reviewer's Signature

Radhika Rajagopalan 6/6/03

B. Endorsement Block

Radhika Rajagopalan/5/29/03:
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

Pending review.

33. ESTABLISHMENT INSPECTION

Filed on 2/13/03.

34. BIOEQUIVALENCE

Pending waiver review.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Filed on page 1700.

APPEARS THIS WAY
ON ORIGINAL

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-617 APPLICANT: Faulding Pharmaceutical Company

DRUG PRODUCT: Fluconazole Injection in Sodium Chloride Diluent, 200 mg/100 mL and 400 mg/200 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]
2.
3.
4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF [redacted] was reviewed and found inadequate. Deficiencies in the DMF would have to be addressed satisfactorily, prior to ANDA approval.

2. Methods validation has been initiated at an FDA Laboratory. Please provide them samples, and reference standard(s), when requested.

Sincerely yours,

for 6/6/03

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-617
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/RRajagopalan/5/28/03~~,5/29~~/03 R. Rajagopalan 6/6/03

HFD-645/BArnwine/6/4/03 B Arnwine 6/6/03

HFD-617/NPark/6/4/03

F/T by: EW 6/5/03

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TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA #76-617

Fluconazole Injection in Sodium chloride Diluent

Faulding Pharmaceutical Company

Radhika Rajagopalan, Ph.D.,
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-617

2. REVIEW #: 2

3. REVIEW DATE: 8/27/03

4. REVIEWER: Radhika Rajagopalan

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	12/30/02
Amendment	1/17/03
Amendment	5/2/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	7/24/03
Labeling Amendment	8/20/03
Labeling Amendment	8/27/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Faulding Pharmaceutical Co.
Address:	650 From Road Mack-Cali Center II, 2nd Floor Main lobby Paramas, NJ 07652

Chemistry Review Data Sheet

Representative: Heather A. Bradley

Telephone: 201-225-5526

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Roerig/Diflucan®
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:
U.S. Patent 4,404,216 will expire on 1/29/2004. A Paragraph III certification is enclosed on page 8. Page 11 indicates that there is no market exclusivity identified in the 22nd edition of Orange Book.

10. PHARMACOL. CATEGORY:
Antifungal; Indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis.

10. DOSAGE FORM:
Injectable solution

11. STRENGTH/POTENCY:
200 mg/100 mL and 400 mg/200 mL

12. ROUTE OF ADMINISTRATION:
Intravenous infusion

14. Rx/OTC DISPENSED: __x_Rx ___OTC

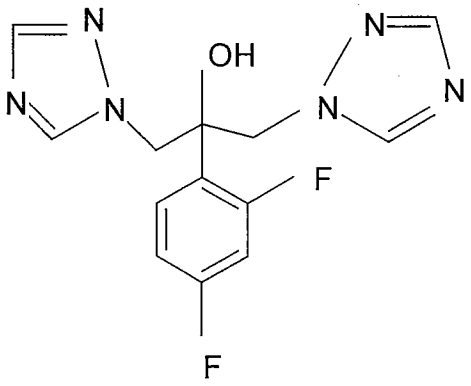
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x_Not a SPOTS product

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

APPEARS THIS WAY
ON ORIGINAL



NAME:	Fluconazole
CHEMICAL NAME:	2-(2,4-difluorphenyl)-1,3-bis(1H-1,24-triazol-1-yl)2propanol
CAS NUMBER	86386-73-4
MOLECULAR WEIGHT:	306.3
CHEMICAL FORMULA:	$C_{13}H_{12}N_6OF_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	adequate	8/29/03	
	III			4			
	III			4			
	III			4			

[1] 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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-950	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Satisfactory	8/13/03	Lynne A. Ensor
EES	Satisfactory	10/10/03	
Methods Validation	Initiated	6/16/03	R. Rajagopalan
Labeling	Acceptable	9/29/03	
Bioequivalence	Satisfactory	8/11/03	Xiaojian Jiang
EA			
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Inter-branch assignment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA #76-617

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA can be approved in this review cycle.

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

NA

II. Summary of Chemistry Assessments

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

Drug Product: Fluconazole and Sodium chloride are formulated in Water for Injection. The solution is non-buffered, and ——————. It is packaged in ready to administer flexible bags with ports. The flexible bags are protected by overwrap. Fluconazole is administered intravenously.

Drug Substance: Fluconazole is readily soluble in water and exhibits polymorphism. Since the drug substance is dissolved in Water for Injection, polymorph concerns do not exist for this ANDA. It has reasonable chemical and physical stability.

B. Description of How the Drug Product is Intended to be Used

IV

C. Basis for Approvability or Not-Approval Recommendation

ANDA is recommended for approval based on adequate DMF status, acceptable micro and CMC review, and stability data.

III. Administrative

A. Reviewer's Signature Ruchika Rajagopalan 10/17/03

B. Endorsement Block

Radhika Rajagopalan/9/3/03
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 76-617
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/RRajagopalan/9/3/03 R. Rajagopalan 10/17/03

HFD-645/BArnwine/10/16/03 B Arnwine 10/23/03

HFD-617/NPark/10/3/03

F/T by: EW 10/16/03

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TYPE OF LETTER: TA

APPEARS THIS WAY
ON ORIGINAL

ANDA #76-617

Fluconazole Injection in Sodium chloride Diluent

Faulding Pharmaceutical Company

Radhika Rajagopalan, Ph.D.,
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-617

2. REVIEW #: 3

3. REVIEW DATE: 6/29/04

4. REVIEWER: Radhika Rajagopalan

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	12/30/02
Amendment	1/17/03
Amendment	5/2/03
Amendment	7/24/03
Labeling Amendment	8/20/03
Labeling Amendment	8/27/03
Tentative Approval	10/30/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor (Label) Amendment	12/17/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Mayne Pharma (USA) Inc.
Address:	650 From Road Mack-Cali Center II, 2nd Floor Main lobby Paramas, NJ 07652

Chemistry Review Data Sheet

Representative: Heather A. Bradley

Telephone: 201-225-5526

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Roerig/Diflucan®
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:
U.S. Patent 4,404,216 will expire on 1/29/2004. A Paragraph III certification is enclosed on page 8. Pediatric exclusivity expires 7/28/04.

10. PHARMACOL. CATEGORY:
Antifungal; Indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis.

10. DOSAGE FORM:
Injectable solution

11. STRENGTH/POTENCY:
200 mg/100 mL and 400 mg/200 mL

12. ROUTE OF ADMINISTRATION:
Intravenous infusion

14. Rx/OTC DISPENSED: __x_Rx ___OTC

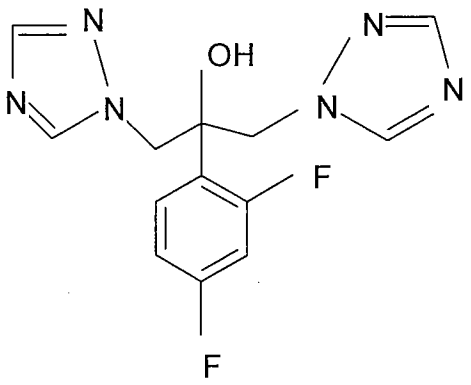
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x_Not a SPOTS product

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

APPEARS THIS WAY
ON ORIGINAL



NAME:	Fluconazole
CHEMICAL NAME:	2-(2,4-difluorphenyl)-1,3-bis(1H-1,24-triazol-1-yl)2propanol
CAS NUMBER	86386-73-4
MOLECULAR WEIGHT:	306.3
CHEMICAL FORMULA:	$C_{13}H_{12}N_6OF_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	adequate	8/29/03	
	III			4			
	III			4			
	III			4			

[1] 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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-950	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Satisfactory	8/13/03	Lynne A. Ensor
EES	Satisfactory	10/10/03	
Methods Validation	Initiated	6/16/03	R. Rajagopalan
Labeling	Acceptable	1/20/04	C. Park
Bioequivalence	Satisfactory	8/11/03	Xiaojian Jiang
EA			
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Inter-branch assignment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA #76-617

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is recommended for full approval. The minor amendment does not include any CMC changes.

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

NA

II. Summary of Chemistry Assessments

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

Drug Product: Fluconazole and Sodium chloride are formulated in Water for Injection. The solution is non-buffered, and [redacted]. It is packaged in ready to administer flexible bags with ports. The flexible bags are protected by overwrap. Fluconazole is administered intravenously.

Drug Substance: Fluconazole is readily soluble in water and exhibits polymorphism. Since the drug substance is dissolved in Water for Injection, polymorph concerns do not exist for this ANDA. It has reasonable chemical and physical stability.

B. Description of How the Drug Product is Intended to be Used

IV

C. Basis for Approvability or Not-Approval Recommendation

ANDA is recommended for approval based on adequate DMF status, acceptable micro, label and CMC review, and stability data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Radhika Rajagopalan/6/29/04 R. Rajagopalan 7/21/04
Brenda Arnwine/
Nicole Park/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-617
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/RRajagopalan/6/29/04 R. Rajagopalan 7/21/04

HFD-645/BArnwine/ B1 7/21/04

HFD-617/NPark/

F/T by: rad7/20/04

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TYPE OF LETTER: Full Approval

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-617
Drug Product Name	Fluconazole Injection in 0.9% Sodium Chloride
Strength	200 mg/ 100 ml (100 ml and 200 ml)
Applicant Name	Faulding Pharmaceutical Company
Address	650 From Road, Mack-Cail Center II, 2nd Floor, Main Lobby Paramus, NJ 07652
Submission Date(s)	December 30, 2002
Amendment Date(s)	1/17/03, 5/2/03
Reviewer	**Xiaojian Jiang**
First Generic	**no**
File Location	**V:\firmsam\ Faulding\ltrs&rev\76617W1202.doc**

I. Executive Summary

The firm has requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR 320.22(b)(1) for its test product, Fluconazole Injection 200 mg/100 ml in 0.9% Sodium Chloride, manufactured as 100 ml and 200 ml bulk packages in Plastic Containers. The reference listed drug used in this application is Diflucan® Injection, 200 mg/100 ml in 0.9% Sodium Chloride, manufactured in volumes of 100 ml and 200 ml and packaged in Plastic Containers (held by Pfizer Inc., NDA# 19-950, approved 1/29/90). The test drug product is a parenteral solution intended solely for administration by intravenous infusion and contains the same active and inactive ingredients in the same concentration as the approved reference listed product. The Division of Bioequivalence grants the waiver of in vivo bioequivalence study requirements under 21 CFR section 320.22 (b) (1).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Fluconazole Injection, 200 mg/100 ml in 0.9% Sodium Chloride, (100 ml and 200 ml) packaged in Plastic Containers
Reference Product	Diflucan® Injection, 2 mg/ml in 0.9% Sodium Chloride, (100 ml and 200 ml) packaged in Plastic Containers
RLD Manufacturer	Roerig, Division of Pfizer
NDA No.	19-950
RLD Approval Date	January, 29, 1990
Indication	Treatment of oropharyngeal and esophageal candidiasis, and crytococcal meningitis, and prophylaxis of candidiasis in patients undergoing bone marrow transplantation.

B. PK/PD Information

Bioavailability	The PK properties of fluconazole are similar following administration by the intravenous or oral routes. The bioavailability for the injection should be 100%.
Food Effect	N/A
Tmax	N/A
Metabolism	Not provided
Excretion	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.
Half-life	Approximately 30 hours (range: 20-50 hours)
Relevant OGD or DBE History	ANDA#76-303 of Abbott (12/14/01), ANDA#76-087 of Bedford (12/21/00)
Agency Guidance	None
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	

D. Pre-Study Bioanalytical Method Validation-----Not Applicable

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study-----Not Applicable

2. Single-dose Fed Bioequivalence Study-----Not Applicable

F. Formulation

Location in appendix	See below
Inactive ingredients within IIG Limits (yes or no)	**Yes, identical to RLD**
If no, list ingredients outside of limits	**Not Applicable**
If a tablet, is the product scored? (yes or no)	**Not Applicable**
If yes, which strengths are scored?	**Not Applicable**
Is scoring of RLD the same as test? (yes or no)	**Not Applicable**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	**Not Applicable**

Table 1. Comparative Composition of Test and Reference Products

Ingredients	Test Product (mg/ml)	RLD (mg/ml)
Fluconazole	2.00	2.00
Sodium Chloride, USP	9.00	9.00
Water for Injection, USP	q.s. to 1ml	q.s. to 1ml

Comments

1. The drug product is a parenteral solution intended solely for administration by intravenous infusion.
2. The test drug product contains the same active and inactive ingredients in the same concentration as the approved reference listed product.
3. Diflucan® injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride diluent. Each ml contains 2 mg fluconazole and 9 mg of sodium chloride in volumes of 100 ml and 200 ml packaged in Viaflex® Plus.plastic containers.

G. In Vitro Dissolution----Not Applicable

H. Waiver Request(s)

The firm has requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR 320.22(b)(1) for its test product, Fluconazole Injection, 200 mg/100 ml in 0.9% Sodium Chloride, (100 ml and 200 ml) packaged in Plastic Containers.

I. Deficiency Comments----None

J. Recommendations

Division of Bioequivalence agrees that the information submitted by Faulding Pharmaceutical Company demonstrates that Fluconazole Injection, 200 mg/100 ml in 0.9% Sodium Chloride, (100 ml and 200 ml) packaged in Plastic Containers falls under 21 CFR section 320.22 (b) (1) of the Bioavailability /Bioequivalence Regulations. The wavier of *in vivo* bioequivalence study for Faulding's Fluconazole Injection, 200 mg/100 ml in 0.9% Sodium Chloride, (100 ml and 200 ml) packaged in Plastic Containers, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Faulding's Fluconazole Injection, 200 mg/100 ml in 0.9% Sodium Chloride, bioequivalent to the RLD, Diflucan® Injection, 200 mg/100 ml in 0.9% Sodium Chloride, manufactured by Pfizer.

Xiaojian Jiang, Ph.D.
Division of Bioequivalence
Review Branch II

JIANG Xiaojian 8/11/2003

Xiaojian Jiang, Branch II, Date signed

8/11/2003

Shriniwas Nerurkar, Branch II, Date signed

for Barbara Mayer Davis 8/12/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:#76-617 APPLICANT: Faulding Pharmaceutical Company

DRUG PRODUCT: Fluconazole Injection in 0.9% Sodium Chloride, 200 mg/100 ml,(100 ml and 200 ml) packaged in plastic containers

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,

Barbara Myers Davit

for Dale P. Conner, Pharm. D.
Director, Divisionof Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA#76-617
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Xiaojian Jiang

V:\FIRMSAM\faulding\ltrs&rev\76617W1202.doc
Printed in final on 8/11/2003

Endorsements: (Final with Dates)
HFD-655/ Xiaojian Jiang Jiang Huaqian 8/11/2003 8/11/03
HFD-655/ S. Nerurkar
for HFD-650/ D. Conner 8/12/03

BIOEQUIVALENCY - ACCEPTABLE submission date: December 30, 2002

6.**WAIVER** (WAI) Strengths: 200 mg/100 ml, (100 ml and 200 ml) packaged in plastic containers

Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comment: A waiver is granted

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-617	SPONSOR : Faulding Pharmaceutical Company
DRUG AND DOSAGE FORM :	Fluconazole Injection in 0.9% Sodium Chloride
STRENGTH(S) :	200 mg/ 100 ml, (100 ml and 200 ml) packaged in plastic containers
TYPES OF STUDIES :	N/A
CLINICAL STUDY SITE(S) :	N/A
ANALYTICAL SITE(S) :	N/A

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

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Xiaojian Jiang, Ph.D. BRANCH : II

INITIAL : Xiaojian DATE : 8/11/2003

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : DATE : 8/11/2003

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

INITIAL : Barbara M. Davit DATE : 8/12/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-640

August 12, 2003

ANDA: 76-617

Drug Product Name
Proprietary: n/a
Non-proprietary: Fluconazole Injection in Sodium Chloride Diluent
Drug Product Classification: n/a

Review Number: 1

Subject of this Review
Submission Date: December 30, 2002 (original) & July 24, 2003 (amendment)
Receipt Date: December 31, 2002 (original) & July 25, 2003 (amendment)
Consult Date: n/a
Date Assigned for Review: August 5, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): none
Date(s) of Previous Micro Review(s): none

Applicant/Sponsor
Name: Faulding Pharmaceutical Co.
Address: Mack Cali Centre II
650 From Road, 2nd Floor
Paramus, NJ 07652
Representative: Steve Richardson
Telephone: 201-225-5514

Name of Reviewer: Lynne A. Ensor, Ph. D.

Conclusion: Recommended

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** n/a

2. **SUPPLEMENT PROVIDES FOR:** n/a

3. **MANUFACTURING SITE:** Haemonetics Corp., Union, SC

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 200 mg/100 mL and 400 mg/mL (2 mg/mL in 100 and 200 mL plastic single dose containers), sterile injectable solution

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Indicated for treatment of oropharangeal and esophageal candidiasis and cryptococcal meningitis

B. **SUPPORTING/RELATED DOCUMENTS:** none

C. **REMARKS:** Although the July 24, 2003 amendment provides responses to Chemistry deficiencies, the amendment is included as part of this review since some of the applicant's responses pertain to the sterility assurance of the drug product.

filename: v:\microrev\76617.doc

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability – recommended

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 – The drug solution is [redacted]

B. Brief Description of Microbiology Deficiencies – none identified.

C. Assessment of Risk Due to Microbiology Deficiencies – n/a

III. Administrative

A. Reviewer's Signature Lynne A Ensor 8/13/03

Lynne A. Ensor, Ph. D.

B. Endorsement Block Neal J. Sweeney 8-13-03

L. Ensor
N. Sweeney

C. CC Block

cc:
Original ANDA
Division File
Field Copy

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-617 **Applicant** Fauding Pharmaceutical Co
Drug Fluconazole Injection **Strength** 2mg/mL

ROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

1. Project Manager, Review Support Br Team (7)

DRAFT Package Date 10-3-03 Initials MP
FINAL Package Date 10/23/03 Initials for

Application Summary:

Original Rec'd date 12-30-02
Date Acceptable for Filing 12-31-02 ✓
Patent Certification (type) III
Date Patent/Exclus.expires Jan 29, 2004
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# 19-950
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status possible Warning letter
Date of Office Bio Review 8-12-03 (folder)
Date of Labeling Approv. Sum 9-29-03 (folder)
Date of Sterility Assur. App. 8-13-03 (folder)
Methods Val. Samples Pending Yes ☒ No ☐
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

Gregg Davis **PPIV ANDAs Only**
Deputy Director, DLPS
Date 10/30/03 Initials (AW)
Date 10/30/03 Initials (AW)

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder: Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked 10/30/03 (AW)
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

RLD - Diflucan in Sodium Chloride 0.9% in Plastic Container, 200mg/100mL, 400mg/200mL (Pfizer Central Research), NDA 19-950/002.

Paragraph III

Fauding made a paragraph III Certification to the '216 patent which is due to expire on 1/29/04. There is no exclusivity listed in the current Orange Book for this drug product.

3. Div. Dir./Deputy Dir.
Chemistry Div. I
Comments:
Date _____ Initials _____
Date 10/30/03 Initials AM

CMC satisfactory.

REVIEWER:	DRAFT Package	FINAL Package
4. Frank Holcombe Assoc. Dir. For Chemistry	Date_____ Initials_____	Date_____ Initials_____

Comments: (First generic drug review)
N/A. Tentative approval letters for this drug product have previously issued to Bedford (76-087), APP (76-145), and abbott (76303).

5. Peter Rickman Director, DLPS	Date 10/30/03 Initials PW	Date 10/30/03 (left for) Initials

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

Comments: Acceptable CES dtd 10/10/03 (verified 10/30/03). No OAE alerts noted. Bioequivalence waiver granted under 21 CFR 320.22(b)(1). Drug product is "AB" to the RLD. Office-level bio endorsed 8/12/03. Labeling found acceptable for TA on 9/29/03. CMC found acceptable 10/23/03. Methods validation has been requested. Stability/microbiology found acceptable 8/13/03.

OR

5. Robert L. West Deputy Director, OGD	Date 10/30/03 Initials PW	Date 10/30/2003 Initials (for RLW)

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

Comments:

Faulding made a paragraph III certification to the 216 patent that is due to expire on 1/29/04.

This ANDA is recommended for tentative approval.

6. Gary Buehler Director, OGD	Date 10/30/03 Initials GB	Date 10/30/03 Initials GB

Comments:

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

7. Project Manager, Nicole Park Review Support Br Team	Date 10/30/03 Initials NP	Date 10/30/03 Initials NP

NA Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
_____Time notified of approval by phone _____Time approval letter faxed

FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Sarah\Templates\Approvrou2.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-617 Applicant Mayne Pharma (USA), Inc.
Drug Fluconazole Injection in Sodium Chloride Diluent Strength(s) 200mg/100mL, 400mg/200mL

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date ____ Initials ____
Date 7/21/04 Initials [signature]

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 19-950 (003)
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked Previously granted
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ N/A
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ N/A
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day N/A
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments:

2. Project Manager, NLL Team 7
Review Support Branch
Date 7/9/04 Initials M
Date ____ Initials ____

Original Rec'd date 12-30-02
Date Acceptable for Filing 12-31-02
Patent Certification (type) ~~II~~ II
Date Patent/Exclus.expires 7/29/04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 10-10-03
Date of Office Bio Review 8-11-03
Date of Labeling Approv. Sum 1-20-04
Date of Sterility Assur. App. 8-13-03
Methods Val. Samples Pending Yes ☒ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☒ Date 10-30-03
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 ☐
Comments:
N/A

Date ____ Initials ____

4. Div. Dir. (Deputy Dir.)
Chemistry Div. I (II) OR III
Comments:
CMC OK
RCA

Date 7/26/04 Initials RCA

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A

6. Vacant RLD=Diltiazem in Sodium Chloride 0.9% in Plastic Container
Deputy Dir., DLPS 200mg/100mL; 400mg/200mL Date_____
Pfizer Inc. NDA 19-950 (2002) Initials_____

7. Peter Rickman Date 7/26/04
Director, DLPS Initials Per e-mail
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition Yes ☐ No ☐
Comments: Acceptable EES dated 10/10/03 (received 12/2004). No outstanding labeling issues noted. Refer to the administrative item-of-form completed at the time of the tentative approval issued to Hayne (Faulding) on October 30, 2003. On 12/11/03, Hayne submitted a minor amendment providing final printed labeling and requesting final approval effective 7/29/04. PPL found acceptable 7/21/04. CMC found acceptable 7/21/04. Methods validation was requested but the request has been withdrawn 2° current OGD/OPS policy - does not meet current criteria for methods validation.

Robert L. West Date 7/26/2004
Deputy Director, OGD Initials Per e-mail
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition Yes ☐ No ☐
Comments: Hayne Pharma (Faulding) made a paragraph III certification to the '216 patent that expired on 1/29/04. However, the '216 patent was effectively extended until July 29, 2004 upon the granting of pediatric exclusivity to Pfizer. This ANDA is recommended for final approval upon the expiration of Pfizer's pediatric exclusivity on 7/29/04.

9. Gary Buehler Date 7/29/04
Director, OGD Initials RWA for
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

10. Project Manager, Team Nicole Lee Date 7/29/04
Review Support Branch Initials NL
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10:15 Time notified of approval by phone 10:20 Time approval letter faxed
FDA Notification:
7/29 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/29 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

We revised the patent certification to paragraph II, and acknowledged Pfizer's period of pediatric exclusivity.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-617

CORRESPONDENCE

Baxter
Baxter Healthcare
2 Esterbrook Lane
Cherry Hill, NJ 08003

ORIGINAL ANDA SUBMISSION

December 30, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FLUCONAZOLE INJECTION
IN SODIUM CHLORIDE DILUENT
200 mg/100 mL AND 400 mg/200 mL
PLASTIC CONTAINERS

Dear Sir/Madam:

We are submitting a complete Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluconazole Injection in Sodium Chloride Diluent, packaged in 200 mg/100 mL and 400 mg/200 mL polyvinyl chloride plastic containers.

This application provides for the manufacturing, processing, labeling, packaging and testing of Fluconazole Injection in Sodium Chloride Diluent at our contract manufacturing facility, Haemonetics Corporation, located at 155 Medical Sciences Drive, Union, SC 29379. We are also providing a brief general description of the Union, SC manufacturing facility's operations and controls.

On December 20, 2002, the assets of Wyeth's generic injectable division, ESI Lederle (including Fluconazole Injection in Sodium Chloride Diluent) were sold to Baxter Healthcare Corporation. Baxter Healthcare Corporation is divesting the intellectual and property rights of this Fluconazole Injection in Sodium Chloride Diluent application to *Faulding Pharmaceuticals Co.*

It should be noted that the documents presented in this ANDA were prepared in advance of the divestiture and, hence, contain either the ESI Lederle or Haemonetics letterheads.

This application, which contains five (5) unnumbered volumes, is organized in the format suggested in the February 1999 Guidance for Industry, entitled "Organization of an ANDA."

The reference listed drug in this application is Roerig's, Division of Pfizer Diflucan® Fluconazole Injection in Sodium Chloride Diluent. The active ingredient, dosage form, strength, and route of administration of the proposed product are the same as those of the reference listed drug. However, the pH specification of our proposed drug product differs from the reference listed drug Diflucan® Injection. Please refer to Section XIV (2), "Justification for pH Specification Report #256-PD-17" enclosed in Attachment 2, and Section XXI for copies of previous correspondence with FDA dated October 22, 2002, and a Telephone Contact Report dated December 17, 2002.

A side-by-side comparison of the proposed product labeling to that of the reference listed drug is included in this application. The proposed product, like the reference product, will be marketed as a prescription drug as stated in the labeling.

According to the information published in the list, the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act.

This application contains a Paragraph III certification with respect to the claimed U.S. Patent 4,404,216 which will expire January 29, 2004. We request that approval of the Application be made effective on the expiration of this patent.

We are requesting a waiver of evidence of *in vivo* bioequivalence under 21 CFR 320.22(b)(1)(i) and (ii) since the proposed product (i) is a parenteral solution intended solely for injection and (ii) contains the same active and inactive ingredients in the same concentration as the reference listed drug.

We are using the active pharmaceutical ingredient Fluconazole, manufactured by ——— and distributed by ——— in the United States as the active ingredient supplier in our drug product. A copy of their letter authorizing FDA referencing DMF # ———on behalf of ESI Lederle is included in this application.

The reference listed drug is packaged in 100 mL and 200 mL plastic containers. The proposed drug product is packaged in 100 mL and 200 mL plastic containers. The submission batch size for the 100 mL and 200 mL plastic containers was ——— each and the yield was ——— 100 mL plastic containers and ——— 200 mL plastic containers. The anticipated production batch size is ———

To provide a general understanding of the batch record format and facilitate it's review, certain aspects of this application (Master Batch Record) are elucidated, via notes to the reviewer. These notes include a summary of the SOP system used to prepare the Manufacturer Work Order, and initiate activities associated with the product production/release.

The sterility assurance data includes complete method validation reports and a description of the microbiological controls use in production of the drug product. This information can be found in Section XXII.

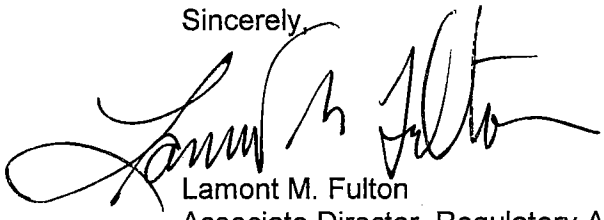
Two copies of the method validation packages are being submitted with this application since the drug substance and drug product are non-compendial articles. In addition, we have included the Testing Specifications portion of the Active Ingredient Raw Material (Section VIII), Controls for Finished Dosage Form (Section XIV), and Stability of Finished Dosage Form (Section XVI).

In accordance with 21 CFR 314.94(d)(5) requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications to the field office, we are providing a field copy directly to Ms. Nancy L. Rolli in the Newark FDA District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

This application contains a certification statement with respect to convictions or persons debarred under 21 USC 355a(a) or (b).

Please contact the undersigned if you need any additional information. Our fax number is (856) 424-1461.

Sincerely,



Lamont M. Fulton
Associate Director, Regulatory Affairs
Baxter Healthcare
(856) 489-2237

LMF:hk
Enc.
c: Ms. Nancy L. Rolli
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

76-617 NDA S. Middleton 2/12/03 76-617

Faulding Pharmaceutical Company
A division of Mayne Pharma

Mack-Cali Centre II
650 From Road
2nd Floor
Paramus
New Jersey 07652
United States

Telephone
+1 201 225 5500
Regulatory Facsimile
+1 201 225 5530

www.faulding.com

AMENDMENT

January 17, 2003

Via Federal Express AWB #8330-6562-9485-0215

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Fluconazole Injection in Sodium Chloride Diluent 200mg/100mL and 400mg/200mL Plastic Containers

Dear Sir/Madam:

Reference is made to an original ANDA for the above listed products submitted by Baxter Healthcare Corporation (Baxter) on behalf of Faulding Pharmaceutical Company (Faulding) dated December 30, 2002 (copy of cover letter provided as Attachment I).

This Amendment is submitted to include a debarment certification from Faulding (Attachment II).

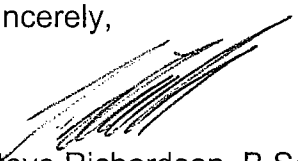
As highlighted in the cover letter of the original ANDA, the intellectual and property rights of the Fluconazole Injection in Sodium Chloride Diluent have been divested to Faulding from Baxter. As such, all future correspondence pertaining to the ANDA should be addressed to the following:

Mr. Stephen Richardson
Director, Regulatory Affairs
Faulding Pharmaceutical Co.
650 From Road
Mack-Cali Center II, 2nd Floor, Main Lobby
Paramus, NJ 07652

Phone: (201) 225-5514
Fax: (201) 225-5530

We have provided an archival, a review and a field copy of this amendment. The field copy will be provided directly to Ms. Nancy Rolli in the Newark FDA District Office. We certify that the field copy is a true copy of the chemistry manufacturing and controls section of our application.

Sincerely,



Steve Richardson, B.Sc., MBA
Director, Regulatory Affairs
United States and Puerto Rico
Telephone: (201) 225-5514
Facsimile: (201) 225-5530

APPEARS THIS WAY
ON ORIGINAL

Faulding Pharmaceutical Company
A division of Mayne Pharma

Faulding

Mack-Call Centre II
650 From Road
2nd Floor
Paramus
New Jersey 07652
United States

Telephone
+1 201 225 5500
Regulatory Facsimile
+1 201 225 5530
www.faulding.com

AMENDMENT

February 11, 2003

Via Federal Express AWB #8371-9937-0539-0215 and
Via Telefax: (301) 594-1174

Saundra Middleton, Project Manager
Regulatory Support Branch, Office of Generic Drugs
Centre for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA #76-617 Fluconazole Injection in Sodium Chloride Diluent 200mg/100mL and 400mg/200mL Plastic Containers

Dear Ms. Middleton:

I refer to our telephone conversation on February 10, 2003 regarding the above referenced product.

As you requested, I am providing with this letter a revised DMF Access Letter for DMF # _____. The attached DMF Access Letter (a replacement for that provided on page 179 of the original ANDA) has been revised to authorize FDA to reference the DMF in relation to ANDA #76-617.

We have provided an archival, a review and a field copy of the Amendment. The field copy will be provided directly to Mrs. Nancy Rolli in the Newark FDA District Office. We certify that the field copy is a true copy of the information provided with this letter.

Should you have any further questions, please do not hesitate to give me a call.

Sincerely,

Stephen Richardson, B.Sc., MBA
Director, Regulatory Affairs
United States and Puerto Rico

SR/dmr
Enclosure

ANDA 76-617

Faulding Pharmaceutical Co.
Attention: Stephen Richardson
650 From Road
Mack-Cali Center II, 2nd Floor Main Lobby
Paramus, NJ 07652

FEB 14 2003

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated February 10, 2003 and your correspondence dated February 11, 2003.

Reference is also made to your correspondence dated January 17, 2003.

NAME OF DRUG: Fluconazole in Sodium Chloride 0.9%
Injection in Plastic Container, 2 mg/mL,
100 mL and 200 mL plastic containers

DATE OF APPLICATION: December 30, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-617
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB 14-FEB-2003 date
HFD-615/SMiddleton, CSO date 2/12/03
Word File
V:\FIRMSAM\FAULDING\LTRS&REV\76617.ACK
F/T EEH 2/12/03

ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

EES Submitted 5/23/03

Faulding Pharmaceutical Company
A division of Mayne Pharma

Faulding

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www.faulding.com

VIA FEDERAL EXPRESS

May 2, 2003

ORIG AMENDMENT

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Voluntary Amendment

Re: ANDA 76-617, Fluconazole Injection in Sodium Chloride Diluent 200mg/100mL and 400mg/200mL Plastic Containers

Dear Mr. Buehler:

Reference is made to the original application for ANDA 76-617 for Fluconazole Injection in Sodium Chloride Diluent, submitted on December 30, 2002. Please also refer to the communication dated January 17, 2003 regarding the divestiture of ANDA 76-617 from Baxter Healthcare Corporation to Faulding Pharmacuetical Co.

Pursuant to 21 CFR 314.96, Faulding is hereby submitting a voluntary amendment to the unapproved ANDA referenced above. This amendment serves as notice of a change in analytical testing site for Fluconazole drug substance and finished drug product from Baxter Healthcare Corporation (formerly ESI Lederle) to Faulding Puerto Rico, Inc. This transfer entails a change in testing site only, and no change to any testing method has been incorporated.

We have provided a review, field, and archival copy of this amendment. The field copy will be provided directly to Ms. Nancy Rolli in the Newark FDA District Office.

Please contact me at the number provided below if you have any questions regarding this submission.

Sincerely,

Steve Richardson, B.Sc., MBA
Director, Regulatory Affairs
United States and Puerto Rico
Tel: (201) 225-5514
Fax: (201) 225-5530

RECEIVED
MAY 5 - 2003
OGD / CDER

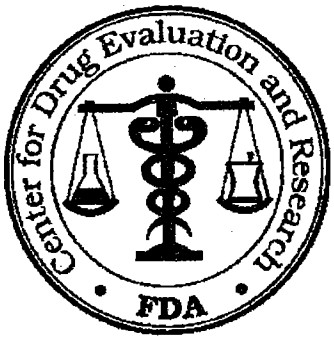
5/14/03

MINOR AMENDMENT

JUN - 9 2003

NDA 76-617

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Faulding Pharmaceutical Co

TEL: 201-225-5514

ATTN: Stephen Richardson

FAX: 201-225-5530

FROM: Nicole Park

PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection in Sodium Chloride Diluent, 200 mg/100 mL and 400 mg/200 mL.

May 2, 2003 amendment npark 6/10/03.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

np

JUN - 9 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-617 APPLICANT: Faulding Pharmaceutical Company

DRUG PRODUCT: Fluconazole Injection in Sodium Chloride Diluent, 200 mg/100 mL and 400 mg/200 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF [redacted] was reviewed and found inadequate. Deficiencies in the DMF would have to be addressed satisfactorily, prior to ANDA approval.

2. Methods validation has been initiated at an FDA Laboratory. Please provide them samples, and reference standard(s), when requested.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Faulding Pharmaceutical Company
A division of Mayne Pharma

Faulding

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VIA FEDERAL EXPRESS

July 7, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

N/AF

Voluntary Amendment
Revised Proposed Labeling

Re: ANDA 76-617 Fluconazole Injection in Sodium Chloride Diluent 200mg/100mL and 400mg/200mL Plastic Containers

Dear Sir:

Reference is made to ANDA 76-617 for Fluconazole Injection in Sodium Chloride Diluent submitted on December 30, 2002. Please also refer to the communication dated January 17, 2003 regarding the divestiture of ANDA 76-617 from Baxter Healthcare Corporation to Faulding Pharmaceutical Co.

Due to the acquisition of ANDA 76-617 by Faulding Pharmaceutical Co., the draft labeling submitted in ANDA 76-617 has been revised to reflect the transfer of ownership. Enclosed in this amendment to ANDA 76-617 is draft labeling for Fluconazole Injection in Sodium Chloride Diluent manufactured for Faulding Pharmaceutical Co.

Please be advised that there have been no text changes to the labeling provided in ANDA 76-617. Only signature information, NDC numbers, and pack sizes have been revised to reflect the proposed marketing of Fluconazole Injection in Sodium Chloride Diluent manufactured by Faulding Pharmaceutical Co. Four (4) copies of draft labeling for each component are enclosed.

We have provided a review, archive and field copy of this amendment. The field copy will be provided directly to Ms. Nancy Rolli in the Newark FDA District Office. Faulding certifies that the field copy is a true copy of the amendment as supplied in the archive and review copies.

If you require any additional information regarding this submission, please contact me at the number provided below.

RECEIVED
JUL 08 2003
OGD/CDER

Sincerely,

Heather A. Bradley
Regulatory Associate
Tel: 201-225-5526
Fax: 201-225-5530

Nicole

********** -COMM. JOURNAL- ********** DATE JUL-09-2003 ***** TIME 09:39 ********

21

MODE = MEMORY TRANSMISSION START=JUL-09 09:38 END=JUL-09 09:39

FILE NO.=002

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	918564241461	004/004	00:00:50

76-617
Nadine

-FDA CDER OGD LPS -

********** - ***** - **********

Fax Cover Sheet

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 7/8/03

To: Jamant M. Fulton

Phone: 856-489-2237 **Fax:** 856-424-1461

From: Chan Park

Phone: 301-827-5846 **Fax:** 301-443-3847

Re: ANDA 76-617

Number of Pages: _____
(Including Cover Sheet)

Comments: Labeling deficiencies per the phonecall.
Thanks,
Chan

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

ANDA Number: 76-617 Date of Submission: December 30, 2002

Applicant's Name: Faulding Pharmaceutical Co.

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

1. GENERAL COMMENT

We acknowledge that this application was transferred from ESI Lederle to Baxter Healthcare Corporation on December 20, 2002. We also acknowledge that Baxter Healthcare Corporation is divesting the rights of this application to Faulding Pharmaceuticals Co. Please revise your labels and labeling to reflect these changes.

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

a. See GENERAL COMMENT above.

b. We encourage you to differentiate your drug product strengths by using boxing, contrasting colors, and/or some other means. In addition, we recommend that you use the same color for the established name and expression of strength of one drug product for all labeling pieces except the insert labeling.

c. Revise the expression of strength to read "200 mg (2 mg/mL)"" as the total volume appears on the labels. Since the unit strength (2 mg/mL) is also included, we believe that it is not necessary to express as "200 mg/100 mL (2 mg/mL)". This comment also applies to the 400 mg strength.

d. Revise the text "[redacted]' to read "Iso-Osmotic Sodium Chloride Dilution" and delete the term "Iso-Osmotic" appearing in association with "Sterile, Nonpyrogenic".

e. Add the text "FOR INTRAVENOUS INFUSION ONLY" immediately after the text "ISO-OSMOTIC, STERILE, NONPYROGENIC".

f. Add the text "Discard Unused Portion" at the end of the Cautions statement.

g. Revise to read:

After removing... leaks by squeezing firmly.

2. OVERWRAP

We acknowledge that you proposed a clear and unprinted overwrap. Hence, the text on the overwrap is represented by the text on the container labels. We find this proposal acceptable only if the text on the container labels is sufficiently legible through the clear plastic overwrap. Please comment.

3. CARTON

a. See GENERAL COMMENT above.

b. See comments under CONTAINER, where applicable.

c. We encourage the Inclusion of the text "Do not remove unit from overwrap until ready for use." in a prominent manner as the first sentence under 'CAUTIONS:".

4. INSERT

a. GNERAL

i. It is preferable to use the term "to" rather than a hyphen to express a numerical range.

ii. It is preferable to use the term "mcg" rather than ""μg" throughout the text..

b. DESCRIPTION - Second paragraph:

"chemical formula" rather than " ——— formula"

c. CLINICAL PHARMACOLOGY (Drug Interaction Studies) -

i. Antacid:

Please include a disclaimer for Maalox®.

ii. Phenytoin - First sentence:

...the administration of oral fluconazole 200 mg daily...

iii. Microbiology

Delete the third paragraph as this information is specific to the 150 mg tablet.

d. INDICATIONS AND USAGE

i. Revise to read "Fluconazole injection is ...

ii. Prophylaxis

Delete the ——————— as this does not appear in the innovator's labeling.

e. CONTRAINIDICATIONS

See comment e(i) above.

f. PRECAUTIONS

It is preferable to use the term "times" rather than the symbol "x". [e.g. "2 to 7 times" rather than "2-7 x' in 3 instances]

g. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults:

A) Delete the subsection heading " ———————".

B) Include the following as the new first sentence of the first paragraph:

SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION.

C) Second paragraph, first sentence - Revise to read:

The daily dose of fluconazole for the treatment of infections should...

ii. Administration

A) First paragraph:

Fluconazole injection is administered... [rather than ' [redacted] "]

B) Second paragraph:

Fluconazole injection in plastic containers is intended...

iii. [redacted]

Revise this subsection heading to read "Directions for IV Use of Fluconazole in Plastic Containers".

iv. To Open - Last sentence:

Revise to read "After removing overwrap, check the inner...

v. Preparation for Administration - Add the following as the end:

WARNING: Must not be used in series connections.

h. HOW SUPPLIED

a. See GENERAL COMMENT above.

b. Include the text "Avoid excessive heat" in your storage temperature statement as it appears on your labels and carton labeling.

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.

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

Faulding Pharmaceutical Company
A division of Mayne Pharma

Mack-Cali Centre II
650 From Road
2nd Floor
Paramus
New Jersey 07652
United States

Telephone
+1 201 225 5500
Regulatory Facsimile
+1 201 225 5530

www.faulding.com

VIA FEDERAL EXPRESS

July 24, 2003

ORIG AMENDMENT
N|Am

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: ANDA 76-617: Fluconazole Injection in Sodium Chloride Diluent 200 mg/100mL and 400 mg/200 mL

Dear Sir/Madam:

Reference is made to Faulding Pharmaceutical Co.'s (Faulding's) Abbreviated New Drug Application for Fluconazole Injection in Sodium Chloride Diluent. Faulding is hereby responding to the Minor Deficiency Letter dated June 9, 2003.

For ease of review, this Minor Amendment is arranged as follows:

- **Section 1:** FDA Form 356h
- **Section 2:** FDA deficiency comments and responses (with attachments)
- **Section 3:** Field Copy Certification

We have provided a Review, Archive and Field copy of this amendment. The Field Copy will be provided directly to Ms. Nancy Rolli in the Newark FDA District Office.

Please note that the proposed packaging for Fluconazole Injection has been changed from a ——— (as described in the original ANDA) to a 10-pack. Revised labeling is currently being prepared and will be submitted as an Amendment in a separate response to the labeling deficiency dated July 9, 2003.

If you require any additional information regarding this submission, please contact me at the number provided below.

Sincerely,

Steve Richardson, B.Sc., MBA
Director, Regulatory Affairs
Tel: 201-225-5514
Fax: 201-225-5530

RECEIVED
JUL 25 2003
OGD/CDER

8/5/03

Faulding Pharmaceutical Company
A subsidiary of Mayne Pharma

Mack-Cali Centre II
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VIA FEDERAL EXPRESS

August 20, 2003

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N|AF

Minor Amendment - Labeling

Re: ANDA 76-617, Fluconazole Injection in Sodium Chloride Diluent 2 mg/mL; 100 mL and 200 mL Plastic Containers

Dear Sir:

Reference is made to our Abbreviated New Drug Application for Fluconazole Injection (ANDA 76-617). Please also refer to a voluntary labeling amendment submitted on July 7, 2003.

Faulding Pharmaceutical Co. is hereby responding the labeling deficiency comments received by fax on July 9, 2003.

For ease of review, this response has been arranged as follows:

- Section 1: FDA Form 356h
- Section 2: Agency Labeling comments, followed by Faulding's response
- Section 3: Side-by-Side Comparison of revised labeling with previously submitted labeling
- Section 4: 12 copies of revised labeling
- Section 5: New submission of shelf carton labeling
- Section 6: Field Copy Certification

A review copy and archive copy have been provided. A field copy has been submitted directly to Ms. Nancy Rolli in the Newark FDA District Office.

If you require any additional information, please contact me at the number provided below.

Sincerely,

Heather A. Bradley

Heather A. Bradley
Regulatory Associate
Tel: 201-225-5526
Fax: 201-225-5530

RECEIVED
AUG 21 2003
OGD/CDER

Faulding Pharmaceutical Company
A subsidiary of Mayne Pharma

Faulding

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VIA FEDERAL EXPRESS

August 27, 2003

Office of Generic Drugs
CDER, FDA
Metro Park North II
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF

Amendment – Labeling

Re: Fluconazole Injection
200 mg/100 mL and 400 mg/200 mL
ANDA ~~76-627~~ 76-617

Dear Sir/Madame:

Reference is made to ANDA 76-617 for Fluconazole Injection. Please also refer to the Minor Amendment – Labeling to ANDA 76-617 submitted on August 20, 2003.

Faulding is hereby submitting an amendment to the August 20, 2003 submission to provide for a corrected label copy. The 200 mL carton label supplied in the August 20, 2003 Amendment contained an incorrect reference to a 100mL bag.

Enclosed in this amendment is a side by side comparison of the revised 200 mL carton label with the incorrect text highlighted. We have also provided twelve (12) copies of the revised draft 200 mL carton label.

We have provided a Review and Archive copy of this submission. A Field copy has been provided directly to Ms. Nancy Rolli in the Newark FDA District Office. If you require any additional information regarding this submission, please contact me at the number provided below.

Sincerely,

Heather A Bradley

Heather A. Bradley
Regulatory Associate
Tel: 201-225-5526
Fax: 201-225-5530

Faulding Pharmaceutical Company
A subsidiary of Mayne Pharma

November 14, 2003

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

Mack-Cali Centre II
650 From Road
2nd Floor
Paramus
New Jersey 07652
United States

Telephone
1 201 225 5500
Facsimile
1 201 225 5515

www.faulding.com

[redacted]
XS

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

Effective November 15, 2003, Faulding Pharmaceutical Co. (Faulding) will be changing its corporate name to Mayne Pharma (USA) Inc. Attached is a listing of Faulding's approved ANDAs and NDAs, pending applications, and supplements effected by this correspondence. Also, Form FDA 356h for these products is provided as Attachment I.

The postal address of Mayne Pharma (USA) Inc., provided below, will remain unchanged.

Mayne Pharma (USA) Inc.
650 From Road,
Mack-Cali Centre II
Second Floor, Main Lobby
Paramus, NJ 07652).

This correspondence pertains only to the change in corporate name. There are no changes to any manufacturing site addresses provided in these applications.

Should you have any questions, please do not hesitate to contact me at 201-225-5523.

Sincerely,

Krista Waz
Regulatory Affairs Associate
Tel: 201-225-5523
Fax: 201-225-5530

Enclosures

VIA FEDERAL EXPRESS

Mayne Pharma (USA) Inc.

Mack-Cali Centre II
650 From Road, Second Floor
Paramus, NJ 07652
United States

Telephone
(201) 225-5500
Facsimile
(201) 225-5530
www.maynepharma.com/us

December 17, 2003

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
(N/AM)

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Re: ANDA 76-617, Fluconazole Injection in Sodium Chloride Diluent 2 mg/mL; 100 mL and 200 mL Plastic Containers

Dear Sir/Madam:

Mayne Pharma (USA) Inc., formerly Faulding Pharmaceutical Co., is hereby requesting final approval for ANDA 76-617 for Fluconazole Injection. Please refer to the tentative approval letter for this ANDA dated October 30, 2003. We also refer you to the submission of November 14, 2003, in which the Office of Generic Drugs was notified of the corporate name change from Faulding Pharmaceutical Co. to Mayne Pharma (USA) Inc.

There have been no CMC changes to ANDA 76-617 since the receipt of the tentative approval. Samples of final printed labeling are now available, and four (4) samples of each component have been provided with this submission. We have provided a review, archive, and field copy of this submission. Mayne certifies that the field copy is a true copy of that contained in the review and archive copies.

We trust that this request for final approval is complete. If you require any additional information, please contact me at the number provided below.

Sincerely,

Heather A Bradley

Heather A. Bradley
Regulatory Associate
Tel: 201-225-5526
Fax: 201-225-5530

RECEIVED
DEC 18 2003
OGD / CDER

January 14, 2004

VIA FACSIMILE TO:
Chan Park
Office of Generic Drugs
301-443-3847

VIA FEDERAL EXPRESS TO:
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NAF
C Park
1/23/04

Mayne Pharma (USA) Inc.

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United States

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Facsimile
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www.maynepharma.com/us

Re: Fluconazole Injection in Sodium Chloride Dilution (ANDA 76-617)
Commitment Statement for Revised Final Printed Labeling

Dear Mr. Park:
Please refer to our conversation on January 14, 2004 regarding the final printed labeling of Fluconazole Injection submitted with the request for final approval of ANDA 76-617 on Decmeber 17, 2003. Please also note our company name change from Faulding Pharmaceutical Co. to Mayne Pharma (USA) Inc, submitted via FDA Form 2656 on November 14, 2003.

Mayne Pharma acknowledges that the final printed labeling for Fluconazole Injection submitted on December 17, 2003 contained our former name, Faulding Pharmaceutical Co. Due to the timing of labeling production and the official company name change, final printed labeling with the new company name is not available at this time. However, Mayne Pharma (USA) Inc. has already begun the internal revision of this labeling. Mayne commits to submitting revised final printed labeling for Fluconazole Injection that shows the manufacturer as Mayne Pharma (USA) Inc. in the first annual report for ANDA 76-617. We apologize for not providing this clarification in our submission of final printed labeling.

We trust that this commitment will provide assurance of our intentions, and that this will not impact the request for final approval for ANDA 76-617. A hard copy of this submission is being sent to the Office of Generic Drugs. If you require any additional information, please contact me at the number provided below.

Sincerely,

Heather A. Bradley
Regulatory Associate
Tel: 201-225-5526
Fax: 201-225-5530

ORIGINAL

VIA DHL EXPRESS

NAI
PII cert to '216
Address Exc. exp.
July 29, 2004.
7/26/04 XP

Mayne Pharma (USA) Inc.

Mack-Cali Centre II
650 From Road, Second Floor
Paramus, NJ 07652
United States

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Facsimile
(201) 225-5530
www.maynepharma.com/us

July 19, 2004

Office of Generic Drugs
FDA/CDER
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT UPDATE

Re: Fluconazole Injection
2 mg/mL; 100mL and 200mL Plastic Containers
ANDA 76-617

Dear Sir/Madam:

Please refer to ANDA 76-617 for Fluconazole Injection, tentatively approved on October 30, 2003. As requested, Mayne Pharma (USA) Inc. is providing the enclosed patent certification update.

ANDA 76-617 is based on NDA 19-950 for DIFLUCAN® (Fluconazole Injection) 2 mg/mL in Sodium Chloride Diluent. DIFLUCAN®, as approved per NDA 19-950, was subject to protection under patent 4,404,216 which was to expire on January 29, 2004. ANDA 76-617, as originally submitted on December 30, 2002, contained a Paragraph III Patent Certification for the 216 patent, acknowledging the expiration date of January 29, 2004. The original ANDA 76-617 submission also contained an Exclusivity Statement saying that there were no periods of market exclusivity identified at that time.

Subsequent to the tentative approval of ANDA 76-617 on December 30, 2003, patent 4,404,216 has expired, however DIFLUCAN® was granted a period of pediatric exclusivity extending to July 29, 2004. Therefore, Mayne Pharma (USA) Inc. is providing an updated Paragraph II Patent Certification for the expired 216 patent, and an updated Exclusivity Statement for the pediatric exclusivity period extending to July 29, 2004. Mayne Pharma acknowledges that ANDA 76-617 is not eligible for final approval until July 29, 2004.

Also enclosed is FDA Form 356h for this submission. We have provided a Review and Archive copy of this submission, and have provided a Field Copy to the Newark District Office.

If you require any additional information, please contact the undersigned at the numbers provided.

Sincerely,

Steve Richardson
Director, Regulatory and Medical Affairs
Tel: 201-225-5526
Fax: 201-225-5530

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