CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-304

***Name*:** Fluconazole Injection, 2 mg/mL, (in 5% Dextrose Injection), packaged in 200 mg/100 mL and 400 mg/200 mL single-dose flexible plastic containers

***Sponsor*:** Hospira, Inc.

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

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APPLICATION NUMBER:

ANDA 76-304

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

APPROVAL LETTER

ANDA 76-304

JUL 29 2004

Hospira, Inc.
Attention: Lisa K. Zboril
275 North Field Drive, Bldg. H2-2
Lake Forest, IL 60045-5046

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 5% Dextrose Injection), packaged in 200 mg/100 mL and 400 mg/200 mL single-dose flexible plastic containers.

Reference is also made to the Tentative Approval letters issued by this office on June 18, 2003, and May 21, 2004, and to your amendments dated May 3, May 7, May 26, July 13, July 15, and July 20, 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 5% Dextrose Injection), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Diflucan® Injection, 2 mg/mL, (in 5% Dextrose 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,

Robert Lumpkin for 1/29/2004

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

cc: ANDA 76-304
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/M.Farahani/ 7,23,04
HFD-647/G.Smith/ 7/26/04
HFD-617/T.Palat/ 7/26/04
HFD-613/C.Park/7/22/04 7/26/04
HFD-613/L.Golson/ 7/26/04
HFD-600/L.Shelton/ 7/26/04
HFD-600/N.Sweeney/ 7-27-04

CMC OK 7/27/04 RCA

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F/T by rad7/22/04

APPROVAL

Robert Rest 1/29/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

TENTATIVE APPROVAL LETTERS

ANDA 76-304

JUN 18 2003

Abbott Laboratories
Hospital Products Division
Attention: Tom Stothoff
200 Abbott Park Rd., D-389, J-45/2
Abbott Park, IL 60064-6133

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 5% Dextrose Injection), packaged in 200 mg/100 mL and 400 mg/200 mL Flexible Plastic Containers.

Reference is also made to your amendments dated August 16, 2002; and January 10, and January 21, 2003.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, 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 patent issues noted below, the application is **tentatively approved.** This tentative approval 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). This 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 Dextrose 5% 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) will 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 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 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide a justification for the reasons you believe the ANDA is eligible 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, and it should be designated clearly in your cover letter that it represents a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the final date of 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 application 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 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 not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Orange Book". Furthermore, 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 prior to submitting additional amendments, please contact Ted Palat, Pharm.D., Project Manager, at 301-827-5849.

Sincerely yours,

Robert Lesko for 6/18/2003

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

cc: ANDA 76-304
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff
HFD-92

Endorsements:
HFD-645/M.Farahani/ 3,4,03
HFD-647/G.Smith/ 3/5/03
HFD-617/T.Palat/ 3/5/03
HFD-600/L.Shelton/ 3/5/03
HFD-600/N.Sweeney/ 3/5/03
HFD-613/C.Park/ 3/5/03
HFD-613/L.Golson/ 3/5/03

Robert Rad 6/18/2003

F/T by rad3/4/03

TENTATIVE APPROVAL

cont satisfactory
3/10/03

ANDA 76-304

MAY 21 2004

Hospira, Inc.
Attention: Richard J. Stec Jr., Ph.D.
275 North Field Dr., Bldg 2-J45-2
Lake Forest, IL 60045-5046

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 5% Dextrose Injection), packaged in 200 mg/100 mL and 400 mg/200 mL Flexible Plastic Containers.

Reference is also made to your amendments dated October 30, 2003; and May 3, and May 7, 2004.

We have completed the review of this abbreviated application as amended, and based upon the information you have presented to date we have concluded that the drug remains safe and effective for use as recommended in the submitted labeling. However, final approval of your application is blocked at this time by a period of exclusivity granted to the NDA-holder, Pfizer, as discussed below. Thus, your application remains **tentatively approved**. This tentative approval 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). This 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 Dextrose of Pfizer Inc., was 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) expired on January 29, 2004.

However, as currently noted in the Orange Book, the '216 patent has effectively been extended by an additional 6 months of marketing exclusivity under Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act created Section 505(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505(A) permits certain applications to obtain an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA sponsor submits requested information relating to the use of Fluconazole in the pediatric population. Pfizer Inc. (Pfizer) has submitted such information to the agency. The agency has determined that this information meets the criteria stated in the statute and has granted Pfizer 6 months of additional marketing exclusivity with respect to the '216 patent for its drug products containing Fluconazole. 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 period of market exclusivity associated with the '216 patent has expired, i.e., July 29, 2004. The final approval date may be further extended if, upon review of the pediatric data submitted by Pfizer, the agency decides that Pfizer is eligible for an additional period of Hatch-Waxman exclusivity.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide a justification for the reasons you believe the ANDA is eligible 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, and it should be designated clearly in your cover letter that it represents a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the final date of 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 application 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 lead to a delay in the issuance of the final approval letter.

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

For further information on the status of this application, or prior to submitting additional amendments, please contact Ted Palat, PharmD, Project Manager, at 301-827-5849.

Sincerely yours,

Robert Lee Lest for
5/21/2004

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

cc ANDA 76-304
Division File
Field Copy
HFD-610/R. West
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HFD-647/G.Smith/ 3/12/04
HFD-617/T.Palat/ 3/12/04
HFD-613/C.Park/3/8/04 3/15/04
HFD-613/L.Golson/ 3/15/04

3/18/04

5/21/2004

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F/T by rad3/9/04

TENTATIVE APPROVAL (2nd)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

LABELING

FLUCONAZOLE INJECTION

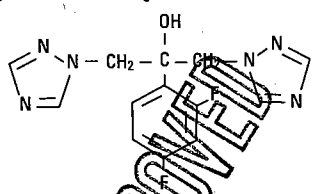
For Intravenous Infusion Only

JUL - 3

DESCRIPTION

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

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



Fluconazole is a white crystalline solid which is slightly soluble in water and saline.

Fluconazole injections are iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride or dextrose diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride or 56 mg of dextrose, hydrous. The pH ranges from 4.0 to 8.0 in the sodium chloride diluent and from 3.5 to 6.5 in the dextrose diluent. Injection volumes of 100 mL and 200 mL are packaged in flexible plastic containers.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. Exposure to temperatures above 25°C (77°F) during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that

these minor losses will lead to clinically significant changes within the expiration period.

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. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

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 Consumer Health, Inc.

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

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

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

CONTRAINDICATIONS

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles. 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	Terfenadine
Coumarin-type anticoagulants	Cisapride
Phenytoin	Astemizole
Cyclosporine	Rifabutin
Rifampin	Tacrolimus
Theophylline	

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

these minor losses will lead to clinically significant changes within the expiration period.

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.

penetrated into vaginal fluid, resulting in fluid:plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

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 (super-numerary 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

Pharmacokinetics in Children

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 for Other Infections:

Sixteen percent of over 4,000 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 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 4,048 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 8,200 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 (TABLETS AND SUSPENSION) 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 judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

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

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

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

suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

Prophylaxis in patients undergoing bone marrow transplantation: The recommended fluconazole daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg, once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1,000 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 Candidia 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:

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

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

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:

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

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

Administration

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

Fluconazole injections in flexible plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for IV Use of Fluconazole in Flexible 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 flexible plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open

Tear outer wrap at notch slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

DO NOT ADD SUPPLEMENTARY MEDICATION.

Preparation for Administration:

(Use Aseptic Technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **NOTE:** When using a vented administration set, replace bacterial retentive air filter with piercing pin cover. Insert piercing pin with twisting motion until shoulder of air filter housing rests against the outlet port flange. **NOTE:** See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close flow control clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Fluconazole Injections: Fluconazole injections for intravenous infusion administration are formulated as sterile iso-osmotic solutions containing 2 mg/mL of fluconazole. They are supplied in flexible plastic containers containing volumes of 100 mL or 200 mL affording doses of 200 mg and 400 mg of fluconazole, respectively. Fluconazole injections in flexible plastic containers are available in both sodium chloride and dextrose diluents.

Fluconazole Injections in Flexible Plastic Containers are supplied in the following:

NDC	Size
0074-4684-23	Fluconazole in Dextrose Diluent 200 mg/100 mL
0074-4684-02	Fluconazole in Dextrose Diluent 400 mg/200 mL
0074-4688-23	Fluconazole in Sodium Chloride Diluent 200 mg/100 mL
0074-4688-02	Fluconazole in Sodium Chloride Diluent 400 mg/200 mL

Storage: Room temperature (25°C). Brief exposure up to 104°F (40°C) does not adversely affect the product. Protect from freezing.

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Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA

 Printed in USA

100 mL

NDC 0074-4684-23

FLUCONAZOLE

INJECTION

200 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

FOR I.V. USE. EACH 100 mL CONTAINS 200 mg OF FLUCONAZOLE AND 5.6 g OF DEXTROSE, HYDROUS, USP, IN WATER FOR INJECTION, USP. OSMOLARITY 282 mOsmol/L (CALC.) STERILE, NONPYROGENIC. SINGLE-DOSE CONTAINER. DISCARD UNUSED PORTION. **USUAL DOSAGE:** SEE INSERT. **CAUTIONS:** DO NOT ADD SUPPLEMENTARY MEDICATION. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS.

(01) 0 30074 46842 3 9

LATEX

Rx only

3 V

RAO6483-2/R3-1/03

PRINTED IN USA

ABBOTT LABS., N. CHICAGO, IL 60064, USA

RED

BLUE

200 mL NDC 0074-4684-02

FLUCONAZOLE

INJECTION

400 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

FOR I.V. USE. EACH 200 mL CONTAINS 400 mg OF FLUCONAZOLE AND 11.2 g OF DEXTROSE, HYDROUS, USP, IN WATER FOR INJECTION, USP.
OSMOLARITY 289 mOsmol/L (CALC.)
STERILE, NONPYROGENIC.
SINGLE-DOSE CONTAINER. DISCARD UNUSED PORTION. **USUAL DOSAGE:** SEE INSERT.
CAUTIONS: DO NOT ADD SUPPLEMENTARY MEDICATION. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS.

Rx only

LATEX

3
V

 RA06486-2/R3-1/03 PRINTED IN USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

FRONT

TO OPEN – TEAR AT NOTCH

100 mL

NDC 0074-4684-23

FLUCONAZOLE
INJECTION

200 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

APPROVED

(01) 0 30074 46842 3 9

FOR I.V. USE. Each 100 mL contains 200 mg of Fluconazole and 5.6 g of Dextrose, Hydrous, USP, in Water for Injection, USP.
Osmolarity 289 mOsmol/L (Calc.). Sterile, nonpyrogenic.

Single-dose container

CAUTIONS: Do not add supplementary medication. The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when overwrap is opened.

RECOMMENDED STORAGE: Room temperature (25°C). Avoid excessive heat. Protect from freezing.

USUAL DOSAGE: See insert. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use unless solution is clear.

MUST NOT BE USED IN SERIES CONNECTIONS.

℞ only

F RAO6484-2/R3-1/03

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

BACK

100 mL

FLUCONAZOLE
INJECTION

200 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

APPROVED

B RAO6484-2/R3-1/03

FRONT

TO OPEN — TEAR AT NOTCH

200 mL NDC 0074-4684-02

FLUCONAZOLE INJECTION

400 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

(01) 0 030074 468402 4

APPROVED

FOR I.V. USE. Each 200 mL contains 400 mg of Fluconazole and 11.2 g of Dextrose, Hydrous, USP, in Water for Injection, USP. Osmolarity 289 mOsmol/L (Calc.). Sterile, nonpyrogenic.

Single-dose container

CAUTIONS: Do not add supplementary medication. The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when overwrap is opened.

RECOMMENDED STORAGE: Room temperature (25°C). Avoid excessive heat. Protect from freezing.

USUAL DOSAGE: See insert. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use unless solution is clear.

MUST NOT BE USED IN SERIES CONNECTIONS.

℞ only

 F RA06487-2/R3-1/03 Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

BACK

200 mL

FLUCONAZOLE INJECTION

400 mg (2 mg/mL)

ISO-OSMOTIC DEXTROSE DILUENT

100 mL 6 Flexible Plastic Containers

NDC 0074-4684-23

FLUCONAZOLE
INJECTION
ISO-OSMOTIC DEXTROSE DILUENT

200 mg (2 mg/mL)

FOR I.V. USE. Each 100 mL contains 200 mg of Fluconazole and 5.6 g of Dextrose, Hydrous, USP, in Water for Injection, USP.
Osmolarity 289 mOsmol/L (Calc.). Sterile, nonpyrogenic.

Single-dose container

CAUTIONS: Do not add supplementary medication. The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when overwrap is opened.
RECOMMENDED STORAGE: Room temperature (25°C). Avoid excessive heat. Protect from freezing.
USUAL DOSAGE: See insert. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use unless solution is clear.
MUST NOT BE USED IN SERIES CONNECTIONS.

℞ only

RAO6485-2/R3-1/03

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

(01) 1 030074 468423 6

Lot:

Exp:

200 mL 6 Flexible Plastic Containers

NDC 0074-4684-02

FLUCONAZOLE
INJECTION
400 mg (2 mg/mL)
ISO-OSMOTIC DEXTROSE DILUENT

FOR I.V. USE. Each 200 mL contains 400 mg of Fluconazole and 11.2 g of Dextrose, Hydrous, USP, in Water for Injection, USP. Osmolarity 289 mOsmol/L (Calc.). Sterile, nonpyrogenic.

Single-dose container.

CAUTIONS: Do not add supplementary medication. The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when overwrap is opened.

RECOMMENDED STORAGE: Room temperature (25°C). Avoid excessive heat. Protect from freezing.

USUAL DOSAGE: See insert. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use unless solution is clear.

MUSTNOTBEUSEDINSERIESCONNECTIONS.

℞ only

RAO6488-2/R3-1/03

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

(01) 1 030074 468402 1

Lot:

Exp:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

LABELING REVIEWS

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

ANDA Number: 76-304 Date of Submission: December 14 & February 12, 2002

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

1. GENERAL

   a. We note that you refer to your drug product "Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection" on your application form. However, we note that your drug product contains approximately 50 mg of dextrose anhydrous (*i.e.*, 56 mg of hydrous form). Consequently, it should read "5%" rather than "5.6%". Please revise accordingly in your subsequent submissions.

   b. We acknowledge your proposal for a combined package insert for your separate applications, in sodium chloride injection (76-303) and in dextrose injection (76-304). Please note that these applications must be approved at the same time, or further revisions will be necessary prior to approval.

   c. We encourage differentiation of this drug product from your other proposed product (ANDA 76-303) by use of boxing, contrasting colors, or other means to promote proper product selection and prevent errors.

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

   a. We encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) 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 rather than using two different colors (*i.e.*, red and blue).

   b. It may be preferable to revise to read "Do not add supplementary medication" rather than "[redacted]". We believe the former convey the information more clearly. Please revise and/or comment.

3. OVERWRAP

   See comments under CONTAINER.

4. CARTON

   a. See comments under CONTAINER.

   b. Add the text "Do not use unless the solution is clear." as it appears on the innovator's labeling.

5. INSERT

a. General

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.

iii. We ask that you delete all information specifically associated with "Vaginal Candidiasis" throughout the text as a single oral dose of fluconazole 150 mg is indicated for the treatment of "Vaginal Candidiasis".

b. DESCRIPTION - Second paragraph:

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

c. INDICATIONS AND USAGE

i. See comment 5a(iii) above.

ii. Item #2

"candidiasis" rather than "candidasis"

d. CLINICAL STUDIES

See comment 5a(iii) above.

e. WARNINGS - Hepatic injury:

i. (1) Hepatic injury: Fluconazole... [add a colon]

ii. Second sentence:

...fluconazole-associated hepatotoxicity... [add a hyphen]

f. PRECAUTIONS

i. General, Single Dose:

See comment 5a(iii) above.

ii. It is preferable to use the term "times" rather than the symbol "x". [e.g. "20 to 50 times" rather than "20-50 x"]

g. ADVERSE REACTIONS - In Patients Receiving a Single Dose for Vaginal Candidiasis:

See comment 5a(iii) above.

h. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults, Single Dose:

See comment 5a(iii) above.

ii. Dosage in Patients with Impaired Renal Function:

See comment 5a(iii) above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

QUESTION/COMMENT TO THE CHEMIST (These questions were forwarded to the chemist via e-mail on 3/5/02)

1. We note that the sponsor's storage temperature recommendation is different from the one appearing on the innovator's labels as follows: Is the proposal acceptable considering the upper limit of the proposed storage temperature exceeds the one of the innovator's?

   RLD - Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect this product. Protect from freezing.

   ANDA: Store at [redacted]. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40°C) does not adversely affect this product.

2. In an approved application using this flexible plastic container from this same sponsor (e.g., 74-468), it reads "Exposure to temperatures above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." under DESCRIPTION section of the insert labeling. However, in this application, the sponsor revised to read "[redacted]". Is this acceptable? Has the sponsor submitted the stability data to support this revised temperature? Please advise me so that I can make an appropriate labeling comment if necessary.

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 labels and labeling

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

PROFESSIONAL PACKAGE INSERT LABELING:

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 #:

19-950/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

Other Comments:

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 This is the **FIRST** generic application in dextrose injection.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 50 (Volume1.1).

5. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	001	4404216	JAN 29,2004	
019950	001	4416682	JUN 02,2001	

Exclusivity Data

There is no unexpired exclusivity for this product.

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

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at [redacted]. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product. See comment under CNTAINER.

7. PACKAGING CONFIGURATIONS

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

8. CONTAINER/CLOSURE

PVC Flexible Plastic Container

See p.1336, vol.1.4

9. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection). However, see comment (ii) under DESCRIPTION section.

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

The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." Also, the D&A section reads that "Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. The majority

of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will have the generic sponsors silent on all information specifically associated with "Vaginal Candidiasis"

11. 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

12. 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

13. We will assure that the labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

15. See general comment (a) for the concentration of dextrose in this drug preparation.

Date of Review: 2/28/02 **Date of Submission: December 14 & February 12, 02**

Primary Reviewer: Chan Park C Park **Date:** 3/6/02

Team Leader: **Date:**

3/6/02

cc:

ANDA: 76-304
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSAM\ABBOTT\LTRS&REV\76304na1.LABELING.doc
Review

APPEARS THIS WAY
ON ORIGINAL

(This review supersedes the one prepared on 2/28/02)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-304 Date of Submission: December 14 & February 12, 2002

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

1. GENERAL

   a. We note that you refer to your drug product "Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection" on your application form. However, we note that your drug product contains approximately 50 mg of dextrose anhydrous (*i.e.*, 56 mg of hydrous form). Consequently, it should read "5%" rather than "5.6%". Please revise accordingly in your subsequent submissions.

   b. We acknowledge your proposal for a combined package insert for your separate applications, in sodium chloride injection (76-303) and in dextrose injection (76-304). Please note that these applications must be approved at the same time, or further revisions will be necessary prior to approval.

   c. We encourage differentiation of this drug product from your other proposed product (ANDA 76-303) by use of boxing, contrasting colors, or other means to promote proper product selection and prevent errors.

   d. We note that your storage temperature statement is not the same as the innovator (*i.e.*, 25°C vs ——). We also note that you have not reported the specification of ~~bacterial~~ endotoxin at ——. Please revise to be the same as the innovator and/or comment, and if necessary, please submit the supporting data for your proposal.

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

   a. We encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) 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 rather than using two different colors (*i.e.*, red and blue).

   b. It may be preferable to revise to read "Do not add supplementary medication" rather than "——.". We believe the former convey the information more clearly.

   c. See comment 1d above.

3. OVERWRAP

   See comments under CONTAINER.

4. CARTON

   a. See comments under CONTAINER.

b. Add the text "Do not use unless the solution is clear." as it appears on the innovator's labeling.

5. INSERT

a. General

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.

iii. We ask that you delete all information specifically associated with "Vaginal Candidiasis" throughout the text as a single oral dose of fluconazole 150 mg is indicated for the treatment of "Vaginal Candidiasis".

b. DESCRIPTION

i. Second paragraph:

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

ii. Last paragraph:

In the labeling of your approved drug product using the flexible plastic container (e.g., 74-468), you stated that "Exposure to temperature above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." However, we note that you have revised to read "30°C (86°F)" in this application. Please revise to read "25°C (77°F)" and/or comment, and if necessary, please submit the supporting data for your proposal.

c. INDICATIONS AND USAGE

i. See comment 5a(iii) above.

ii. Item #2

"candidiasis" rather than "candidasis"

d. CLINICAL STUDIES

See comment 5a(iii) above.

e. WARNINGS - Hepatic injury:

i. (1) Hepatic injury: Fluconazole... [add a colon]

ii. Second sentence:

...fluconazole-associated hepatotoxicity:... [add a hyphen]

f. PRECAUTIONS

i. General, Single Dose:

See comment 5a(iii) above.

ii. It is preferable to use the term "times" rather than the symbol "x". [e.g. "20 to 50 times" rather than "20-50 x"]

g. ADVERSE REACTIONS - In Patients Receiving a Single Dose for Vaginal Candidiasis:

See comment 5a(iii) above.

h. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults, Single Dose:

See comment 5a(iii) above.

ii. Dosage in Patients with Impaired Renal Function:

See comment 5a(iii) above.

i. HOW SUPPLIED

See comment 1d above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

QUESTION/COMMENT TO THE CHEMIST (These questions were forwarded to the chemist via e-mail on 3/5/02)

1. We note that the sponsor's storage temperature recommendation is different from the one appearing on the innovator's labels as follows: Is the proposal acceptable considering the upper limit of the proposed storage temperature exceeds the one of the innovator's?

   RLD - Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect this product. Protect from freezing.

   ANDA: Store at [redacted]. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40°C) does not adversely affect this product.

2. In an approved application using this flexible plastic container from this same sponsor (e.g., 74-468), it reads "Exposure to temperatures above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." under DESCRIPTION section of the insert labeling. However, in this application, the sponsor revised to read " [redacted] ". Is this acceptable? Has the sponsor submitted the stability data to support this revised temperature? Please advise me so that I can make an appropriate labeling comment if necessary.

Answer form the Chemist on 3/12/02

The firm has not reported the specification of bacterial Endotoxin at [redacted] I think, we should not accept the maximum storage temperature of [redacted]

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 labels and labeling

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

PROFESSIONAL PACKAGE INSERT LABELING:

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 #:

19-950/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

Other Comments:

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 This is the **FIRST** generic application in dextrose injection.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 50 (Volume1.1).

5. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	001	4404216	JAN 29,2004	
019950	001	4416682	JUN 02,2001	

Exclusivity Data

There is no unexpired exclusivity for this product.

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

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at ——————————————————Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product. See comment under CNTAINER.

7. PACKAGING CONFIGURATIONS

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

8. CONTAINER/CLOSURE

PVC Flexible Plastic Container

See p.1336, vol.1.4

9. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection). However, see comment (ii) under DESCRIPTION section.

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

The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following

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

11. 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

12. 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

13. We will assure that the labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

15. See general comment (a) for the concentration of dextrose in this drug preparation.

Date of Review: 2/28/02 **Date of Submission: December 14 & February 12, 02**

Primary Reviewer: Chan Park C Park **Date:** 3/13/02

Team Leader: **Date:** 3/13/02

cc:

ANDA: 76-304
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSAM\ABBOTT\LTRS&REV\76304na1A.LABELING.doc

Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 76-304 Date of Submission: June 28, 2002

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

1. GENERAL

   a. We ask you to revise the storage temperature statement to be the same as the innovator:

      Storage: Store between 5°C (41°F) and 25°C (77°F). Brief exposure... freezing.

   b. We note that you printed the established name and expression for strength in red color for both 200mg/100mL and 400 mg/200 mL container labels and carton labeling, while you printed these in blue color for the overwrap labeling for both strengths. It can be very confusing. We recommend that you use the same color for the established name and expression of strength of one drug product for all labeling pieces rather than using two different colors (*i.e.*, red and blue). In addition, as addressed in the Agency's previous letter, we strongly encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) by using boxing, contrasting colors, and/or some other means.

   c. We note that you printed the term "DEXTROSE" in red color for the container labels and carton labeling, while printed this in blue color for the overwrap. We recommend that you print the term "DEXTROSE" using the same color for all labeling pieces (not the same color used for the term "SOLIUM CHLORIDE"). We believe this would help to differentiate your drug product from the one in sodium chloride.

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

   a. See general comments above, where appropriate.

   b. We ask you to relocate the route of administration statement "For I.V.USE" to appear immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

   c. The format of you container labels makes it difficult to readily obtain necessary information. Please refer to the Diflucan® Injection labels for guidance. We suggest the following revisions regarding format changes for your consideration.

      i. It is preferable to print the text "USUAL DOSAGE" in bold face type.

      ii. Include the term "CAUTIONS" in bold face type and revise to read:

         CAUTIONS: DO NOT ADD SUPPLEMENTARY MEDICATION. USE ONLY IF SOLUTION ...CONNECTIONS.

      iii. Relocate the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

3. OVERWRAP

a. See general comments above, where appropriate.

b. Include the text "For I.V.USE" to appear immediately beneath the statement "ISO-OSMOTIC SODIUM CHLORIDE DILUENT".

c. Include the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

d. We encourage you to reformat the text with break up by the different categories (*i.e.*, storage, usual dosage, cautions, etc) rather than having one continuous text including all information.

e. Include the text "**USUAL DOSAGE**" immediately prior to the text "See insert.".

f. Print the text "Recommended storage:" in bold face type.

4. CARTON

i. See comments under GENERAL, CONTAINER and OVERWRAP above, where appropriate.

ii. We note that you included both "Usual dosage: See insert" and "See insert." You may delete the text "See insert.". [redundant]

5. INSERT

a. General

We note that you submitted the insert labeling in several separate pieces as final printed labeling. Please be reminded that the whole text should appear as one piece to be considered as final printing.

b. Precautions

Delete the subsection heading " ——— " as no information appears under this subsection.

c. HOW SUPPLIED

See comment 1(a) above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

QUESTION/COMMENT TO THE CHEMIST (These questions were forwarded to the chemist via e-mail on 3/5/02)

1. We note that the sponsor's storage temperature recommendation is different from the one appearing on the innovator's labels as follows: Is the proposal acceptable considering the upper limit of the proposed storage temperature exceeds the one of the innovator's?

   RLD - Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect this product. Protect from freezing.

   ANDA: Store at ——————————————— Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40°C) does not adversely affect this product.

2. In an approved application using this flexible plastic container from this same sponsor (e.g., 74-468), it reads "Exposure to temperatures above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." under DESCRIPTION section of the insert labeling. However, in this application, the sponsor revised to read " ——————. Is this acceptable? Has the sponsor submitted the stability data to support this revised temperature? Please advise me so that I can make an appropriate labeling comment if necessary.

Answer from the Chemist on 3/12/02

The firm has not reported the specification of bacterial Endotoxin at —— I think, we should not accept the maximum storage temperature of ——

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 labels and labeling

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

PROFESSIONAL PACKAGE INSERT LABELING:

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 #:

19-950/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

Other Comments:

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 51 (Volume1.1).

4. Patent Data

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

Exclusivity Data

here is no unexpired exclusivity for this product.

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

4,404,216 Antifungal 1,3-bis-triazolyl-2-propanol derivative

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. Protect from freezing.

   ANDA: Store at room temperature, 25oC. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product.

   We will ask the sponsor to revise the storage temperature statement to be the same as the innovator.

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 (Flexible plastic container; in Sodium Chloride & Dextrose)

7. CONTAINER/CLOSURE

   PVC Flexible Plastic Container

   See p.1345, vol.1.4

8. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection). However, see comment (ii) under DESCRIPTION section.

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

The innovator has a combined package insert labeling for fluconazole tablet, oral solution

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

10. 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

11. 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

12. We will assure that the labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

The combined insert for the oral tablet, suspension & injection contains indications for Oropharyngeal and Esophageal

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

Date of Review: 7/11/02 **Date of Submission: 6/28/02**

Primary Reviewer: Chan Park **Date:** 8/19/02

Acting Team Leader: Lillie Golson **Date:** 8/15/02

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cc:

ANDA: 76-303
DUP/DIVISION FILE
HFD-613/Cpark/LGolson (no cc)
V:\FIRMSAM\ABBOTT\LTRS&REV\76303na2.LABELING.doc
Review

2-1 (This TA Summary is superseded by the TAP#2 Summary on 3/8/04. C Parr).

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

ANDA Number: 76-304 Date of Submission: January 21, 2003

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

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 for the tentative approval.

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in draft as of January 21, 2003 submission

OVERWRAP - 100 mL & 200 mL

Satisfactory in draft as of January 21, 2003 submission

CARTON LABELING - 100 mL & 200 mL

Satisfactory in draft as of January 21, 2003 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of January 21, 2003 submission

REVISIONS NEEDED POST-APPROVAL:

None

QUESTION/COMMENT TO THE CHEMIST

The sponsor's proposed storage temperature statement is acceptable per the Chemist reviewer. See file folder for detail.

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 #:

19-950/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

Other Comments:

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 This is the **FIRST** generic application in dextrose injection.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 50 (Volume1.1).

5. 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.**

4,404,216 Antifungal 1,3-bis-triazolyl-2-propanol derivative

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at room temperature, 25oC. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product.

7. PACKAGING CONFIGURATIONS

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

8. CONTAINER/CLOSURE

PVC Flexible Plastic Container

See p.1336, vol.1.4

9. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection).

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

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

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Chan

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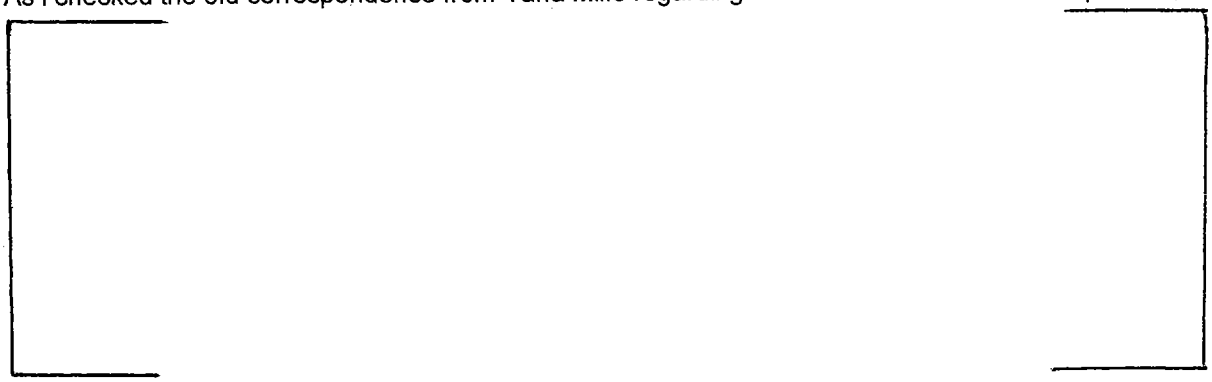
Hi Matthew:

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



Chan

13. We will assure that the labeling does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

15. Color-coding (See e-mails between Tom Stothoff and Chan Park regarding this issue in the file folder)

    a. Overwrap and Carton

       Used same color scheme for these two labeling pieces. Made differentiation between two different strengths and diluents using different colors.

    b. Container labels

       CONTAINER - 200mg/100 mL and 400 mg/200 mL

       Although it should be ideal to use the color-codes consistent with the overwrap and carton labeling, we find the sponsor's proposed labels acceptable considering their limitations in selecting colors for the primary container labels, as elaborated in this submission. We agree with the sponsor's statement that since the primary bag should **not** be removed from the overwrap until ready for use, as declared on the labeling, the chance of mix-up with the other bags of different strength and/or diluent may be minimal. This is particularly true since the overwrap and carton labeling is clearly differentiated from other products of different strength and diluent by using distinct color-codes. In addition, the sponsor's proposal for the different container sizes for different strengths, and different format of expression of strengths also may help reduce the chance of nix-up of the strengths

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Date of Review: 2/6/03 **Date of Submission: 1/21/03**

Primary Reviewer: Chan Park Chan Park **Date:** 2/14/03

~~Acting~~Team Leader: Lillie Golson Lillie Golson **Date:** 2/14/03

(This TAP#2 is superseded by the AP Summary prepared on 7/21/04)

(This TAP#2 Summary supersedes the TAP Summary prepared on 2/6/03)
(TENTATIVE APPROVAL SUMMARY# 2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Chan

ANDA Number: 76-304 Date of Submission: January 21, 2003

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

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** for the tentative approval.

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in **draft** as of January 21, 2003 submission (vol.3.1)

OVERWRAP - 100 mL & 200 mL

Satisfactory in **draft** as of January 21, 2003 submission (vol.3.1)

CARTON LABELING - 100 mL & 200 mL

Satisfactory in **draft** as of January 21, 2003 submission (vol.3.1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in **draft** as of January 21, 2003 submission (vol.3.1)

REVISIONS NEEDED POST-APPROVAL:

None

QUESTION/COMMENT TO THE CHEMIST

The sponsor's proposed storage temperature statement is acceptable per the Chemist reviewer. See file folder for detail.

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 #:

19-950/S-028, approved February 22, 1999 (Package Insert Labeling)
19-950/S-034, approved August 7, 2002 (Patient Information Leaflet for the 150 mg tablet)

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

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 This is the **FIRST** generic application in dextrose injection.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 50 (Volume1.1).

5. Patent Data

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

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor has **filed Patent Certification III.**

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at room temperature, 25oC. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product.

7. PACKAGING CONFIGURATIONS

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

8. CONTAINER/CLOSURE

PVC Flexible Plastic Container

See p.1336, vol.1.4

9. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection).

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

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

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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.

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12. Color-coding (See e-mails between Tom Stothoff and Chan Park regarding this issue in the file folder)

    a. Overwrap and Carton

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       CONTAINER - 200mg/100 mL and 400 mg/200 mL

       Although it should be ideal to use the color-codes consistent with the overwrap and carton labeling, we find the sponsor's proposed labels acceptable considering their limitations in selecting colors for the primary container labels, as elaborated in this submission. We agree with the sponsor's statement that since the primary bag should **not** be removed from the overwrap until ready for use, as declared on the labeling, the chance of mix-up with the other bags of different strength and/or diluent may be minimal. This is particularly true since the overwrap and carton labeling is clearly differentiated from other products of different strength and diluent by using distinct color-codes. In addition, the sponsor's proposal for the different container sizes for different strengths, and different format of expression of strengths also may help reduce the chance of nix-up of the strengths

Date of Review: 3/8/04 **Date of Submission: 1/21/03**

Primary Reviewer: Chan Park Date: 3/8/04

ActingTeam Leader: Lillie Golson Date: 3/15/04

cc:

ANDA: 76-304
DUP/DIVISION FILE
HFD-613/CparkLGolson (no cc)
V:\FIRMSAM\ABBOTT\LTRS&REV\76304TAP#2.LABELING.doc
Review

(This AP summary supersedes the TAP summary #2 prepared on 3/8/04)

(APPROVAL SUMMARY)

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

ANDA Number: 76-304 Date of Submission: July 15, 2004 and July 20, 2004

Applicant's Name: Hospira, Inc.

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

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

Do you have 12 Final Printed Labels and Labeling? **Yes**

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in **FPL** as of July 15, 2004 submission (vol.5.1)

OVERWRAP - 100 mL & 200 mL

Satisfactory in **FPL** as of July 15, 2004 submission (vol.5.1)

CARTON LABELING - 100 mL & 200 mL

Satisfactory in **FPL** as of July 15, 2004 submission (vol.5.1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in **FPL** as of **July 20, 2004** submission (T90171, Rev. July, 03; Code # 58-7214)

REVISIONS NEEDED POST-APPROVAL:

The sponsor has changed the name to "Hospira, Inc." from "Abbott, Inc." The sponsor submitted a written commitment on July 20, 2004 that they will revise the labeling to reflect the Hospira logo and associated information on their labeling as a post-approval revision.

QUESTION/COMMENT TO THE CHEMIST

The sponsor's proposed storage temperature statement is acceptable per the Chemist reviewer. See file folder for detail.

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 #:

19-950/S-028, approved February 22, 1999 (Package Insert Labeling)
19-950/S-037, approved March 24, 2004 (Revised Patient Information Leaflet for the 150 mg tablet)

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

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 PPI for the 150 mg tablets.

2. This drug product is **not** the subject of a USP monograph

3 This is the **FIRST** generic application in dextrose injection.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 50 (Volume1.1).

5. Patent Data

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

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor has **filed Patent Certification III.**

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at room temperature, 25oC. Avoid excessive heat. Protect from freezing. Brief exposure up to 104oF (40oC) does not adversely affect this product.

7. PACKAGING CONFIGURATIONS

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

8. CONTAINER/CLOSURE

PVC Flexible Plastic Container

See p.1336, vol.1.4

9. The language associated with the plastic container in the DESCRIPTION and D & A sections has been approved for other applications using this same container (e.g., 74-468, Cimetidine Injection).

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

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

12. Color-coding (See e-mails between Tom Stothoff and Chan Park regarding this issue in the file folder)

    a. Overwrap and Carton

       Used same color scheme for these two labeling pieces. Made differentiation between two different strengths and diluents using different colors.

    b. Container labels

       CONTAINER - 200mg/100 mL and 400 mg/200 mL

       Although it should be ideal to use the color-codes consistent with the overwrap and carton labeling, we find the sponsor's proposed labels acceptable considering their limitations in selecting colors for the primary container labels, as elaborated in this submission. We agree with the sponsor's statement that since the primary bag should **not** be removed from the overwrap until ready for use, as declared on the labeling, the chance of mix-up with the other bags of different strength and/or diluent may be minimal. This is particularly true since the overwrap and carton labeling is clearly differentiated from other products of different strength and diluent by using distinct color-codes. In addition, the sponsor's proposal for the different container sizes for different strengths, and different format of expression of strengths also may help reduce the chance of nix-up of the strengths

Date of Review: 7/21/04 **Date of Submission:** July 15, 2004 and July 20, 2004

Primary Reviewer: Chan Park **Date:** 7/22/04

ActingTeam Leader: Lillie Golson **Date:** 7/26/04

cc:

ANDA: 76-304
DUP/DIVISION FILE
HFD-613/CparkLGolson (no cc)
V:\FIRMSAM\HOSPIRA\LTRS&REV\76304AP.LABELING.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-304

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Lisa K. Zboril
200 Abbott Park Rd., D-389, J45-2
Abbott Park, IL 60064-6133

4. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan manufactured by Pfizer. Patents 4404216 and 4416682 expire on January 29, 2004 and June 2, 2001, respectively. There are currently no patent exclusivities.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Sub 12/14/01

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 19-950, 931, 5506, [redacted]

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

15. CHEMICAL NAME AND STRUCTURE
2,4 difluoro, -a, a1-bis (1H-1, 2,4-triazol-1-ylmethyl benzyl alcohol

16. COMMENTS
Non-USP drug substance and drug product

17. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Minor

18. REVIEWER:
Mahnaz Farahani Ph.D.

19. DATE COMPLETED:
03/20/02

Redacted 12 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #1

E. [ ]

4. Regarding stability, we have the following question:

Please include the chemical names of the known impurities in the stability specifications.

Sincerely yours,

5/7/02

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 76-304
DIV FILE
Field Copy

Endorsements:
HFD-645/MFarahani/03/20/02 Mahmood Farahani 5,3,02
HFD-647/GSmith/4/24/02 5/3/02
HFD-617/Jmin/5/1/02 Jean Min 5/6/02

F/T by dss/5/2/02

V:\firmsam\Abbott\ltrs&rev\76304.1rev.napp.maf

CHEMISTRY REVIEW -Not Approved

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-304

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Tom Stothoff
200 Abbott Park Rd., D-389, J-45-2
Abbott Park, IL 60064-6133

4. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan manufactured by Pfizer. Patents 4404216 expire on January 29, 2004. There are currently no patent exclusivities.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Sub 12/14/01
Amendment 6/28/02
Amendment 8/8/02
Amendment 8/16/02
Telephone amendment 10/17/02
Telephone amendment 12/5/02

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 19-950, 931, 5506, _____

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

15. CHEMICAL NAME AND STRUCTURE
2,4 difluoro, -a, a1-bis (1H-1, 2,4-triazol-1-ylmethyl benzyl alcohol

16. COMMENTS
Non-USP drug substance and drug product

17. CONCLUSIONS AND RECOMMENDATIONS
Approval - Pending Labeling

18. REVIEWER:
Mahnaz Farahani Ph.D.

19. DATE COMPLETED:
09/11/02 and 11/1/02

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CHEMISTRY REVIEW #2

37. DMF CHECKLIST FOR ANDA #76-304 REVIEW # 2

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	1	adequate	9/12/02

Comments: Adequate

931	III/PVC/Abbott Laboratory	1	Adequate	4/23/02

Comments:

5506 III/ [redacted] /Abbott Laboratory 4

Comments:

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (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").

Reviewer Signature Date

38. Chemistry Comments to be provided to the Applicant

ANDA: 76-304 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL (in Dextrose Injection)

The deficiencies presented below represent Minor deficiencies.

We refer to the facsimile dated November 26, 2002 regarding your deficiencies in the labeling section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Your response will be considered a Minor Amendment.

Sincerely yours,

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

cc: ANDA 76-304
DIV FILE
Field Copy

Endorsements:
HFD-645/MFarahani/09/12/02;11/1/02;12/17/02 for MF 1/14/03
HFD-647/GSmith/12/18/02 1/15/03
HFD-617/Jmin/1/14/03 for 01-14-03

F/T by jsm/1/14/03

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CHEMISTRY REVIEW - Minor (Pending Label)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 76-304

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Tom Stothoff
200 Abbott Park Rd., D-389, J-45-2
Abbott Park, IL 60064-6133

4. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan manufactured by Pfizer. Patent 4404216 expires on January 29, 2004. There are currently no patent exclusivities.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Sub 12/14/01
Amendment 6/28/02
Amendment 8/08/02
Amendment 8/16/02
Amendment 10/17/02
Amendment 12/05/02
Amendment 01/10/03
Amendment 01/21/03

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 19-950, 931, 5506, [redacted]

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

15. CHEMICAL NAME AND STRUCTURE
2,4 difluoro, -a, a1-bis (1H-1, 2,4-triazol-1-ylmethyl benzyl alcohol

16. COMMENTS
Non-USP drug substance and drug product

17. CONCLUSIONS AND RECOMMENDATIONS
Approvable

18. REVIEWER:
Mahnaz Farahani Ph.D.

19. DATE COMPLETED:
09/11/02,11/1/02 and 1/30/03

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #3

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS
Waiver request provided on p. 48
Micro Acceptable 08/23/02

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
The applicant claims categorical exclusion (page 1921).

36. 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:

SPOT? Yes _____ No x

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. DMF CHECKLIST FOR ANDA #76-304 REVIEW # 3

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/[redacted]	1	adequate	9/12/02

Comments: Adequate

931	III/PVC/Abbott Laboratory	1	Adequate	4/23/02

Comments:

5506 III/[redacted] Abbott Laboratory 4

Comments:

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (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").

Reviewer Signature Date

cc: ANDA 76-304
DIV FILE
Field Copy

Endorsements:
HFD-645/MFarahani/09/12/02,11/1/02 and 1/30/03 3,4,03
HFD-647/GSmith/ 3/5/03
HFD-617/Jmin/ fw 3/5/03

F/T by

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CHEMISTRY REVIEW - Approved

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-304

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Tom Stothoff
200 Abbott Park Rd., D-389, J-45-2
Abbott Park, IL 60064-6133

4. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan manufactured by Pfizer. Patent 4404216 expires on January 29, 2004. There are currently no patent exclusivities.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Sub 12/14/01
Amendment 6/28/02
Amendment 8/08/02
Amendment 8/16/02
Amendment 10/17/02
Amendment 12/05/02
Amendment 01/10/03
Amendment 01/21/03
Amendment 10/30/03

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 19-950, 931, 5506,

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

15. CHEMICAL NAME AND STRUCTURE
2,4 difluoro, -a, a1-bis (1H-1, 2,4-triazol-1-ylmethyl benzyl alcohol

16. COMMENTS

Non-USP drug substance and drug product

17. CONCLUSIONS AND RECOMMENDATIONS
Approvable

18. REVIEWER:
Mahnaz Farahani Ph.D.

19. DATE COMPLETED:
09/11/02,11/1/02,1/30/03 and 10,30/04

Redacted 13 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #4

The subject finished drug product will be manufactured, tested and evaluated on stability at the following Abbott Laboratories facilities:

Manufacturing site: Abbott Laboratories
Hospital Products Division
3900 Howard Lane
Austin, Texas 78728

Testing site: Abbott Laboratories
Hospital Products Division
3900 Howard Lane
Austin, Texas 78728

Abbott Laboratories
Hospital Products Division
100 Abbot Park Road
Abbott Park, Illinois 60064

Abbott Laboratories
Hospital Products Division
Highway 301 North
Rocky Mount, North Carolina 27801

30. CONTROL NUMBERS
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Methods validation - acceptable.

32. LABELING
Approved 02/14/03

33. ESTABLISHMENT INSPECTION
Acceptable 12/19/02

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS
Waiver request provided on p. 48
Micro Acceptable 08/23/02

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
The applicant claims categorical exclusion (page 1921).

36. 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:

SPOT? Yes _____ No ___x___

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. DMF CHECKLIST FOR ANDA #76-304 REVIEW # 4

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	1	adequate	9/12/02

Comments: Adequate

931	III/PVC/Abbott Laboratory	1	Adequate	4/23/02

Comments:

5506 III/ [redacted] Abbott Laboratory 4

Comments:

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (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").

Reviewer Signature Date

cc: ANDA 76-304
DIV FILE
Field Copy

Endorsements: Mahmoud Farahani 3/11/04
HFD-645/MFarahani/09/12/02,11/1/02,1/30/03 and 1/20/04
HFD-647/GSmith/2/13/04 3/12/04
HFD-617/TPalat/2/25/04 3/17/04

F/T by rad3/9/04

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CHEMISTRY REVIEW - Approved

APPEARS THIS WAY
ON ORIGINAL

Full Approval Assessment

1. ANDA # 76-304

2. NAME AND ADDRESS OF APPLICANT
Hospira, Inc.
Attention: Johnathan Dohnalek
275 North Field Drive, Bldg 2
Lake Forest, IL 60045-5045

3. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan manufactured by Pfizer. There are no unexpired patents or periods of exclusivity.

4. PROPRIETARY NAME
N/A

5. NONPROPRIETARY NAME
Fluconazole

6. CURRENT SUBMISSIONS AND OTHER DATES:

Original Submission	12/14/01
Tentatively Approved	05/21/04
Amendment	05/26/04

7. PHARMACOLOGICAL CATEGORY
Anti-fungal

8. Rx or OTC
Rx

9. RELATED DMF(s)
NDA 19-950, 931, 5506, [redacted]

10. Samples and Results
N/A

11. LABELING STATUS - Acceptable 02/14/03

12. BIOEQUIVALENCY STATUS - Acceptable 03/28/02

13. MICROBIOLOGY STATUS - Acceptable 08/23/02

14. ESTABLISHMENT INSPECTION - Acceptable 06/03/04

15. CONCLUSIONS AND RECOMMENDATIONS - The firm submitted certification that no changes have been made to the Chemistry, Manufacturing and Controls Sections of the application since receiving Tentative Approval on 05/26/04.

Recommend Approval.

PROJECT MANAGER: Ted Palat DATE COMPLETED: 07/02/04

cc: ANDA 76-304
Division File
Field Copy

Endorsements:

HFD-617\T.Palat\07/02/04
HFD-647\G.Smith\ 7/26/04

f/t by: rad7/22/04

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Approval

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

BIOEQUIVALENCE REVIEW

A 1.1 Ack
Glen

Fluconazole injection
2 mg/ml in 5.6% dextrose
ANDA #76-304
Reviewer: J. Lee
76304W1201

Abbott Laboratories
Abbott Park, Illinois
Submission date:
December 14, 2001

Review of a Request for Waiver

The sponsor has submitted an application for fluconazole injection, 2 mg/ml in 5.6% dextrose, and is requesting waiver of in-vivo studies per 21 CFR 320.22 (b)(1).

The drug product is indicated for: 1) vaginal candidiasis; 2) oropharyngeal and esophageal candidiasis; 3) crytococcal meningitis; 4) prophylaxis

Presented below is a quantitative formulation comparison between the test product vs Diflucan® in Dextrose 5%:

	Abbott per ml	Diflucan® per ml
Fluconazole	2 mg	2 mg
Dextrose, hydrous	56 mg	56 mg
Water for injection	q.s.	q.s.

Comment:

1. The brand product's proprietary name is Diflucan® in Dextrose 5% in plastic container while the generic is known as fluconazole in 5.6% dextrose injection. 5% dextrose, anhydrous is equivalent to 5.6% dextrose, hydrous.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories demonstrates that fluconazole injection, 2 mg/ml in 5.6% dextrose, falls under 21 CFR 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Abbott's test product is deemed bioequivalent to Diflucan® in dextrose 5%, manufactured by Pfizer Inc.

R. Lee 2/20/02

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 2/22/2002

Concur: Date: 3/28/2002

for Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/2-20-02

cc: NDA #76-304 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-304
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-655/ JLee R.P. 2/20/02
HFD-655/ Bio team Leader
HFD-650/ D. Conner for Rwt 2/28/2002

2/22/02

BIOEQUIVALENCY - ACCEPTABLE submission date: Sept 14, 2001

6. **WAIVER** (WAI) Strengths:
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Waiver granted per 21 CFR 320.22 (b)(1)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-304 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Fluconazole Injection, 2 mg/ml in 5.6% dextrose

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,

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

CC: ANDA 76-304
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Printed in final on / /

2/22/02

Endorsements: (Final with Dates)
HFD-655/ JLee 2/20/02
HFD-655/ Bio team Leader
HFD-650/ D. Conner 3/28/2002

December 14, 2001 NCN

BIOEQUIVALENCY - ACCEPTABLE submission date: ~~Sept 14~~, 2001

6. **WAIVER** (WAI) Strengths:
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Waiver granted per 21 CFR 320.22 (b)(1)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-304 SPONSOR : Abbott Laboratories

DRUG AND DOSAGE FORM : Fluconazole inj.

STRENGTH(S) : 2mg/ml in 5.6% dextrose

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

~~STUDY~~ SUMMARY : Waiver granted per 21 CFR 320.22 (b)(1)

~~DISSOLUTION :~~

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : J. Lee BRANCH : II

INITIAL : C.L. DATE : 2/20/02

TEAM LEADER : SG Nerurkar BRANCH : II

INITIAL : [signature] DATE : 2/22/2002

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

INITIAL : [signature] DATE : 3/28/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

MICROBIOLOGY REVIEW

1.1

Product Quality Microbiology Review
Review for HFD-640

23 August 2002

ANDA: 76-304

Drug Product Name
Proprietary: N/A
Non-proprietary: Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection
Drug Product Classification: N/A

Review Number: #1

Subject of this Review
Submission Date: December 14, 2001 (original application) and August 8 and 16, 2002 (Telephone amendments)
Receipt Date: December 20, 2001
Consult Date: N/A
Date Assigned for Review: July 25, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Abbott Laboratories
Address: 200 Abbott Park Road, D-37K, J45-2, Abbott Park, IL 60064-6133
Representative: Lisa K. Zboril
Telephone: 847-935-3227

Name of Reviewer: Lisa S.G. Shelton

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

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:**
Abbott Laboratories
Hospital Products Division
3900 Howard Lane
Austin, TX 78728

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injectable, IV infusion, 2 mg/mL packaged as 200 mg/100 mL and 400 mg/200 mL in flexible plastic containers,100 mL and 250 mL, respectively

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

6. **PHARMACOLOGICAL CATEGORY:** Antifungal Agent - Systemic

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF [redacted]
DMF 931 – Abbott Laboratories – PVC Flexible Container
DMF 5506 – Abbott Laboratories – ADD-Vantage Flexible Container

C. **REMARKS:**

Questions regarding container/closure integrity validation were sent by FAX on 8/2/02 and discussed by phone on 8/7/02. Telephone amendment was received by FAX on 8/8/02.

The question regarding who is responsible for reviewing records and determination of disposition of a production lot was addressed in a telephone conversation on 8/8/02 and provided by telephone amendment dated 8/16/02 (received by FAX on 8/19/02).

A clarification of the results for the physical testing of the PVC [redacted] was requested by phone on 8/13/02, and these results were included in the telephone amendment dated 8/16/02.

filename: V:\MICROREV\76-304.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment".

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 subject drug product is [redacted]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk is considered minimal.

III. Administrative

A. Reviewer's Signature Lisa S.G. Shelton

B. Endorsement Block
Microbiologist, Lisa S.G. Shelton, Ph.D. LSS 8/23/02
Microbiology Team Leader, Neal J. Sweeney, Ph.D.
Neal Sweeney 8/23/02

C. CC Block
cc:
Original ANDA 76-304
Division File
Field Copy

Redacted 9 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : January 4, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 04-JAN-2002

SUBJECT: Examination of the request for waiver submitted with an ANDA for Fluconazole Injection, 200 mg/100 mL (in 5% Dextrose Injection) to determine if the application is substantially complete for filing.

Abbott Laboratories has submitted ANDA 76-304 for Fluconazole Injection, 200 mg/100 mL (in 5% Dextrose Injection). It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Abbott Laboratories on December 14, 2001 for its Fluconazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

✓ Waiver meets statutory requirements Chandra S. Chowdhury 01/07/2002
Yi Tsong 1/8/2002

_____ Waiver does **NOT** meet statutory requirements

Reason:

Gene P. Sonner 1/8/02
Director, Division of Bioequivalence Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76304 DRUG NAME Fluconazole 2mg/mL in 5.6% Dextrose Injection FIRM Abbott Lab

DOSAGE FORM(s) Injection (IV Administration)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol		✓			
Assay Methodology		✓			N/A. However, Assay methodology is provided in the assay of finished pdt Vol. 1.
Procedure SOP		✓			
Methods Validation		✓			N/A. However, method validation for analytical assay methodology is given. Vol. 1.
Study Results Ln/Lin		✓			
Adverse Events		✓			
IRB Approval		✓			
Dissolution Data		✓			
Pre-screening of patients		✓			
Chromatograms		✓			
Consent forms		✓			
Composition	✓	✓			
Summary of study		✓			
Individual Data & Graphs , Linear & Ln		✓			
PK/PD data disk		✓			
Randomization Schedule		✓			
Protocol Deviations		✓			

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site		✓			N/A
Analytical site		✓			N/A
Study investigators		✓			N/A
Medical Records		✓			N/A
Clinical Raw Data		✓			N/A
Test Article Inventory		✓			N/A
BIO Batch Size					N/A
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				7/12/00
Exp. Date RLD		✓			N/A
Biostudy lot numbers	✓				98-799 RD
Statistics		✓			
Summary results provided by the firm indicate studies pass BE criteria		✓			
Waiver requests for other strengths / supporting data	✓ 1				Waiver Request per CFR 21 320.22(b)(1)

Additional comments: RLD is Diflucan 200mg/100mL in Dextrose 5% in plastic container. The RLD labeling indicates "Each ~~200~~ 100 mL contains ... 5.6 gms of dextrose hydrous USP in water for Injection". The test drug labeling also states the same, i.e. "each 100 mL contains ... 5.6 gms of Dextrose, Hydrous, USP, in water for Injection".

Recommendation: (COMPLETE) INCOMPLETE 1/8/2002

Reviewed by
Chandra S. Chaurasia

Chandra S. Chaurasia

Date 01/07/2002

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

Telecon Record

Date: February 5, 2002

ANDA: 76-304

Firm: Abbott Laboratories

Drug: Fluconazole, 2 mg/mL, in 5.6% Dextrose Inj.

FDA Participants: Martin Shimer

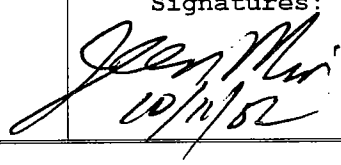
Industry Participants: Lisa Zboril

Phone #: (847) 935-3227

Agenda: Marty called Lisa and requested that she submit revised blank batch records requesting a maximum scale-up of [redacted]. Marty stated that it would be acceptable for Abbott to simply submit the few pages in Section XI that are specific to the proposed scale up. Marty also requested that Abbott submit side-by-side comparison of the carton label for this product, currently the carton label states in NaCL.

2.1

Record of Telephone Conversation

APPEARS THIS WAY ON ORIGINAL The DMF holder's response has been found satisfactory. Please revise your specifications to match the DMF accordingly.	**Date:** October 11, 2002
	ANDA Number: 76-303 76-304
	Product Name: Fluconazole
	Firm Name: Abbott
	Firm Representative: Richard Stac
	Phone Number: 847-938-0162
	FDA Representative: Jeen Min
	Signatures: 

CC: ANDA 76-303
ANDA 76-304

V:\FIRMSAM\ABBOTT\TELECONS\76303.tc1.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-304 Applicant Abbott Laboratories
Drug ~~Fluconazole~~ IN 5% Dextrose Injection Strength 2mg/mL

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

REVIEWER:

	DRAFT Package	FINAL Package
1. Project Manager, Team Ted Palat	Date 2/28/03	Date 3/7/03
Review Support Branch Team 9	Initials [illegible]	Initials [illegible]

Application Summary:

Original Rec'd date ~~12-14-01~~ 12-20-01 ✓
Date Acceptable for Filing 12-20-01 ✓
Patent Certification (type) III
Date Patent/Exclus.expires 01/29/04
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 = Diflucan
Date checked 2/28/03 NDA# 19950
Nothing Submitted ☑ ✓
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ ✓ OAI ☐
Date of EER Status 12-19-2002
Date of Office Bio Review 3-28-02
Date of Labeling Approv. Sum 2-14-03
Date of Sterility Assur. App. 8-23-02 ✓
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:

2. Gregg Davis PPIV ANDAs Only	Date 03-MAR-2003	Date 03-MAR-2003
Supv., Reg. Support Branch	Initials [illegible]	Initials [illegible]

Contains GDEA certification: Yes ☒ ✓ No ☐ Determ. of Involvement? Yes ☐ No ☒ ✓
(required if sub after 6/1/92)
Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ ✓ No ☐
Date Checked 6/18/03
If Para. IV Certification- did applicant
Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted (on) ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Comments:
ack w/ PIII for '216 exp. 1/29/04
OK for TA

RLD Diflucan in Dextrose 5% Pfizer, Inc 2mg/mL Plastic Container NDA 19-950 (003)

3. Div. Dir./Deputy Dir.	Date 3/7/03	Date 3/10/03
Chemistry Div. I or II	Initials [illegible]	Initials [illegible]
Comments: cmc satisfactory		

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date _____ Initials _____
Satisfactory

Date 6/16/03 Initials [illegible]

5. Peter Rickman
Acting Director, DLPS

Date 6/18/03 Initials [illegible]

Date 6/18/03 Initials [illegible] for

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

Comments: Acceptable EES dated 2/19/02 (verified 6/18/03) No OAI alerts noted. Bioequivalence waiver granted under 21 CFR 320.22 (b)(1). Drug product is "RX" to the RLD. Office-level bioendorsed 3/28/02. Microbiology/sterility assurance found acceptable 8/23/02. Labeling found acceptable for tentative approval 2/14/03. CMC found acceptable 3/5/03. Methods validation acceptable per Chemistry review #3. First-generic CMC audit has been completed.

OB

5. Robert L. West
Acting Deputy Director, OGD

Date 6/18/03 Initials [illegible]

Date 6/18/2003 Initials [illegible] (Electronic Sig)

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

Comments: Abbott made a paragraph III certification to the '216 patent - due to expire on 1/29/04.

This ANDA is recommended for tentative approval.

6. Gary Buehler
Director, OGD
Comments: Large volume parenteral w/ dextrose diluent.

Date _____ Initials _____

Date _____ Initials _____

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

7. Project Manager, Team Review Support Branch Ted Palat

Date _____ Initials _____

Date _____ Initials _____

N/A 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.

:PORTS\APPROVAL\Approvrou3.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-304 Applicant Abbott Laboratories
Drug Fluconazole Injection in 5% Dextrose Strength(s) 2mg/mL

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

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

1. Martin Shimer — Chief, Reg. Support Branch
   - DRAFT Package: Date 3-3-04, Initials MHS
   - FINAL Package: Date 3/24/04, Initials [signature] for

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA#
Date Checked Previously granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

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:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter: TA
Comments: firm to submit PII to '216 & not Ped Exclusivity

2. Project Manager, Ted Palat Team 9 — Review Support Branch
   - Date 2/25/04, Initials [initials]
   - Date ______ Initials ______

Original Rec'd date 12-26-01
Date Acceptable for Filing 12-20-01
Patent Certification (type) II
Date Patent/Exclus.expires ~~7/29/~~ 1/29/04
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 12-19-2002
Date of Office Bio Review 3-28-02
Date of Labeling Approv. Sum 2-14-03
Date of Sterility Assur. App. 8-23-02
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 6-18-03
Previously reviewed and CGMP def./NA Minor issued ☐ Date ______
Comments:

3. Div. Dir./Deputy Dir. — Chemistry Div. I or II
   - Date 3/18/04, Initials [initials]

Comments:
10/30 amendment Stability Testing site change
CMC OK

4. Frank Holcombe **First Generics Only** — Assoc. Dir. For Chemistry
   - Date ______ Initials ______

Comments: (First generic drug review)
N/A. The first-generic CMC audit was completed at the time of the initial tentative approval.

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date_____
Initials_____

RLD = Diflucan Injection in Dextrose 5% 2 mg/ml (in plastic containers)
Pfizer Inc. NDA 19-950(-003).

6. Peter Rickman
Director, DLPS
Date 3/24/04
Initials Recommend for

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Refer to the administrative sign-off form completed at the time of the tentative approval issued on 6/18/03. On October 30, 2003 Abbott submitted a minor amendment to propose some minor CMC changes and to request final approval based upon Abbott's expectation that the '216 patent would expire on 1/29/04. Labeling remains acceptable for tentative approval as of 3/15/04. CMC remains acceptable for approval 3/12/04. Methods validation is acceptable. Acceptable EES dated 5/6/04.

6. Robert L. West
Deputy Director, OGD
Date 5/21/2004
Initials Robert the last

Para.IV Patent Cert: Yes☐ No☒ Pending Legal Action: Yes☐ No☒ Petition: Yes☐ No☒
Comments: Abbott made a paragraph III certification to the '216 patent that was scheduled to expire on 1/29/04. However, the Agency awarded pediatric exclusivity to Pfizer for Diflucan. This effectively extended the expiration of the '216 patent until July 29, 2004.

Overall EES recommendation is currently pending. Abbott's Austin, TX manufacturing facility is currently subject to an "_____" this facility has an ongoing inspection. - See above. RW 5/21/04

Once the EES status is satisfactorily resolved, this ANDA is recommended for a second tentative approval.

7. Gary Buehler
Director, OGD
Date 5/21/04
Initials Rwffor

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

8. Project Manager, Team Ted Palat
Review Support Branch
Date 5-24-04
Initials CA

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:20 Time notified of approval by phone 2:40 Time approval letter faxed
FDA Notification:
~~5-24-04~~ Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5-24-04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-304 Applicant Hospira
Drug Fluconazole in 5% Dextrose Injection Strength(s) 2mg/mL

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

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date_____ Initials_____	Date_____ Initials_____

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

2. Project Manager, Ted Pelat Team 9 Review Support Branch	Date 7/2/04 Initials SS	Date_____ Initials_____

Original Rec'd date 12-14-01
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 12-20-01
Date of EER Status 6-3-04
Patent Certification (type) II
Date of Office Bio Review 3-26-02
Date Patent/Exclus.expires 7/29/04
Date of Labeling Approv. Sum 2-14-03
Citizens' Petition/Legal Case Yes ☐ No ☒
Date of Sterility Assur. App. 8-23-02
(If YES, attach email from PM to CP coord)
Methods Val. Samples Pending Yes ☐ No ☐
First Generic Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Acceptable Bio reviews tabbed Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☒ Date 5/26/04 (Abbott)
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____ RCA
Comments:

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

Comments:
N/A

4. Div. Dir (/Deputy Dir. Chemistry Div. I II OR III	NO CMC issues	Date 7/22/04 Initials RCA

Comments:

REVIEWER:

FINAL ACTION

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

Date_____
Initials_____

6. Vacant
Deputy Dir., DLPS

RLD = Diflucan Injection in Dextrose 5% (in plastic containers) 200mg/100ml (NDA 19-950 003) 400mg/200ml

Date_____
Initials_____

7. Peter Rickman
Director, DLPS
Pfizer Inc.

Date 7/29/04
Initials

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

Comments: Acceptable EES dated 6/3/04 (verified 7/29/04) No O.A.I. Waiver requested for Refer to the administrative sign-off forms completed at the time of the tentative approvals issued on June 18, 2003 and May 21, 2004.

OR

On 5/26/04, Hospira requested final approval of its ANDA effective 7/29/04. Updated PPI was also submitted. PM found acceptable for approval 7/26/04. CMC found acceptable for approval 7/26/04. Methods validation is acceptable.

Robert L. West
Deputy Director, OGD

Date 7/29/2004
Initials Robert West

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

Comments: Hospira (formerly Abbott) made a paragraph III certification to the '216 patent. The expiration of the '216 patent was effectively extended until 7/29/04 upon the granting of pediatric exclusivity to Pfizer. Hospira has revised its patent certification to paragraph II and has addressed Pfizer's period of exclusivity. With the expiration of Pfizer's exclusivity, this ANDA is recommended for final approval.

9. Gary Buehler
Director, OGD
Comments:

Date 7/29/04
Initials RW for GB

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

10. Project Manager, Team Review Support Branch
TEL Blat
N/A

Date_____
Initials_____

Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10:02 Time notified of approval by phone 10:10 Time approval letter faxed
FDA Notification:
2/25/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/25/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-304

CORRESPONDENCE

ABBOTT

Hospital Products Division
Abbott Laboratories
D-37K, Bldg. J-45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

December 14, 2001

505(j)(2)(A) OK
19 FEB 2002

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Director

Contains Sterilization Assurance Data

Re: Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Abbott Laboratories hereby submits an Abbreviated New Drug Application for Fluconazole Injection, in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act. The subject drug is a prescription drug. The dosage form is injectable and the manufacturing site is 3900 Howard Lane, Austin, Texas 78728.

The basis for this submission is Diflucan®, NDA 19-950, held by Pfizer Inc. NDA 19-950 was approved January 29, 1990.

The data supporting this application is provided in 5 volumes and is organized per *"Guidance for Industry: Organization of an ANDA"* dated February 1999, Revision 1.

The active ingredient, indications, route of administration, dosage form, and strength for Fluconazole Injection are the same as those of the Reference Listed Drug. Comparative information is contained in Section IV.

The labeling is the same in content as that of the reference drug, Diflucan®. A copy of the side by side label comparison is provided in Section IV.

The documentation for Sterilization Process Validation is found under Section XXII Sterilization Assurance Information and Data in a separate volume (5) with a dedicated table of contents. The subject drug is ———————. We request approval of ——————— to support the sterilization of the final product.

Abbott Laboratories will manufacture the finished dosage form at its currently approved Austin, Texas facility (CFN# 1628454). In accordance with 21 CFR 314.94, Abbott Laboratories has submitted a complete copy of the technical section from this application (designated as the "field copy") to the Dallas FDA district office with inspection responsibilities for this site.

Abbott requests twenty-four (24) month expiration dating for these products based on the enclosed accelerated stability data. The first three commercial batches will be placed into our stability program and reported at regular intervals to support the twenty-four (24) month expiration date.

Abbott commits to provide samples, if requested, by the agency and resolve any issues identified in the method validation process after approval.

We trust that this submission is complete.

Sincerely,

ABBOTT LABORATORIES

Lisa K. Zboril, R.Ph.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 935-3227
Fax: (847) 938-7867
E-mail: lisa.zboril@abbott.com

G:d389\lkz\fluconazole\Dextrosechem

ABBOTT

Hospital Products Division
Abbott Laboratories
D-37K, Bldg. J-45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

February 12, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

ATTENTION: Gary J. Buehler, Director
Martin Shimer (cover only via fax)

Re: ANDA 76-304 Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection

AMENDMENT- REQUESTED INFORMATION

Abbott Laboratories (Abbott) is amending the above referenced abbreviated new drug application submitted on December 14, 2001. Reference is made to the telephone conversation between Martin Shimer, R.Ph., of the Regulatory Support Branch and Lisa K. Zboril, R.Ph., of Abbott on February 5, 2002.

Mr. Shimer requested a reduction in the proposed commercial batch size to _____ to correspond with the actual volume of the exhibit batch filled into drug product units. Abbott has updated relevant pages of the original application in ***bold italicized*** text and the proposed commercial batch record Drug Bill of Materials to reflect a proposed batch size of _____ (**Exhibit I**). Additionally, Abbott provides replacement pages for page 27 and 28 of the original application (**Exhibit II**). The replacement pages depict the side by side comparison of the carton labeling for Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection, as requested.

Should you have any questions or require additional information, please contact the undersigned.

Sincerely,

ABBOTT LABORATORIES
Lisa Zboril

Lisa K. Zboril, R.Ph.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 935-3227
Fax: (847) 938-7867

NAI
gm 2/25/02

MP 2/22/02

G:d389\lkz\flucanozole.doc

ANDA 76-304

MAR 19 2002

Abbott Laboratories
Attention: Lisa Zboril
200 Abbott Park Rd.
D-37K, J 45
Abbott Park, IL 60064-6133

Dear Madam:

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 5, 2002 and your correspondence dated February 12, 2002.

NAME OF DRUG: Fluconazole in Dextrose 5% in Plastic Container, 2 mg/mL, 100 mL and 200 mL bags

DATE OF APPLICATION: December 14, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 20, 2001

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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-304
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 Gregory S. Davis 19-FEB-2002 date
HFD-615/MShimer, CSO [signature] date 19 February 2002
Word File V:/Firmsam/Abbott/Ltrs&rev/76304.ack
F/T EEH 02/19/02
ANDA Acknowledgment Letter!

MINOR AMENDMENT

ANDA 76-304

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)

MAY - 8 2002

TO: APPLICANT: Abbott Laboratories

TEL: 847-935-3227

ATTN: Lisa K. Zboril

FAX: 847-938-7867

FROM: Jeen Min

PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (6 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:

Chemistry and Labeling Deficiencies with Bioequivalence comments.

Jm 5/8/02

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information from

5/8/2002 FDA FAX

E. [ ]

4. Regarding stability, we have the following question:

Please include the chemical names of the known impurities in the stability specifications.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

(This review supersedes the one prepared on 2/28/02)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-304 Date of Submission: December 14 & February 12, 2002

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

1. GENERAL

   a. We note that you refer to your drug product "Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection" on your application form. However, we note that your drug product contains approximately 50 mg of dextrose anhydrous (*i.e.*, 56 mg of hydrous form). Consequently, it should read "5%" rather than "5.6%". Please revise accordingly in your subsequent submissions.

   b. We acknowledge your proposal for a combined package insert for your separate applications, in sodium chloride injection (76-303) and in dextrose injection (76-304). Please note that these applications must be approved at the same time, or further revisions will be necessary prior to approval.

   c. We encourage differentiation of this drug product from your other proposed product (ANDA 76-303) by use of boxing, contrasting colors, or other means to promote proper product selection and prevent errors.

   d. We note that your storage temperature statement is not the same as the innovator (*i.e.*, 25°C vs——). We also note that you have not reported the specification of bacterial endotoxin at —— . Please revise to be the same as the innovator and/or comment, and if necessary, please submit the supporting data for your proposal.

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

   a. We encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) 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 rather than using two different colors (*i.e.*, red and blue).

   b. It may be preferable to revise to read "Do not add supplementary medication" rather than " —————————— '. We believe the former convey the information more clearly.

   c. See comment 1d above.

3. OVERWRAP

   See comments under CONTAINER.

4. CARTON

   a. See comments under CONTAINER.

b. Add the text "Do not use unless the solution is clear." as it appears on the innovator's labeling.

5. INSERT

a. General

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.

iii. We ask that you delete all information specifically associated with "Vaginal Candidiasis" throughout the text as a single oral dose of fluconazole 150 mg is indicated for the treatment of "Vaginal Candidiasis".

b. DESCRIPTION

i. Second paragraph:

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

ii. Last paragraph:

In the labeling of your approved drug product using the flexible plastic container (e.g., 74-468), you stated that "Exposure to temperature above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." However, we note that you have revised to read " ——— " in this application. Please revise to read "25°C (77°F)" and/or comment, and if necessary, please submit the supporting data for your proposal.

c. INDICATIONS AND USAGE

i. See comment 5a(iii) above.

ii. Item #2

"candidiasis" rather than "candidasis"

d. CLINICAL STUDIES

See comment 5a(iii) above.

e. WARNINGS - Hepatic injury:

i. (1) Hepatic injury: Fluconazole... [add a colon]

ii. Second sentence:

...fluconazole-associated hepatotoxicity... [add a hyphen]

f. PRECAUTIONS

i. General, Single Dose:

See comment 5a(iii) above.

ii. It is preferable to use the term "times" rather than the symbol "x". [e.g. "20 to 50 times" rather than "20-50 x"]

g. ADVERSE REACTIONS - In Patients Receiving a Single Dose for Vaginal Candidiasis:

See comment 5a(iii) above.

h. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults, Single Dose:

See comment 5a(iii) above.

ii. Dosage in Patients with Impaired Renal Function:

See comment 5a(iii) above.

i. HOW SUPPLIED

See comment 1d above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-304 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Fluconazole Injection, 2 mg/ml in 5.6% dextrose

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,

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

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

June 28, 2002

ORIG AMENDMENT
N/am

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

FPL

Re: ANDA 76-304 Fluconazole 2 mg/mL in 5% Dextrose Injection

MINOR AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the drug product submitted December 14, 2001. We are responding to the Agency's action letter dated May 8, 2002. We wish to thank the Agency for participating in the teleconference on May 22, 2002 between Jeen Min and Glen Jon Smith of FDA and Lisa Zboril of Abbott to clarify items 3A, 3B and 4.

The Agency's action letter requests responses to CHEMISTRY and LABELING DEFICIENCIES with BIOEQUIVALENCE COMMENTS. The Agency's comments with Abbott's responses are as follows:

CHEMISTRY DEFICIENCIES:

COMMENT 1: **DMF #[redacted] has been found to be deficient. A letter has been sent to the holder identifying these issues. All deficiencies must be corrected before the approval of this application.**

RESPONSE: [redacted] has amended DMF No. [redacted] for [redacted] to address all deficiencies cited in the April 23, 2002 action letter issued by FDA. Their amendment was filed on May 10, 2002 and a copy of cover letter is included as **Exhibit I**.

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7/5/02

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6/28/2002 ABBOTT LETTER

√

RESPONSE:

√

[redacted]

COMMENT 4: **Regarding stability, we have the following question:**

Please include the chemical name of the known impurities in the stability specifications.

RESPONSE: Please see response to Item 3.A.

LABELING DEFICIENCIES:

1. GENERAL

a. We note that you refer to your drug product "Fluconazole, 2 mg/mL, in 5.6% Dextrose Injection" on your application form. However, we note that your drug product contains approximately 50 mg of dextrose anhydrous (i.e., 56 mg of hydrous form). Consequently, it should read "5%" rather than "5.6%". Please revise accordingly in your subsequent submissions.

RESPONSE: The Dextrose reference has been revised accordingly.

b. We acknowledge your proposal for a combined package insert for your separate applications in sodium chloride injection (76-303) and in dextrose injection (76-304). Please note that if these applications are not approved at the same time, further revisions may be necessary prior to approval.

RESPONSE: We acknowledge the insert may require further revisions as it is common, but we prefer to keep the insert as such.

c. We encourage differentiation of this drug product from your other proposed product (ANDA 76-303) by use of boxing, contrasting colors, or other means to promote proper product selection and prevent errors.

RESPONSE: We refer you to **Exhibit VI**, side by side labeling comparisons, which detail changes made to differentiate the products.

d. We note that your storage temperature statement is not the same as the innovator (i.e., 25°C vs ———). We also note that you have not reported the specification of bacterial endotoxin at ———. Please revise to be the same as the innovator and/or comment, and if necessary, please submit the supporting data for your proposal.

RESPONSE: We have updated our storage statement to be consistent with the innovator labeling. Bacterial endotoxin testing was completed in our room temperature stability study results.

2. **CONTAINER – 200 mg/100 mL & 400 mg/200 mL**

a. We encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) 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 rather than using two different colors (i.e. red and blue).

RESPONSE: We refer you to **Exhibit VI**, side by side labeling comparisons, which detail changes made to differentiate the products.

b. It may be preferable to revise to read "Do not add supplementary medication" rather than " ——————————— **. We believe the former convey the information more clearly.**

RESPONSE: We have changed our labeling to reflect the statement Drug additive should not be made to this solution.

c. See comment 1d above.

RESPONSE: We have updated our storage statement to be consistent with the innovator labeling. Bacterial endotoxin testing was completed in our room temperature stability study results.

3. OVERWRAP

See comments under CONTAINER.

RESPONSE: Responses as per above.

4. CARTON

a. See comments under CONTAINER.

RESPONSE: Responses as per above.

b. Add the text "Do not use unless the solution is clear", as it appears on the innovator's labeling.

RESPONSE: The text "Do not use unless the solution is clear" has been added to the labeling.

5. INSERT

a. General

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.

iii. We ask that you delete all information specifically associated with "Vaginal Candidiasis" throughout the text as a single oral dose of fluconazole

150 mg is indicated for the treatment of "Vaginal Candidiasis.

b. DESCRIPTION

i. Second paragraph: "chemical formula" rather than "[redacted]formula"

ii. Last paragraph: In the labeling of your approved drug product using the flexible plastic container (e.g., 74-468), you stated that "Exposure to temperature above 25°C (77°F) during transport and storage will lead to minor losses in moisture content." However, we note that you have revised to read "[redacted]' in this application. Please revise to read "25°C (77°F)" and/or comment, and if necessary, please submit the supporting data for your proposal.

c. INDICATIONS AND USAGE

i. See comment 5a(iii) above.

ii. Item #2: "candidiasis" rather than "candidasis"

d. CLINICAL STUDIES

See comment 5a(iii) above.

e. WARNINGS – Hepatic injury:

i. (1) Hepatic injury: Fluconazole… [add a colon]

ii. Second sentence:…fluconazole-associated hepatotoxicity… [add a hyphen]

f. PRECAUTIONS

i. General, Single Dose:

See comment 5a(iii) above

ii. It is preferable to use the term "times" rather than the symbol "x", [e.g. "20 to 50 times" rather than "20-50 x"]

g. ADVERSE REACTIONS – In Patients Receiving a Single Dose for Vaginal Candidiasis:

See comment 5a(iii) above.

h. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults, Single Dose:

See comment 5a(iii) above.

ii. Dosage in Patients with Impaired Renal Function:

See comment 5a(iii) above.

i. HOW SUPPLIED

See comment 1d above.

RESPONSE: All recommended changes to the Insert have been made in our proposed labeling. A side by side comparison of the currently filed labeling and the proposed labeling, with all differences annotated and explained, is provided in **Exhibit VI**. Final printed labeling may be found in **Exhibit VII**.

If there are any further questions or need for additional information, please feel free to contact me.

Sincerely,
ABBOTT LABORATORIES

Lisa K Zboril

Lisa K. Zboril, R.Ph.
Associate Director, CMC Operations, Regulatory Affairs
Hospital Products Division
Phone: (847) 935-3227
Fax: (847) 938-7867

[1] P. W. Atkins, Physical Chemistry, 4th Edition, W.H. Freeman and Company, New York.

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

N/AM

August 8, 2002

OPNG AMENDMENT

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

Re: ANDA 76-303 Fluconazole 2 mg/mL in 0.9% Sodium Chloride Injection
ANDA 76-304 Fluconazole 2 mg/mL in 5.6% Dextrose Injection

cc: Bonnie McNeal, Project Manager (by fax @ 301-443-3839)

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug applications for the drug products originally submitted December 14, 2001. We are responding to the Agency's telephone deficiency dated August 2, 2002. This correspondence summarizes the responses provided verbally by Lisa Zboril (Abbott) to Bonnie McNeal and Lisa Schelton (FDA) in the July 7, 2002 telecon.

The Agency requested responses to MICROBIOLOGY DEFICIENCIES. The Agency's comments with Abbott's responses are as follows:

CHEMISTRY DEFICIENCIES:

COMMENT 1: On page 2202 of ANDA 76-303, you provide Study Report [redacted] used in the subject drug product?

RESPONSE: [redacted]
products.

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8/8/2002 ABBOTT LETTER

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

ORIG AMENDMENT
NDAS

August 16, 2002

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

Re: ANDA 76-303 Fluconazole 2 mg/mL in 0.9% Sodium Chloride Injection
ANDA 76-304 Fluconazole 2 mg/mL in 5.6% Dextrose Injection

cc: Bonnie McNeal, Project Manager (by fax @ 301-443-3839)
Lisa Shelton, Microbiologist (by fax @301-594-0183)

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug applications for the drug products originally submitted December 14, 2001. We are responding to the Agency's telephone deficiency dated August 9 and 13, 2002, as communicated to Lisa Zboril (Abbott) by Lisa Shelton (FDA).

The Agency requested responses to MICROBIOLOGY DEFICIENCIES. The Agency's comments with Abbott's responses are as follows:

DEFICIENCIES

COMMENT 1: Who has responsibility to verify the requirements of _____ have been met for product release.

RESPONSE: [redacted]

release requirements.

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8/16/2002 ABBOTT LETTER

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J-45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

October 17, 2002

OFFICE OF GENERIC DRUGS, HFD-600
CENTER FOR DRUG EVALUATION AND RESEARCH, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Gary Buehler, Director

CC: Jeen Min, Project Manager (via fax 301-443-3839)

RE: **ANDA 76-303 Fluconazole 2mg/mL in 0.9% Sodium Chloride Injection**
ANDA 76-304 Fluconazole 2mg/mL in 5.0% Dextrose Injection

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug applications for the drug products originally submitted December 14, 2001. We are responding to the Agency's telephone deficiency dated October 11, 2002 as communicated to Richard Stec (Abbott) by Jeen Min (FDA).

FDA requested Abbott revise their — specification for ——— to align with the recently revised specification amended in the — vendor's Drug Master File. ——— ——— recently revised the limits for ——— and —. The ——— limit was tightened from NMT ——— to NMT ——— and the — limit was tightened from NMT ——— to NMT ———.

Abbott agrees to tighten the limits for ———and — to NMT ———. Abbott's internal control procedures will be amended to reflect these revised limits.

We trust that this submission is complete. If there are any further questions, please feel free to contact me.

Sincerely,
ABBOTT LABORATORIES
Tom Stothoff

Tom Stothoff
Manager, CMC Operations, Regulatory Affairs
Phone: (847) 936-0162
Fax: (847) 938-7867

RECEIVED
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ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J-45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

NEW CORRESP
NC

November 8, 2002

OFFICE OF GENERIC DRUGS, HFD-600
CENTER FOR DRUG EVALUATION AND RESEARCH, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Document Control Room

RE: **ANDA 76-303 Fluconazole 2mg/mL in 0.9% Sodium Chloride Injection**
ANDA 76-304 Fluconazole 2mg/mL in 5.0% Dextrose Injection

GENERAL CORRESPONDENCE

Pursuant to Ms. Emily Thomas's (FDA) telephone request of November 7, 2002, Abbott Laboratories hereby submits original Form FDA 356h forms for the October 17, 2002 Telephone Amendments submitted to the above-referenced ANDAs. Ms. Thomas communicated to Abbott that only copies were included in the submission.

We apologize for any inconvenience this oversight may have caused. Please contact the undersigned if you have further questions.

Sincerely,
ABBOTT LABORATORIES

Tom Stothoff

Tom Stothoff
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 936-0162
Fax: (847) 938-7867

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Abbott Laboratories — TEL: 847-936-0162

ATTN: Tom Stothoff — FAX: 847-938-7867

FROM: Jeen Min — PROJECT MANAGER: 301-594-0338

Number of pages: 3
(excluding the cover sheet)

Comments:

Labeling Deficiencies for ANDA 76-304, Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection).

Jm 11/24/02

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

ANDA Number: 76-304 Date of Submission: June 28, 2002

Applicant's Name: Abbott Laboratories

Established Name: Fluconazole Injection, 2 mg/mL (in 5% Dextrose Injection)

1. GENERAL

   a. We ask you to revise the storage temperature statement to be the same as the innovator:

      Storage: Store between 5°C (41°F) and 25°C (77°F). Brief exposure... freezing.

   b. We note that you printed the established name and expression for strength in red color for both 200mg/100mL and 400 mg/200 mL container labels and carton labeling, while you printed these in blue color for the overwrap labeling for both strengths. It can be very confusing. We recommend that you use the same color for the established name and expression of strength of one drug product for all labeling pieces rather than using two different colors (*i.e.*, red and blue). In addition, as addressed in the Agency's previous letter, we strongly encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) by using boxing, contrasting colors, and/or some other means.

   c. We note that you printed the term "DEXTROSE" in red color for the container labels and carton labeling, while printed this in blue color for the overwrap. We recommend that you print the term "DEXTROSE" using the same color for all labeling pieces (not the same color used for the term "SOLIUM CHLORIDE"). We believe this would help to differentiate your drug product from the one in sodium chloride.

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

   a. See general comments above, where appropriate.

   b. We ask you to relocate the route of administration statement "For I.V.USE" to appear immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

   c. The format of you container labels makes it difficult to readily obtain necessary information. Please refer to the Diflucan® Injection labels for guidance. We suggest the following revisions regarding format changes for your consideration.

      i. It is preferable to print the text "USUAL DOSAGE" in bold face type.

      ii. Include the term "CAUTIONS" in bold face type and revise to read:

         CAUTIONS: DO NOT ADD SUPPLEMENTARY MEDICATION. USE ONLY IF SOLUTION ...CONNECTIONS.

      iii. Relocate the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

3. OVERWRAP

a. See general comments above, where appropriate.

b. Include the text "For I.V.USE" to appear immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

c. Include the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

d. We encourage you to reformat the text with break up by the different categories (*i.e.*, storage, usual dosage, cautions, etc) rather than having one continuous text including all information.

e. Include the text "**USUAL DOSAGE**" immediately prior to the text "See insert.".

f. Print the text "Recommended storage:" in bold face type.

4. CARTON

i. See comments under GENERAL, CONTAINER and OVERWRAP above, where appropriate.

ii. We note that you included both "Usual dosage: See insert" and "See insert." You may delete the text "See insert.". [redundant]

5. INSERT

a. General

We note that you submitted the insert labeling in several separate pieces as final printed labeling. Please be reminded that the whole text should appear as one piece to be considered as final printing.

b. Precautions

Delete the subsection heading "[redacted]as no information appears under this subsection.

c. HOW SUPPLIED

See comment 1(a) above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ARCHIVAL COPY

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J-45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

December 5, 2002

ORIG AMENDMENT
N/AM

OFFICE OF GENERIC DRUGS, HFD-600
CENTER FOR DRUG EVALUATION AND RESEARCH, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Gary Buehler, Director

CC: Jeen Min, Project Manager (via fax 301-443-3839)

RE: **ANDA 76-303 Fluconazole 2mg/mL in 0.9% Sodium Chloride Injection**
ANDA 76-304 Fluconazole 2mg/mL in 5.0% Dextrose Injection

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug applications for the drug products originally submitted December 14, 2001. We are responding to the Agency's telephone deficiency dated November 25, 2002 as communicated to Tom Stothoff (Abbott) by Jeen Min, Glen Smith and Mahnaz Farahani (FDA).

FDA requested Abbott revise their — specification for ——— to align with the recently revised specification amended in the — vendor's Drug Master File. ——— ——— recently revised the limits for ——— and ——— tested by ———.

Abbott agrees to tighten the limits for ——— to NMT ——— and ——— to NMT ———. Abbott's internal control procedures will be amended to reflect these revised limits. Additional validation work was not required as the currently submitted validation reports support the proposed tighter ———limits.

In accordance with 21 CFR 314.96(b), Abbott Laboratories hereby certifies that we have sent a true copy of this submission to the Dallas, TX FDA District Office.

We trust that this submission is complete. If there are any further questions, please feel free to contact me.

RECEIVED
DEC 0 6 2002
OGD / CDER

Sincerely,
ABBOTT LABORATORIES

Tom Stothoff
Manager, CMC Operations, Regulatory Affairs
Phone: (847) 936-0162
Fax: (847) 938-7867

APPEARS THIS WAY
ON ORIGINAL

ARCHIVAL COPY

ABBOTT

Hospital Products Division
Abbott Laboratories
Dept. 389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157
USA

January 10, 2003

ORIG AMENDMENT
N/AA

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION:
Gary Buehler
Director, OGD

RE: ANDA 76-303 Fluconazole 2mg/mL in 0.9% Sodium Chloride Injection
ANDA 76-304 Fluconazole 2mg/mL in 5.0% Dextrose Injection

GRATUITOUS AMENDMENT – CHEMISTRY

Abbott Laboratories hereby files this amendment to the above-referenced pending applications to provide for a change in the ——— overwrap utilized as a secondary package for Fluconazole Injection.

On May 08, 2002, Abbott Laboratories filed a bundled review Supplement – Changes Being Effected in 30 Days for thirty-four (34) currently approved new and abbreviated drug applications. This supplement was filed to support a change to the ——— overwrap utilized as a secondary package for various Large Volume Parenteral (LVP) drug products packaged in flexible plastic containers. NDA 16-367, Dextrose 5% Injection, USP, in a flexible plastic container, served as the lead submission (agreement reached with Susan Lange, CSO in the Office of New Drug Chemistry on April 17, 2002). Please be advised that the lead supplement (NDA 16-367) was approved on November 8, 2002. Also, of the thirty-four applications, twenty-three (23) were abbreviated new drug applications. The supplements to the twenty-three ANDAs were approved by OGD on November 1, 2002 (see **Exhibit I**).

RECEIVED
JAN 13 2003
OGD / CDER
1/10/03

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

1/10/2003 ABBOTT LETTER

Abbott Laboratories certifies that a true copy of this submission has been provided to the Dallas, Texas FDA District Office.

Should you have any questions or require additional information, please contact the undersigned.

Sincerely,
ABBOTT LABORATORIES

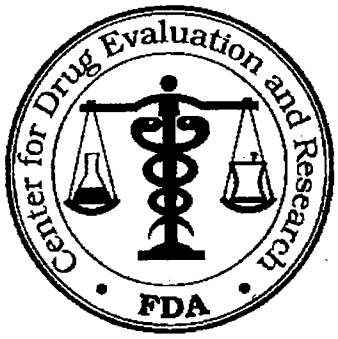
Tom Stothoff
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 936-0162
Fax: (847) 938-7867
email: Tom.Stothoff@abbott.com

MINOR AMENDMENT

ANDA 76-304

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)

JAN 16 2003



TO: APPLICANT: Abbott Laboratoies

TEL: 847-936-0162

ATTN: Tom Stothoff

FAX: 847-938-7867

FROM: Jeen Min

PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL.

Reference is also made to your amendment(s) dated: June 28, August 8, October 17, and December 5, 2002. † August 16, 2002

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. /jm 1/16/03

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:

/jm 1/16/03

JAN 16 2003

38. Chemistry Comments to be provided to the Applicant

ANDA: 76-304 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL (in Dextrose Injection)

The deficiencies presented below represent Minor deficiencies.

We refer to the facsimile dated November 26, 2002 regarding your deficiencies in the labeling section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Your response will be considered a Minor Amendment.

Sincerely yours,

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

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

January 21, 2003

ORIG AMENDMENT
N/AM

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

Attention: Gary Buehler, Director

Re: ANDA 76-304 Fluconazole, 2 mg/mL, in 5% Dextrose Injection

MINOR AMENDMENT – CHEMISTRY AND LABELING

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for ANDA 76-304 Fluconazole, 2 mg/mL, in 5% Dextrose Injection submitted December 14, 2001 and amended. We are responding to the Agency's action letters dated November 26, 2002 (Labeling) and January 16, 2003 (Chemistry). Abbott acknowledges guidance received in teleconferences between Chan Park (FDA) and Tom Stothoff (Abbott) on December 10, 2002 and January 9, 2003.

The Agency's January 16, 2003 action letter requests responses to CHEMISTRY deficiencies. The Agency's comment with Abbott's response is as follows:

1. **We refer to the facsimile dated November 26, 2002 regarding your deficiencies in the labeling section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Your response will be considered a Minor Amendment.**

   RESPONSE: This amendment includes responses to the labeling deficiencies issued in the Agency's November 26, 2002 communication.

Gary Buehler
ANDA 76-304
January 21, 2003

The Agency's November 26, 2002 action letter requests responses to LABELING deficiencies. The Agency's comments with Abbott's responses are as follows:

1. **General**

   a. **We ask you to revise the storage temperature statement to be the same as the innovator:**

      Storage: Store between 5 °C (41 °F) and 25 °C (77 °F). Brief exposure...freezing.

   RESPONSE: As was discussed in a December 10, 2002 telephone communication with FDA's Chan Park, Abbott is maintaining the current storage conditions "**RECOMMENDED STORAGE:** Room temperature (25 °C). Avoid excessive heat. Protect from freezing." to be consistent with other approved Abbott products. Abbott submitted stability data on product stored at 25 °C and 40 °C in the original application to support this storage condition. Mr. Park confirmed the storage condition should be supported by the stability data that was generated.

   b. **We note that you printed the established name and expression for strength in red color for both 200mg/100mL and 400 mg/200 mL container labels and carton labeling, while you printed these in blue color for the overwrap labeling for both strengths. It can be very confusing. We recommend that you use the same color for the established name and expression of strength of one drug product for all labeling pieces rather than using two different colors (i.e., red and blue). In addition, as addressed in the Agency's previous letter, we strongly encourage you to differentiate your drug products of two different strengths (200 mg & 400 mg) by using boxing, contrasting colors, and/or some other means.**

   c. **We note that you printed the term "DEXTROSE" in red color for the container labels and carton labeling, while printed this in blue color for the overwrap. We recommend that you print the term "DEXTROSE" using the same color for all labeling pieces (not the same color used for the term "SODIUM CHLORIDE"). We believe this would help to differentiate your drug product from the one in sodium chloride.**

RESPONSE to b/c: Abbott acknowledges the importance of consistency in the presentation of the established drug name, expression of strength and diluent between the carton, overwrap and container of one drug product. Abbott is additionally balancing labeling design to avoid potential confusion with other drug products that may be stored near fluconazole, both in the warehouse/stockroom setting as well as in the I.V. room/dispensing area.

Following is a description and justification of how Abbott has differentiated the labeling between strengths and between diluents. This is presented starting with the outermost carton and working inward to the overwrap and finally the container imprint.

Carton – The carton has been revised to be consistent with the overwrap labeling.

- Established Name: An aqua blue color is utilized for the established name FLUCONAZOLE throughout carton and overwrap labeling pieces to distinguish from other drugs.
- Diluent: Aqua blue color and increased font/capital text is utilized for DEXTROSE while black color and increased font/capital text is utilized for SODIUM CHLORIDE to consistently differentiate diluents.
- Strength: In accordance with guidance received, the strength for the 200 mg product utilizes aqua blue color, boxed design and right placement to differentiate from the 400 mg product which utilizes black color, bold box design and underneath placement.

Overwrap – The changes described above for the carton have been incorporated into the overwrap label for product consistency.

Container – The following limitations exist for use of color in the primary container labeling design due to the ——— process. Three colors (red, blue, and black) are qualified for use with the ——— process. The ——— does not allow for color changes within panels. Blue or black text must be used for the bottom text panel to enable proper reading of the bar code.

Agency recommendations for the container labeling were mocked up and are provided in **Exhibit I** for both the DEXTROSE and SODIUM CHLORIDE products. Unfortunately, on paper and more pronounced on the actual bags, the blue and black panels do not appear substantially different.

Abbott proposes the use of red for the established name, diluent and strength panel and the contrasting color blue for the lower panel information. This option draws the user's attention to the upper panel information. The design utilizes increased font for established name, boxing and text placement for strength differentiation and increased font for diluent differentiation consistent with outer labeling pieces.

Note, consistent with labeling, the primary bag should not be removed from the overwrap until ready for use. Therefore, the greater differentiation achieved in the overwrap (due to color) remains with the drug product until time of use.

Provided in **Exhibit II** are four copies of proposed draft labeling. Provided in **Exhibit III** are side-by-side comparisons of our proposed labeling compared to the most recently submitted labeling (June 28, 2002 amendment).

2. **CONTAINER – 200 mg/100 mL and 400 mg/200 mL**

a. See general comments above, where appropriate.

RESPONSE: Please see our responses to Comments 1.a, 1.b and 1.c above.

b. We ask you to relocate the route of administration statement "For I.V. USE" to appear immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

RESPONSE: This request has been incorporated into our proposed labeling.

c. The format of you container labels makes it difficult to readily obtain necessary information. Please refer to the Diflucan® Injection labels for guidance. We suggest the following revisions regarding format changes for your consideration.

i. It is preferable to print the text "USUAL DOSAGE" in bold face type.

ii. Include the term "CAUTIONS" in bold face type and revise to read:

CAUTIONS: DO NOT ADD SUPPLEMENTARY MEDICATION. USE ONLY IF SOLUTION...CONNECTIONS.

iii. Relocate the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

RESPONSE: These requests have been incorporated into our proposed labeling.

3. OVERWRAP

a. See general comments above, where appropriate.

RESPONSE: Please see our responses to Comments 1.a, 1.b and 1.c above.

b. Include the text "For I.V. USE" to appear immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

RESPONSE: The text "FOR I.V. USE" has been included as the first statement in the lower panel of information since the bar code appears immediately beneath the statement "ISO-OSMOTIC DEXTROSE DILUENT".

c. Include the text "STERILE, NONPYROGENIC" to appear immediately after the "osmolarity" statement.

d. We encourage you to reformat the text with break up by the different categories (i.e., storage, usual dosage, cautions, etc) rather than having one continuous text including all information.

e. Include the text "USUAL DOSAGE" immediately prior to the text "See insert".

f. Print the text "Recommended storage:" in bold face type.

RESPONSE: The requests listed in comments c-f have been incorporated into our proposed labeling.

4. **CARTON**

a. See comments under GENERAL, CONTAINER, and OVERWRAP above, where appropriate.

RESPONSE: Please see our responses to Items 1.a, 1.b and 1.c above.

b. We note that you included both "Usual dosage: See insert" and "See insert." You may delete the text "See insert." [redundant]

RESPONSE: The second "See insert" has been deleted.

5. **INSERT**

a. General

We note that you submitted the insert labeling in several separate pieces as final printed labeling. Please be reminded that the whole text should appear as one piece to be considered as final printing.

RESPONSE: We acknowledge the Agency's comment. Four copies of draft labeling are provided in **Exhibit II**.

b. Precautions

Delete the subsection heading " ——— ' as no information appears under this subsection.

RESPONSE: The subsection heading " ——— " has been deleted.

c. HOW SUPPLIED

See comment 1(a) above.

RESPONSE: Please see our response to comment 1.a above.

Gary Buehler
ANDA 76-304
January 21, 2003

Abbott Laboratories certifies that a true copy of this submission has been provided to the Dallas, Texas FDA District Office.

If there are any further questions or need for additional information, please feel free to contact the undersigned.

Sincerely,

ABBOTT LABORATORIES

Tom Stothoff

Tom Stothoff
Manager, Regulatory Affairs
Hospital Products Division
Phone:(847) 936-0162
Fax: (847) 938-7867
EMAIL: stothTN@hpd.abbott.com

APPEARS THIS WAY
ON ORIGINAL

North Chicago facility withdrawn. 11/19/2003

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

ORIG AMENDMENT

N/Am

October 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

Attention: Gary Buehler, Director

Re: ANDA 76-303 Fluconazole, 2 mg/mL, in 0.9% Sodium Chloride Injection
ANDA 76-304 Fluconazole, 2 mg/mL, in 5% Dextrose Injection

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Abbott Laboratories hereby amends the above-referenced abbreviated new drug applications submitted December 14, 2001. We are filing this Minor Amendment as required by the Agency's Tentative Approval letters dated June 18, 2003.

Abbott confirms the only changes made to the applications are to remove the North Chicago, Illinois facility as a stability-testing site and to expand the role of the Rocky Mount, North Carolina facility to include storage of stability samples.

In summary, Abbott intends to manufacture product and conduct release and stability testing at Abbott's Austin, Texas facility. Stability samples will reside in chambers at the Rocky Mount facility prior to testing at Austin.

Provided in **Exhibit I** is an updated "Section IX, Description of Manufacturing Facility" section which lists all facilities involved in the manufacture, storage and testing of drug product.

Abbott Laboratories acknowledges the current status of the Austin manufacturing facility. In response to the FDA inspection activities, we have responded fully to all FDA

11-14

observations related to this inspection. At this time, the Austin facility is awaiting re-inspection from the FDA. Abbott anticipates this activity should be completed prior to patent/exclusivity expirations for the above referenced ANDAs.

Abbott Laboratories certifies that a true copy of this submission has been provided to the Dallas, Texas FDA District Office.

If there are any further questions or need for additional information, please feel free to contact the undersigned.

Sincerely,

ABBOTT LABORATORIES

Tom Stothoff
Manager, Regulatory Affairs
Hospital Products Division
Phone:(847) 936-0162
Fax: (847) 938-7867
email: tom.stothoff@abbott.com

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

3.1

February 27, 2004

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

ATTENTION: Gary Buehler, Director

SUPPLEMENT – Changes Being Effected – 30 Days

RE:

ANDA 16-366 SODIUM CHLORIDE 0.9% INJECTION, USP, IN FLEXIBLE CONTAINERS

ANDA 18-080 DEXTROSE 10% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-090 SODIUM CHLORIDE 0.45% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-561 DEXTROSE 70% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-562 DEXTROSE 40% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-563 DEXTROSE 50% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-564 DEXTROSE 20% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 18-890 METRONIDAZOLE INJ. IN FLEXIBLE PLASTIC CONTAINERS

ANDA 19-345 DEXTROSE 30% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

Gary Buehler, Director
February 27, 2004

ANDA 19-346 DEXTROSE 60% INJECTION, USP, IN FLEXIBLE PLASTIC CONTAINERS

ANDA 19-466 DEXTROSE 5% INJECTION, USP, IN ADD-VANTAGE IN FLEXIBLE PLASTIC CONTAINERS

ANDA 19-479 DEXTROSE 5% INJ, USP, IN 250 ML ADD-VANTAGE IN FLEXIBLE PLASTIC CONTAINERS

ANDA 19-893 DEXTROSE 70% INJ, USP, PHARMACY BULK PACKAGE IN FLEXIBLE PLASTIC CONTAINERS

ANDA 19-894 DEXTROSE 50% INJ, USP, PHARMACY BULK PACKAGE IN FLEXIBLE PLASTIC CONTAINERS

ANDA 20-015 AMINOSYN II 10%, (AN AMINO ACID INJ.), PHARMACY BULK PACKAGE

ANDA 20-161 POTASSIUM CHL. INJ., USP 0.745% & 1.49%

ANDA 62-414 GENTAMICIN SULFATE IN 0.9% SODIUM CHLORIDE IN FLEXIBLE PLASTIC CONTAINERS

ANDA 62-588 GENTAMICIN SULFATE IN 0.9% SODIUM CHLORIDE IN CR3 FLEXIBLE CONTAINERS

ANDA 63-081 TOBRAMYCIN SULFATE INJ. IN 0.9% NACL SOLUTION IN PVC FLEXIBLE CONTAINERS

ANDA 76-303 FLUCANOZOLE, 2MG/ML, IN 0.9% SODIUM CHLORIDE INJECTION

ANDA 76-304 FLUCANOZOLE, 2MG/ML, IN 5.6% DEXTROSE INJECTION

Abbott Laboratories hereby files a bundled review Supplement – Changes Being Effected – 30 Days for the referenced forty (40) new and abbreviated drug applications. This supplement contains data to support a change to the ———overwrap utilized as a secondary package for various Large Volume Parenteral (LVP) drug products packaged in flexible plastic containers.

ANDA 16-366 SODIUM CHLORIDE 0.9% INJECTION, USP, IN FLEXIBLE CONTAINERS will serve as the lead submission. A list of the responsible FDA review divisions for each referenced NDA and ANDA is provided in Exhibit I.

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confidential commercial

information from

2/27/2004 ABBOTT LETTER

Gary Buehler, Director
February 27, 2004

We certify that a copy has been provided to the district office with inspectional responsibilities.

If you need additional information, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

Ayse Baker, PhD
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-1842
Fax: (847) 938-7867
E-Mail:bakerau@hpd.abbott.com

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

March 22, 2004

NEW CORRESP
NC

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ATTENTION: Gary Buehler, Director

REQUEST FOR WITHDRAWAL
SUPPLEMENT DATED FEBRUARY 27, 2004

RE:
ANDA 76-303 FLUCONAZOLE, 2MG/ML, IN 0.9% SODIUM CHLORIDE INJECTION
ANDA 76-304 FLUCONAZOLE, 2MG/ML, IN 5.0% DEXTROSE INJECTION

Abbott Laboratories hereby requests the withdrawal of the above referenced applications from the bundled Supplement-Changes Being Effected 30 Days submitted to the Agency on February 27, 2004 to support a change to the ———— overwrap utilized as a secondary package for various Large Volume Parenteral (LVP) drug products packaged in flexible plastic containers. All other applications referenced in the bundle are appropriate.

The products referenced above are "tentatively approved" by the Agency at this time, awaiting expiration of exclusivity. These two applications should not have been included in the bundled supplement due to their pending status. This withdrawal is not associated with any safety or efficacy issues.

We regret any inconvenience this may have caused. If you need additional information, please feel free to contact me.

Sincerely,
ABBOTT LABORATORIES

Ayse Baker, PhD
Manager, Regulatory Affairs
Phone: (847) 938-1842
Fax: (847) 938-7867
E-Mail: bakerau@hpd.abbott.com

ABBOTT

Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1NE
Abbott Park, Illinois 60064-6157

48

May 3, 2004

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ATTENTION: Gary Buehler, Director

Re: ANDA 76-304 Fluconazole, 2 mg/mL, in 5% Dextrose Inj., Flexible Plastic Container

General Correspondence
Transfer of Ownership

This letter is to inform you that Abbott Laboratories in accordance with 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.72 has transferred all rights to this application, effective immediately, to:

Hospira, Inc.
275 North Field Dr.
Lake Forest, IL 60045

Should you have any questions concerning the transfer of ownership, please contact me at the number listed below.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Senior Director
Global Pharmaceutical Regulatory Affairs
Abbott Laboratories
(847) 937-5533

4.1

ORIGINAL

Hospira

May 7, 2004

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

XS

ATTENTION: Gary Buehler, Director

Re: ANDA 76-304 Fluconazole, 2 mg/mL, in 5% Dextrose Inj., Flexible Plastic Container

Effective May 3, 2004, Abbott Laboratories Hospital Products Division has become an independent company registered under the name of Hospira, Inc. As of that day, the ownership of the subject application has been transferred from Abbott Laboratories, North Chicago, IL to Hospira, Inc. Lake Forest, IL. This notification is submitted to the Food and Drug Administration in accordance with 21 CFR 314.72(a)(2).

A letter issued by the former owner, Abbott Laboratories, relinquishing all rights to the subject application to Hospira, Inc. is provided herein. Hospira, Inc. commits to agreements, promises and conditions made by the former owner and contained in the application. Hospira, Inc. has obtained a complete copy of the application including supplements and records that are required to be kept under 21 CFR 314.81.

Manufacturing and testing sites registered with FDA and referenced in the subject application that have changed ownership from Abbott Laboratories to Hospira, Inc. have been updated in the Establishment Information section of the 356h form. Physical location of all plant and laboratory facilities and personnel remains unchanged.

We trust that this informational application is complete.

Please contact me if you have any questions.

Sincerely,

Hospira, Inc.

Richard J. Stec Jr.

Richard J. Stec Jr., Ph.D
Director Regulatory Affairs
Phone: (224) 212-4795
Fax: (224) 212-5401

RECEIVED
MAY 10 2004
OGD/CDER

Hospira, Inc.
275 North Field Drive
Lake Forest, IL 60045
224.212.2000
www.hospira.com

ORIGINAL

Hospira

Wednesday, May 26, 2004

ETR
submitted
6/3/04
ORIG AMENDMENT
N/Am

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

Attention: Gary Buehler, Director

Re: **ANDA 76-303 - Fluconazole, 2 mg/mL, in 0.9% Sodium Chloride Injection**
ANDA 76-304 - Fluconazole, 2 mg/mL, in 5% Dextrose Injection

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Hospira Inc. hereby amends the above-referenced abbreviated new drug applications submitted December 14, 2001. We are filing this Minor Amendment as required by the Agency's Tentative Approval letters dated May 21, 2004.

Except for our corporate name change from Abbott Laboratories' Hospital Products Division to Hospira, Inc., we confirm the only other change made to these applications is to reinstate the North Chicago, Illinois facility as a stability-testing site. We removed this site from the ANDAs in the October 30, 2003 Tentative Approval Minor Amendment.

Provided in **Exhibit I** is an updated "Section IX, Description of Manufacturing Facility" which lists all facilities involved in the manufacture, storage and testing of drug product.

Hospira certifies that a true copy of this submission has been provided to the Dallas, Texas FDA District Office.

Please do not hesitate to contact me if you have questions or require additional information.

Sincerely,

JPDohnalek.

Jonathan P. Dohnalek
Manager, Global Regulatory Affairs
Hospira, Inc.
275 North Field Drive, Bldg 2
Lake Forest, IL 60045-5045
phone: 224-212-4775
fax: 224-212-5401
jonathan.dohnalek@hospira.com

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MAY 27 2004
OGD / CDER

Hospira, Inc
275 North Field Drive
Lake Forest, IL 60045
224.212.2000
www.hospira.com

ORIGINAL

Hospira

Thursday, July 15, 2004

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
METRO PARK NORTH II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

ATTENTION: Gary Buehler, Director HFD-600

CC: Chan Park, Labeling Support Branch
(cover letter via fax only at 301-594-0183)

RE: ANDA 76-304 Fluconazole 2 mg/mL in 5% Dextrose Injection

FINAL PRINTED LABELING

Hospira, Inc. hereby files final printed labeling to the above-referenced tentatively approved application. The final printed labeling in the following exhibit is the same as the labeling that was included in the January 21, 2003 amendment, Exhibit II. A table is provided below to serve as a reviewer aid, demonstrating the commodity numbers are identical. This labeling is submitted in response to the request of Chan Park (FDA) to Lisa K. Zboril (Hospira) on 7/13/04.

Labeling Description	Commodity Number in 1/23/03 labeling minor amendment	Commodity Number in 7/15/04 final printed labeling submission
Primary Container 100 mL	RAO6483-2/R3-1/03	RAO6483-2/R3-1/03
Primary Container 200mL	RAO6486-2/R3-1/03	RAO6486-2/R3-1/03
Overwrap Front 100 mL	F RAO6484-2/R3-1/03	F RAO6484-2/R3-1/03
Overwrap Back 100 mL	B RAO6484-2/R3-1/03	B RAO6484-2/R3-1/03
Overwrap Front 200 mL	F RAO6487-2/R3-1/03	F RAO6487-2/R3-1/03
Overwrap Back 200 mL	B RAO6487-2/R3-1/03	B RAO6487-2/R3-1/03
Carton 100 mL	RAO6485-2/R3-1/03	RAO6485-2/R3-1/03
Carton 200 mL	RAO6488-2/R3-1/03	RAO6488-2/R3-1/03
Enclosure 100 and 200 mL	RAO6489-R3-Rev. January, 2003	RAO6489-R3-Rev. January, 2003

Hospira, Inc.
275 North Field Drive
Lake Forest, IL 60045
224.212.2000
www.hospira.com

Hospira

Please let me know if there are any additional questions.

Sincerely,

Hospira, Inc.

Lisa K. Zboril, R.Ph.
Director, Global Regulatory Affairs
275 North Field Drive, Building H2
Lake Forest, Illinois 60045-4775
Phone. 224-212-4654
Fax. 224-212-5401
lisa.zboril@hospira.com

APPEARS THIS WAY
ON ORIGINAL

Hospira

Thursday, July 20, 2004

ORIG AMENDMENT
N/AF

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
METRO PARK NORTH II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Gary Buehler, Director HFD-600

CC: Chan Park, Labeling Support Branch
(cover letter via fax only at 301-594-0183)

RE: ANDA 76-304 Fluconazole 2 mg/mL in 5% Dextrose Injection

FINAL PRINTED LABELING

Hospira, Inc. hereby files the final printed labeling for the enclosure to the above-referenced tentatively approved application. The final printed labeling following this cover letter is the same in content as the labeling that was included in the January 21, 2003 amendment, Exhibit II, but has been reformatted for use as commercial product labeling and reflects a new revision date and commodity number. This labeling is submitted in response to the request of Chan Park (FDA) to Lisa K. Zboril (Hospira) on 7/20/04.

Hospira hereby commits that all Fluconazole labeling will be updated to reflect the Hospira logo and associated information post approval as part of Hospira's labeling conversion initiative.

Please let me know if there are any additional questions.

Sincerely,

Hospira, Inc. Michael R. Logan for Lisa Zboril

Lisa K. Zboril, R.Ph.
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