CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-087

***Name*:** Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials

***Sponsor*:** Bedford Laboratories

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

APPROVAL LETTER

ANDA 76-087

JUL 29 2004

Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to our Tentative Approval letters dated July 17, 2003, and April 9, 2004, and to your amendment dated May 11, 2004.

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

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

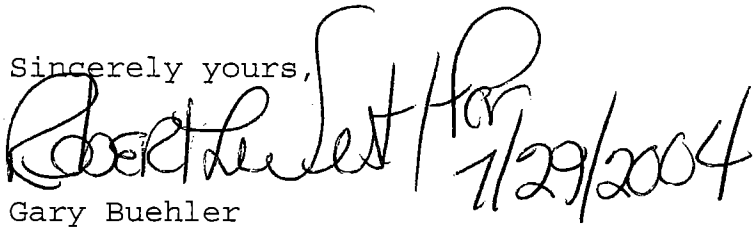
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

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

Sincerely yours,



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

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/A.Langowski/ A. Langowski 7/12/04
HFD-647/G.Smith/ 7/12/04
HFD-617/T.Palat/ 7/16/04
HFD-613/C.Park7/8/04/ 7/16/04
HFD-613/L.Golson/ 7/15/04
HFD-600/M.Stevens-Riley/ M. Stevens-Riley 7/20/04
HFD-600/N.Sweeney/ N. Sweeney 7.20.04

CMC OK
RAS 7/21/04

Robert Rivest
7/22/2004

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F/T by rad7/12/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

TENTATIVE APPROVAL LETTERS

ANDA 76-087

JUL 17 2003

Bedford Laboratories
Attention: Molly Rapp
300 Northfield Rd.
Bedford, Ohio 44146

Dear Madam:

This is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluconazole Injection, 2 mg/mL, in 100 mL and 200 mL vials.

Reference is also made to your amendment dated 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. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore 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 is currently subject to a period of patent protection. Your application contains a Paragraph III Certification to each 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 this 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 period has expired, i.e., January 29, 2004.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment

should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

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.

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 "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to January 29, 2004, you should amend your application accordingly.

At the time you submit any amendments, you should contact Ted Palat, PharmD, Project Manager, at 301-827-5849, for further instructions.

Sincerely yours,

Gary Buehler 7/17/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/A.Langowski/
HFD-647/G.Smith/
HFD-617/T.Palat/
HFD-600/M.Stevens-Riley/
HFD-600/N.Sweeney/
HFD-613/C.Park/6/23/03
HFD-613/L.Golson/

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F/T by rad6/23/03

TENTATIVE APPROVAL

conc satisfactory

ANDA 76-087

APR 9 2004

Bedford Laboratories
Attention: Molly L Rapp
300 Northfield Road
Bedford, Ohio 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to our letter dated July 17, 2003, granting tentative approval to this application, and to your amendments dated December 22, 2003, and February 9, 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 determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Diflucan® (in 0.9% Sodium Chloride Injection) 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 also 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 determined that the information met the criteria stated in the statute and 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 this 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" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the 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. Should you elect to amend your application to provide for such changes prior to approval, we request that the changes be categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt.

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. 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 upon submitting an amendment to the application, please contact Ted Palat, PharmD, Project Manager, (301) 827-5849.

Sincerely yours,

Gary Buehler 4/9/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
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HFD-647/G.Smith/ 4/6/04
HFD-617/T.Palat/ 4/6/04
HFD-613/C.Park/ 4/7/04
HFD-613/L.Golson/ 4/7/04

20 CMC changes since TA dated 7/17/03

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F/T by rad4/2/04

Robert Radwat
4/9/2004

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

LABELING

BEDFORD LABORATORIES

FZC-P00

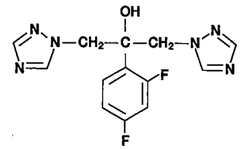
FLUCONAZOLE INJECTION

For Intravenous Infusion Only
Rx ONLY

DESCRIPTION

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

Fluconazole is designated chemically as 2,4-difluoro-α,α-bis(1*H*-1,2,4-triazol-1-ylmethyl) benzyl alcohol with a molecular formula of $C_{13}H_{12}F_2N_6O$ and molecular weight 306.27. The structural formula is:



APPROVED
JUL 29 2004

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

Fluconazole injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride. The pH ranges from 4.0 to 8.0 in the sodium chloride solution. Injection volumes of 100 mL and 200 mL are packaged in glass vials.

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid†	0.5 - 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 - 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-13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	—
9 Months-13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	—
5 - 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 - 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 - 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.

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 fluconazole (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 infection in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* 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 then 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 (2-3 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 patents.

	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

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

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

Coumarin-type anticoagulants: Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies.**)

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

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

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

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

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

Cisapride: There have been reports of cardiac events, including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. The combined use of fluconazole with cisapride is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interaction Studies.**)

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

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

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

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

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

Carcinogenesis, Mutagenesis, 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 7x 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 15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See **CLINICAL PHARMACOLOGY.**)

Pregnancy: Teratogenic Effects; Pregnancy Category C
Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20 to 60x the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20 to 60x 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 comparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of fluconazole for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days. (See **ADVERSE REACTIONS.**)

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

ADVERSE REACTIONS

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

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

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

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

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

Immunologic: In rare cases, anaphylaxis has been reported.

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

Central Nervous System: Seizures.

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

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

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

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

Percentage of Patients With Treatment-Related Side Effects

	Fluconazole (N=577)	Comparative Agents (N=451)
With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

OVERDOSAGE

There has been one reported case of overdosage with fluconazole. A 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hours.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

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

DOSAGE AND ADMINISTRATION

Dosage and Administration in Adults:
SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis 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 candidema, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration 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 in patients undergoing bone marrow transplantation is 400 mg, once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per cu mm.

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

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12*mg/kg	400 mg

*Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

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

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

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

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

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

Dosage In Patients With Impaired Renal Function:
Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

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

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

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

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

Females: 0.85 x above value

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

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

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

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

Fluconazole injection in glass container is intended only for intravenous administration using sterile equipment.

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

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

HOW SUPPLIED

Fluconazole Injection, for intravenous infusion administration is formulated as a sterile iso-osmotic solution containing 2 mg/mL of fluconazole. It is supplied in glass vials, each containing 200 mg and 400 mg of fluconazole in 100 mL and 200 mL of sodium chloride solution, respectively.

NDC 55390-012-01, 200 mg/100 mL; individually boxed.
NDC 55390-046-01, 400 mg/200 mL; individually boxed.

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

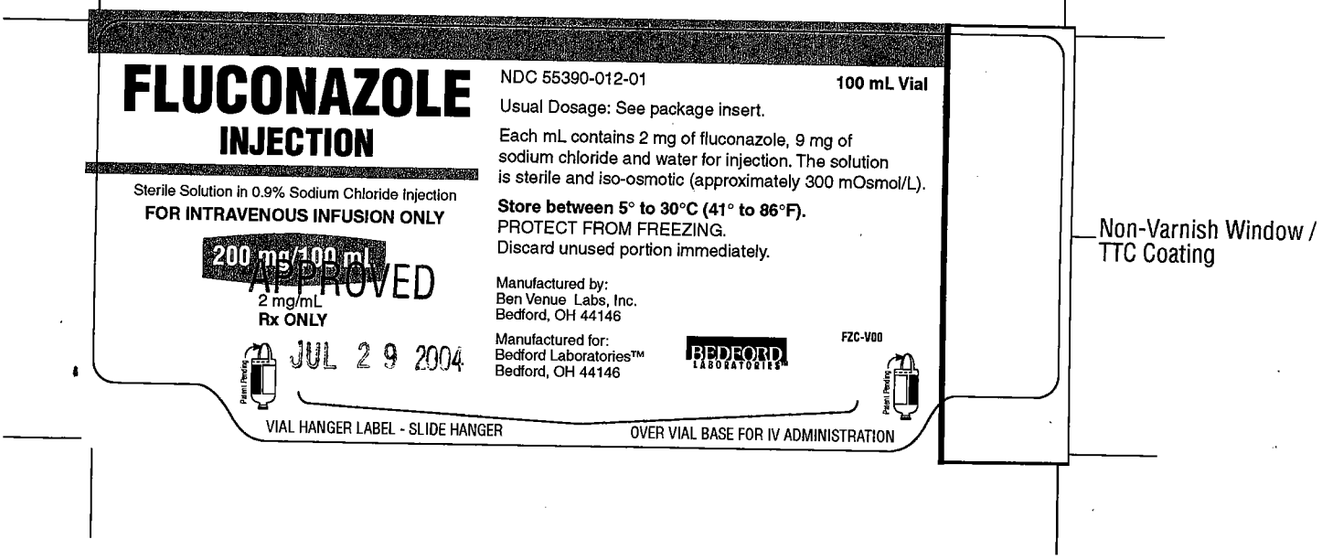
Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

January 2004

FZC-P00

Note: Keyline does not print.



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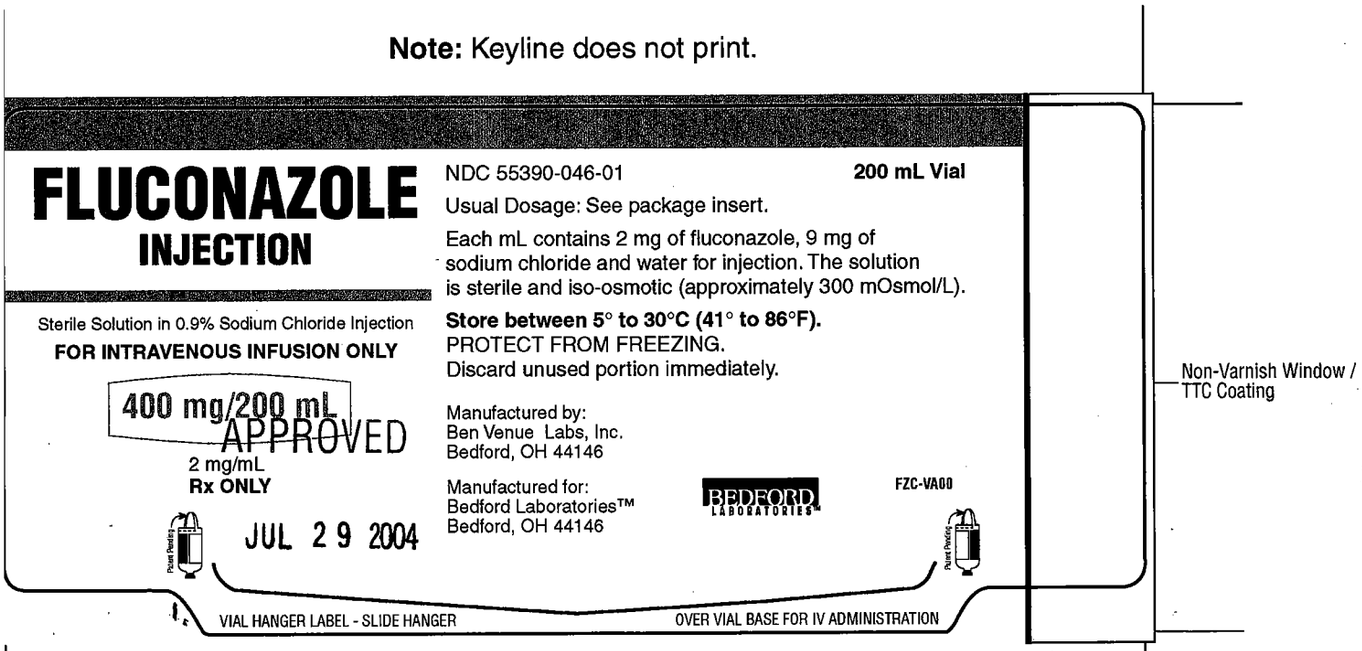

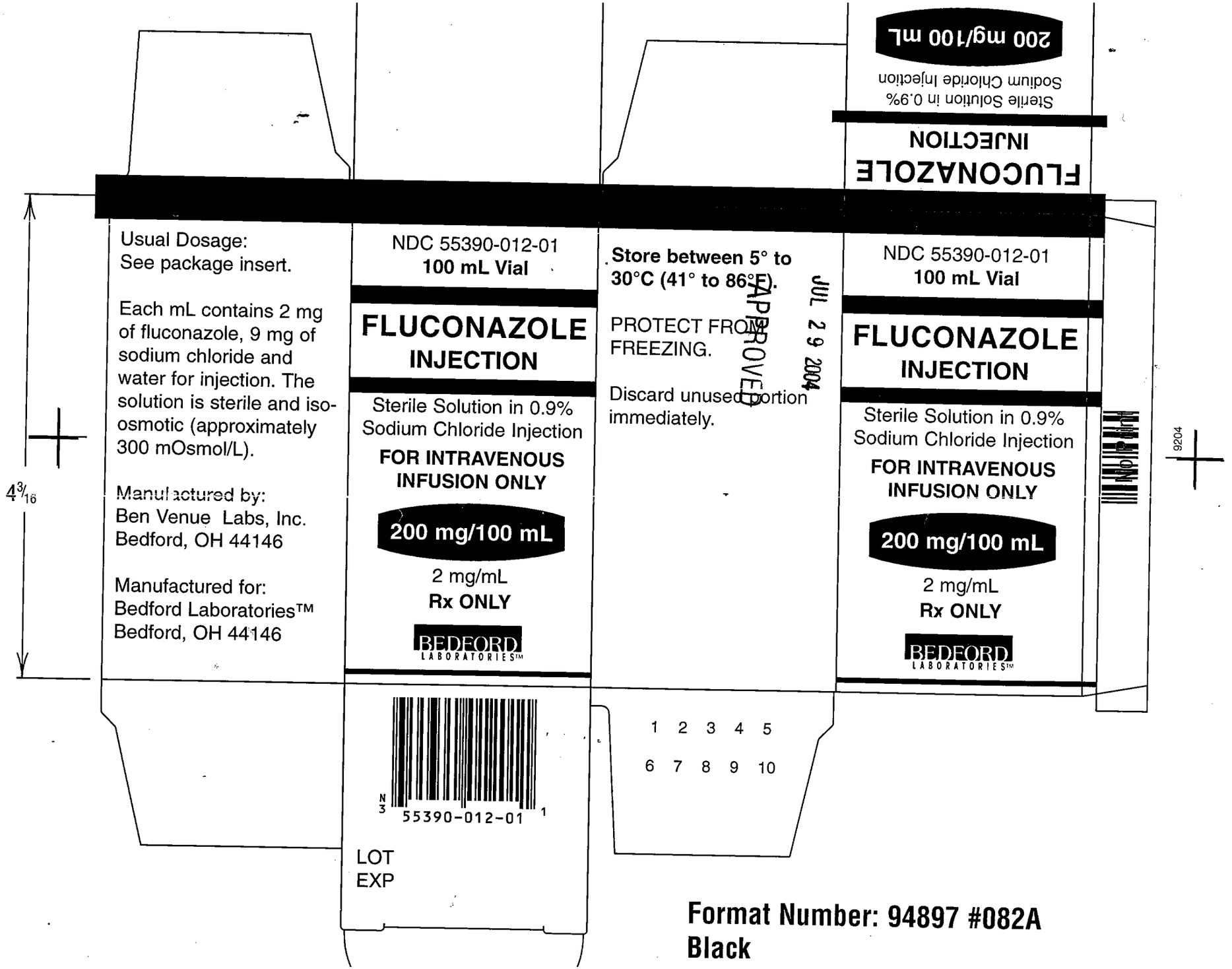

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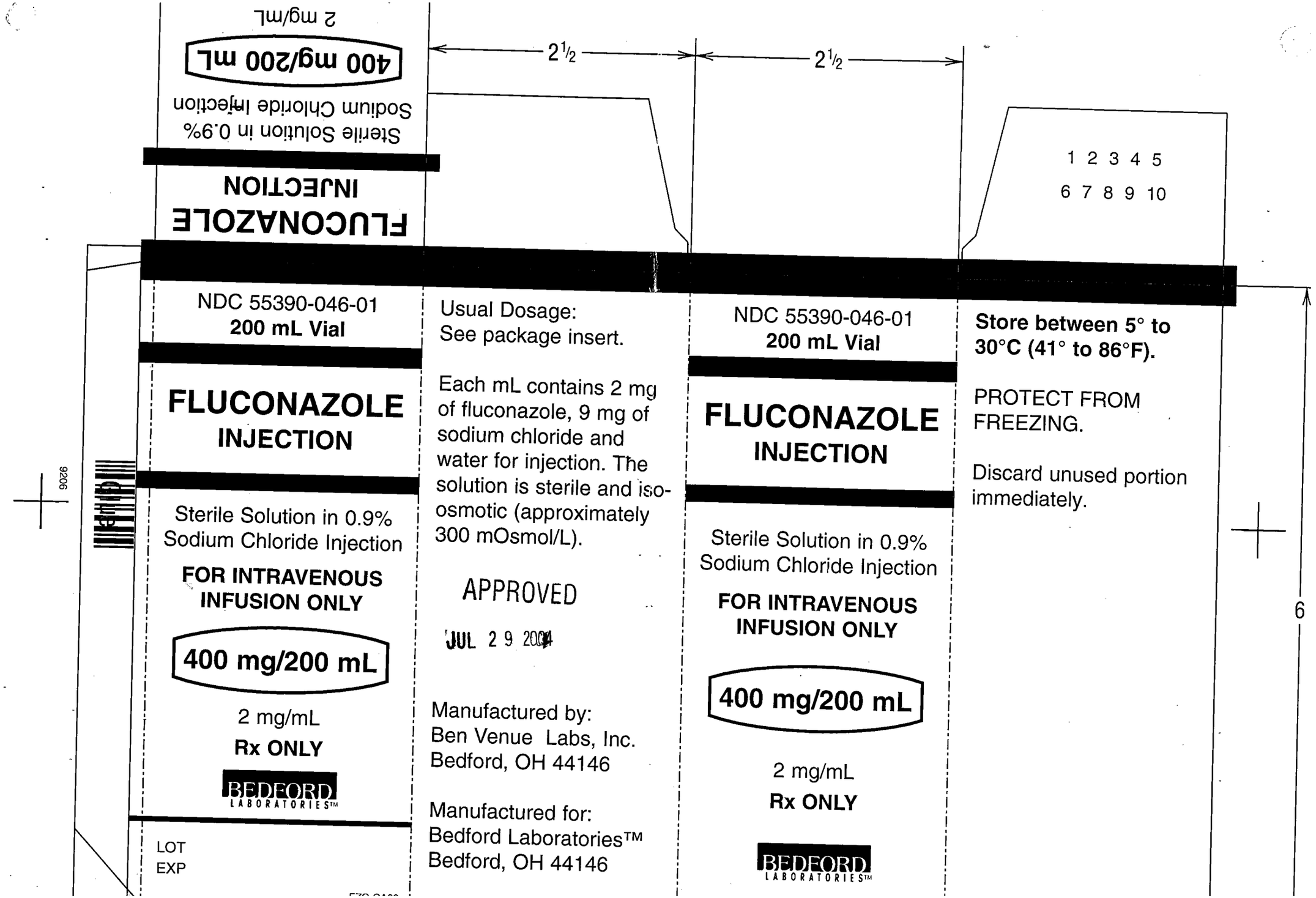

2 mg/mL
400 mg/200 mL
Sterile Solution in 0.9%
Sodium Chloride Injection
FLUCONAZOLE
INJECTION
2½
2½
1 2 3 4 5
6 7 8 9 10
NDC 55390-046-01
200 mL Vial
FLUCONAZOLE
INJECTION
Sterile Solution in 0.9%
Sodium Chloride Injection
FOR INTRAVENOUS
INFUSION ONLY
400 mg/200 mL
2 mg/mL
Rx ONLY
BEDFORD
LABORATORIES™
LOT
EXP
Usual Dosage:
See package insert.
Each mL contains 2 mg of fluconazole, 9 mg of sodium chloride and water for injection. The solution is sterile and iso-osmotic (approximately 300 mOsmol/L).
APPROVED
JUL 2 9 2004
Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146
Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
NDC 55390-046-01
200 mL Vial
FLUCONAZOLE
INJECTION
Sterile Solution in 0.9%
Sodium Chloride Injection
FOR INTRAVENOUS
INFUSION ONLY
400 mg/200 mL
2 mg/mL
Rx ONLY
BEDFORD
LABORATORIES™
Store between 5° to 30°C (41° to 86°F).
PROTECT FROM FREEZING.
Discard unused portion immediately.
9206
6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

LABELING REVIEWS

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

ANDA Number: 76-087 Date of Submission: December 21, 2000

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection

Labeling Deficiencies:

1. CONTAINER - 200 mg/100 mL

   The pictorial illustration on the hanging strip indicates that you will affix your label up side down. Please be advised that the statement of identity shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed. We ask that you affix your label parallel to the orientation of your bottle and make revisions accordingly in terms of the location of the hanging strip. Please ensure that when the vial is hung, the calibration reflects actual volume of the solution remaining in the container.

2. INSERT

   a. DESCRIPTION – Last paragraph, first sentence:

      ... solution of fluconazole in a sodium chloride diluent.

   b. PRECAUTIONS (Pediatric Use) – Penultimate paragraph:

      ...for 1 to 1,616 days.... ["1,616" rather than "1.616"]

   c. ADVERSE REACTIONS (In Patients Multiple... Candidiasis, Hepatobiliary) – Second paragraph, first sentence:

      ...levels from a baseline value of 30 IU/L to ... [add "value"]

   d. DOSAGE AND ADMINISTRATION

      i. Dosage and Administration in Adults – Multiple Dose:

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

         B) Add the following text as the first sentence of the first paragraph.

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

         C) Esophageal candidiasis – Last sentence:

            ...minimum of three weeks and for at least...

ii. Dosage in Patients With Impaired Renal Function – First paragraph:

Delete the second sentence "[redacted]".

iii. Administration

A) First sentence – Revise to read:

Fluconazole injection is administered by intravenous infusion.

B) Add the following as the second paragraph.

Fluconazole injection in glass container is intended only for intravenous administration using sterile equipment.

e. HOW SUPPLIED – Second sentence:

..glass vials, each containing 200 mg of fluconazole in 100 mL of sodium chloride solution.

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

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 ANDA appears to be the **FRIST GENERIC**.

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 082 (Volume B.1.1).

5. Patent Data

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

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

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers
Seal: Flip-off Aluminum Seals [p.539, B.1.2)

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. **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." In addition, 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 ask the generic sponsors to remove 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 per Charlie's advice.

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 (20-090). 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

Here are the answers from Don Hare and Yana Mille.

1. From Don Hare

I defer to more knowledgeable people on the Fluconazole Injection establish name issue but would like to explain how the listings in the Orange Book are determined. A drug product displayed in the Orange Book has a number of fields, among those are an active ingredient, dosage form, route of administration and trade name fields. We did not have an established name field per se. The example that you cited, Cimetidine in Sodium Chloride Injection is listed in the Orange Book as Cimetidine Hydrochloride - Active Ingredient

Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

As you can see we do not include the diluent in the Active ingredient field but it is part of the trade name.

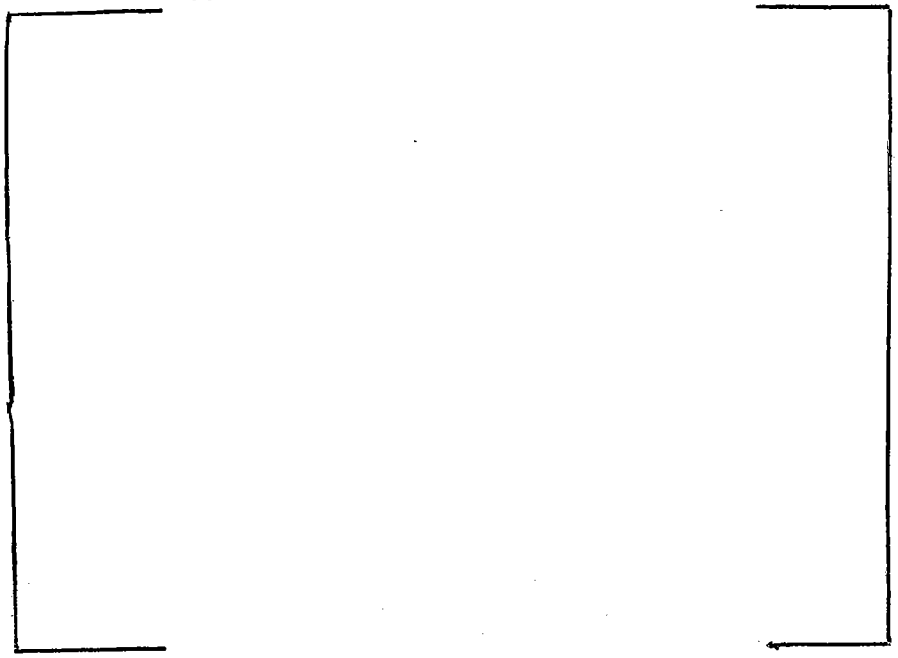
For the active ingredient name we use a hierarchy of (1) USP monograph, USAN, and lastly the active ingredient name in the labeling if not an official article or name.

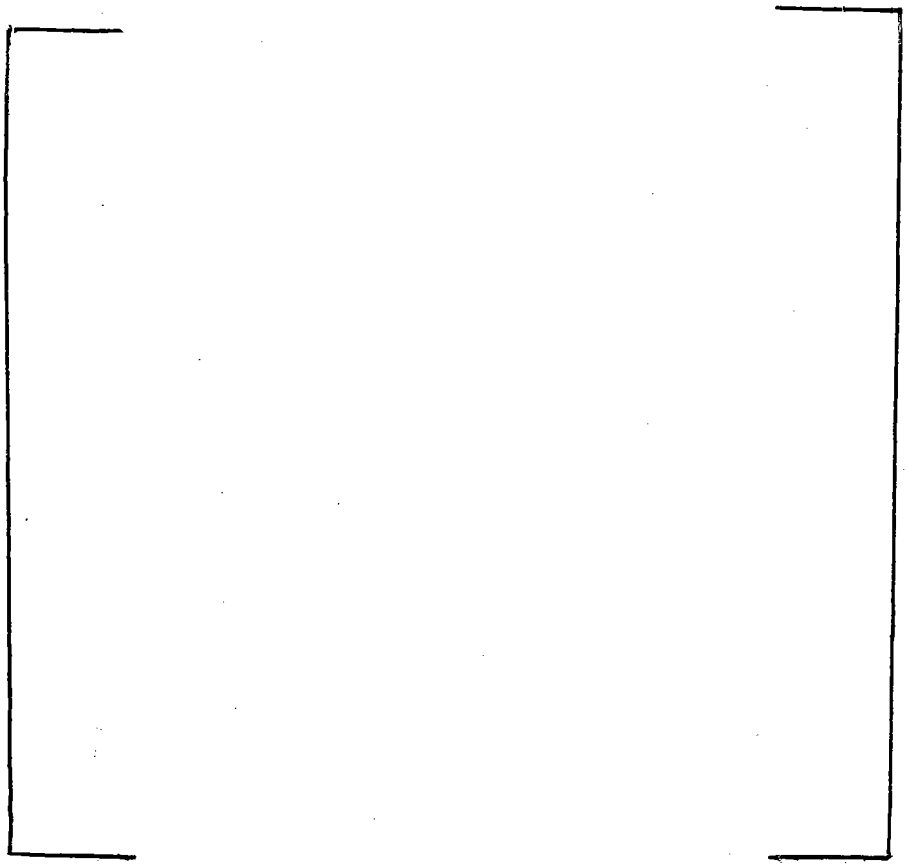
Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

2. From Yana Mille

Thanks for a copy of the labeling. Based on what I see I am now





Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question.

Date of Review: 2/6/01 **Date of Submission: 12/21/00**

Primary Reviewer: Chan Park **Date:** 2/16/01

Team Leader: **Date:** 2/20/01

cc:

ANDA: 76-087
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\76087na1.LABELING Review

Maika Steiner-Riley A 2.1

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

ANDA Number: 76-087 Date of Submission: November 7, 2001

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole 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

CONTAINER LABELS - 200 mg/100 mL

Satisfactory in drat as of 11/7/01 submission

CARTON LABELING:

Satisfactory in draft as of 12/1/00 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of 11/7/01 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 11/26/01)

The firm claims that they will use silk-screened containers with pre-marked with calibration marks. Is this an accurate statement? I do not see the calibration marks in the sponsor's drawing of the proposed container.

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 ANDA appears to be the **FRIST GENERIC**.

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 082 (Volume B.1.1).

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

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

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers
Seal: Flip-off Aluminum Seals [p.539, B.1.2)

The firm claims that they will use silk-screened containers with pre-marked with calibration marks. We will have the chemist confirm this statement.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. **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." In addition, 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 ask the generic sponsors to remove 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 per Charlie's advice.

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 (20-090). 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

Here are the answers from Don Hare and Yana Mille.

1. From Don Hare

I defer to more knowledgeable people on the Fluconazole Injection establish name issue but would like to explain how the listings in the Orange Book are determined. A drug product displayed in the Orange Book has a number of fields, among those are an active ingredient, dosage form, route of administration and trade name fields. We did not have an established name field per se. The example that you cited, Cimetidine in Sodium Chloride Injection is listed in the Orange Book as Cimetidine Hydrochloride - Active Ingredient

Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

As you can see we do not include the diluent in the Active ingredient field but it is part of the trade name.

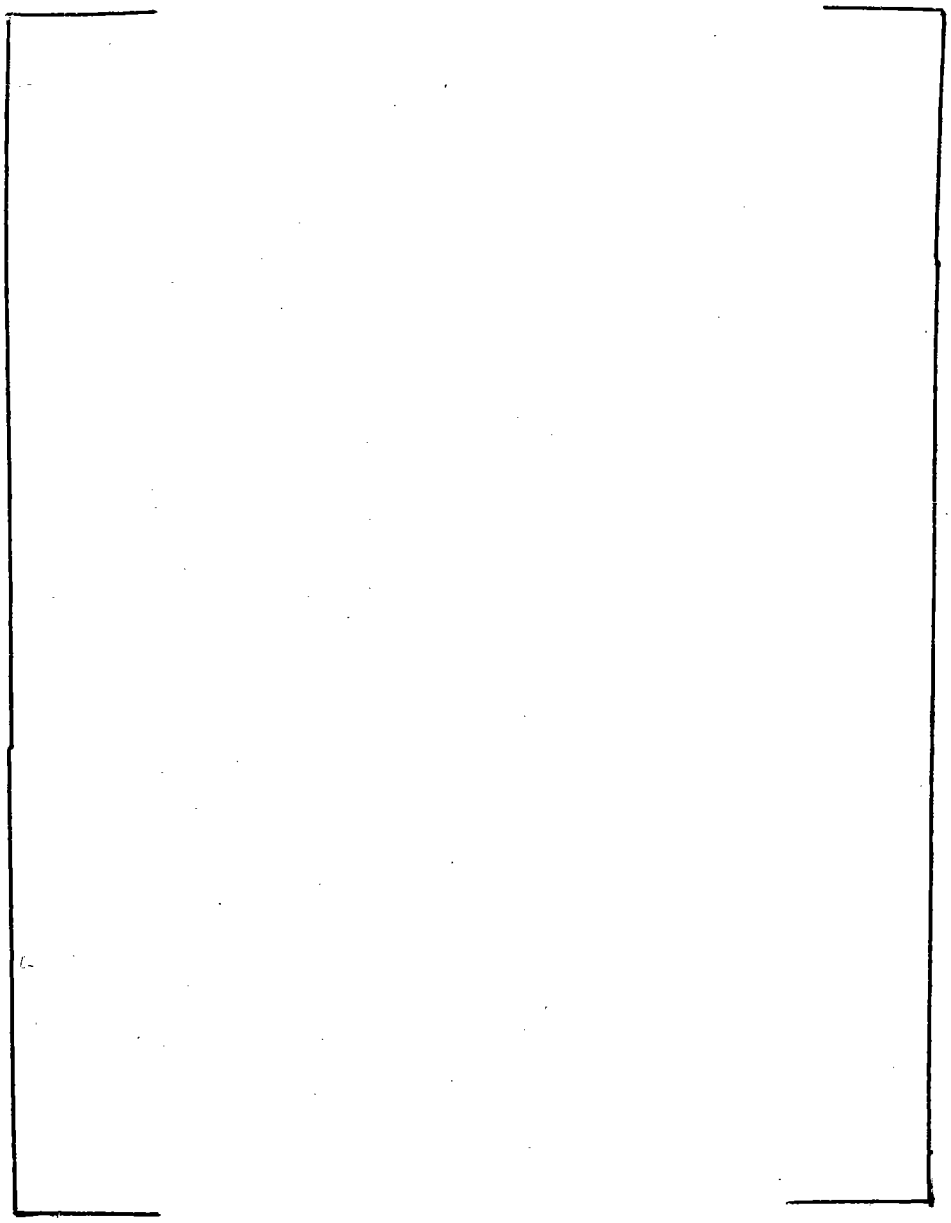
For the active ingredient name we use a hierarchy of (1) USP monograph, USAN, and lastly the active ingredient name in the labeling if not an official article or name.

Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

2. From Yana Mille

Thanks for a copy of the labeling. Based on what I see I am now



Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question. In the mean time, the storage temperature statement on the sponsor's labeling is identical to the one found on the innovator's labeling. We have not received any response from the new drug division or Glen Smith as of today. As indicated in Yana's e-mail, we may wait for the publication of guidance before we address this issue.

Date of Review: 11/16/01 **Date of Submission: 11/7/01**

Primary Reviewer: Chan Park C Park **Date:** 12/10/01

Team Leader: Date:

Linda Ogs 12/11/01

This TAP2 summary supersedes the TAP summary prepared 11/16/01.

(TENTATIVE APPROVAL SUMMARY)

REVIEW OF PROFESSIONAL LABELING

DIVISION OF LABELING AND PROGRAM SUPPORT

LABELING REVIEW BRANCH

ANDA Number: 76-087 Date of Submission: June 20, 2002

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection, 2 mg/mL

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

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in draft as of 11/7/01 (100 mL) and 6/20/02 (200 mL) submission

CARTON LABELING:

Satisfactory in draft as of 12/1/00 (100 mL) and 6/20/02 (200 mL) submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of 11/7/01 (100 mL) and 6/20/02 (200 mL) submission

POST-APPROVAL REVISIONS

1. CONTAINER

   Increase the prominence of the expression of the unit strength (2 mg/mL).

2. INSERT

   a. Two separate insert labeling can be collapsed into one insert for both package sizes. We will inform this to the sponsor so that they may submit a revised insert labeling in FPL.

   b. 200 mL labeling:

      CLINICAL PHARMACOLOGY (Pharmacokinetics in Children) - Table:

      Include the N numbers in the last row, 3rd, 5th and last columns.

   The above comments have been forwarded to Molly Rapp of the firm on October 10, 2002 via a tele-conference.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950
NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 10/9/02)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. Is this an accurate statement? The firm adopted this method rather than having calibration on the container labels. However, I do not see the calibration marks in the sponsor's drawing of the proposed container.
Thanks, Chan

Answer: Yes its true! They are silk screening the volumetric calibration marks. You do not see it on the drawing because only physical engineering specifications are provided. The firm has been asked to provide validation data verifying the accuracy of the calibration marks. However, probably not that critical since this is an anti-fungal as opposed to a narcotic analgesic. Andrew (10/10/02)

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-034 approved 8/7/02 is specifically related to the approval of PPI for the 150 mg tablets.

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

3. This ANDA appears to be the **FRIST GENERIC**.

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 082 (Volume B.1.1).

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.

440,4216 - 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol and its pharmaceutically acceptable acid addition salts are disclosed. This particular bis-triazole derivative and its aforesaid salts are useful for treating fungal infections in animals, including humans. Methods for preparing these compounds from known starting materials are provided.

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

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 400 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL and 400 mg/200 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers (100 mL) & ——Stoppers (200 mL)
Seal: Flip-off Aluminum Seals [p.539, B.1.2 & p.513, B.3.2)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. See comment to/from the chemist above.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. 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." In addition, 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 ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"

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Here are the answers from Don Hare and Yana Mille.

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Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

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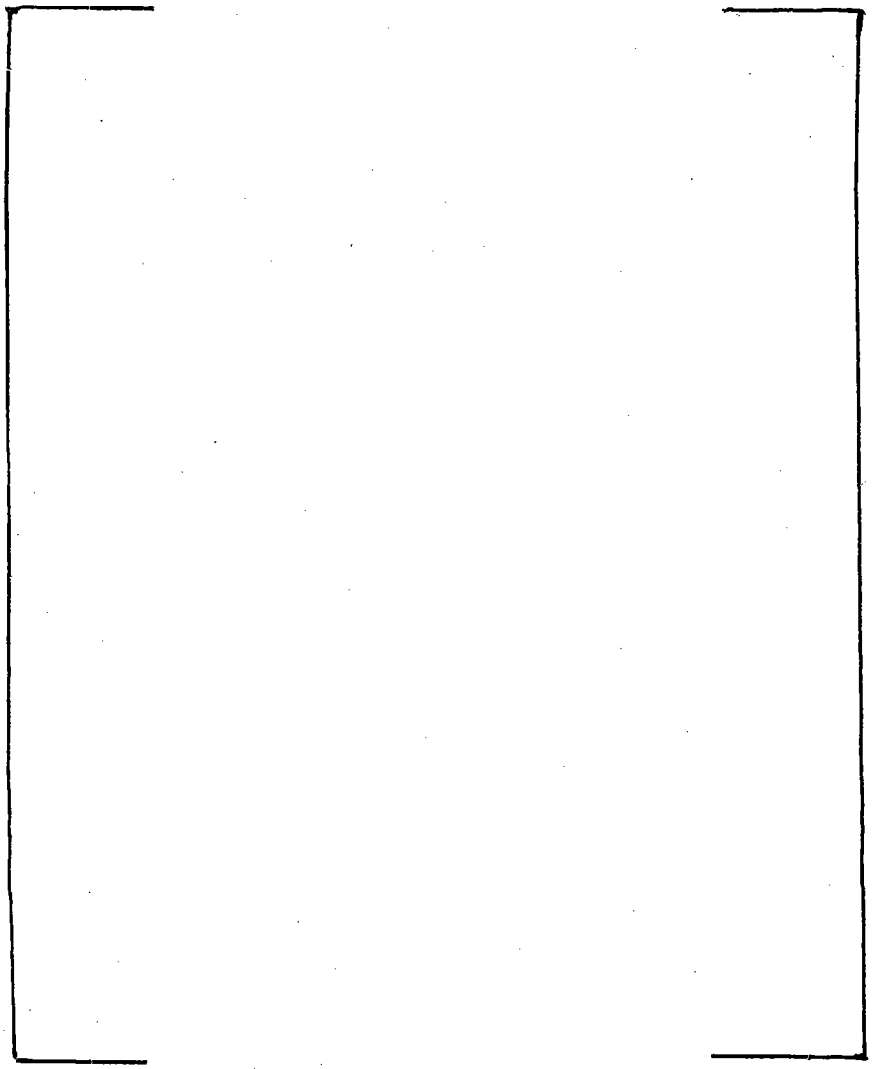
Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

2. From Yana Mille

Thanks for a copy of the labeling. Based on what I see I am now



Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question. In the mean time, the storage temperature statement on the sponsor's labeling is identical to the one found on the innovator's labeling. We have not received any response from the new drug division or Glen Smith as of today. As indicated in Yana's e-mail, we may wait for the publication of guidance before we address this issue.

13. The sponsor has filed another application for the same product, but for a different package size (200 mL) on June 20, 2002. However, the sponsor withdrew this application and made this as an amendment to ANDA 76-087 (originally filed for 100 mL) per Agency's recommendation. The sponsor markets both 100 mL and 200 mL package size.

Date of Review: 10/9/02 **Date of Submission: 6/20/02**

Primary Reviewer: Chan Park C Park **Date:** 10/15/02

Team Leader: J W Golson **Date:** 10/17/02

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cc:

ANDA: 76-087
DUP/DIVISION FILE
HFD-613/Cpark/LGolson (no cc)
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Review

(This TAP3 Summary supersedes the TAP2 summary prepared on 10/9/02)

(TENTATIVE APPROVAL SUMMARY)

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

ANDA Number: 76-087 Date of Submission: December 22, 2003

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection, 2 mg/mL

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 12/22/03 submission (A.4.1)

CARTON LABELING - 1 Vial x 100 mL & 1 Vial x 200 mL

Satisfactory in FPL as of 12/22/03 submission (A.4.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 12/22/03 submission (A.4.1, Rev. Jan, 04, Code # - FZC-P00)

POST-APPROVAL REVISIONS - CONTAINER:

Increase the prominence of the expression of the unit strength (2 mg/mL).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

3. The sponsor collapsed 2 separate package insert labeling (*i.e.,* one for the 100 mL & another one for 200 mL) into one as recommended by the Agency.

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 10/9/02)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. Is this an accurate statement? The firm adopted this method rather than having calibration on the container labels. However, I do not see the calibration marks in the sponsor's drawing of the proposed container.

Thanks, Chan

Answer: Yes it's true! They are silk screening the volumetric calibration marks. You do not see it on the drawing because only physical engineering specifications are provided. The firm has been asked to provide validation data verifying the accuracy of the calibration marks. However, probably not that critical since this is an anti-fungal as opposed to a narcotic analgesic. Andrew (10/10/02)

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-034 approved 8/7/02 is specifically related to the approval of PPI for the 150 mg tablets.

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

3. This ANDA appears to be the **FIRST GENERIC**.

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 082 (Volume B.1.1).

5. **Patent Data**

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

Exclusivity Data

There is no unexpired exclusivity for this product.

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

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 400 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL and 400 mg/200 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers (100 mL) & ——— Stoppers (200 mL)
Seal: Flip-off Aluminum Seals [p.539, B.1.2 & p.513, B.3.2)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. This is accurate. See comment to/from the chemist above.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. 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." In addition, 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 ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"

11. The sponsor has filed another application for the same product, but for a different package size (200 mL) on June 20, 2002. However, the sponsor withdrew this application and made this as an amendment to ANDA 76-087 (originally filed for 100 mL) per Agency's recommendation. The sponsor markets both 100 mL and 200 mL package size.

Date of Review: 1/29/04 **Date of Submission: 12/22/03**

Primary Reviewer: Chan Park C Park **Date:** 2/4/04

Team Leader: [signature] **Date:** 2/4/04

---

cc:

ANDA: 76-087
DUP/DIVISION FILE
HFD-613/Cpark/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\76087AP.LABELING.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-087

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
300 Northfield Road
Bedford Ohio 44146

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 12/21/00
Amendment 3/21/01

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

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

17. COMMENTS
First Generic. Non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
04/06/01

Redacted 11 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 76-087
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/ALangowski/04/06/01 6/21/01
HFD-647/GSmith/6/6/01 6/22/01
HFD-617/JMin/6/14/01 B. McReel for J.M. 6/22/01

F/T by: DJ 6/21/01

V:\FIRMSAM\Bedford\LTRS&REV\76087C01.RNA

TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-087

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly Rapp
300 Northfield Road
Bedford Ohio 44146
Tel: 440-201-3576
Fax: 440-232-2772

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 12/21/00
Amendment 3/21/01
Amendment 11/07/01

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL

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

17. COMMENTS
First Generic. Non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable; Minor.

19. REVIEWER: A.Langowski

DATE COMPLETED: 01/07/02

APPEARS THIS WAY
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

3. Please provide data verifying the accuracy of the volumetric calibration marks indicated on the vial.

Sincerely yours,

2/22/02

for 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 76-087
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/ALangowski/01/07/02 2/29/02
HFD-647/GSmith/2/1/02 2/20/02
HFD-617/JMin/2/15/02

F/T by: rad2/19/02

V:\FIRMSAM\Bedford\LTRS&REV\76087C02

TYPE OF LETTER: NOT APPROVABLE (MINOR)

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 76-087

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146
Tel: 440-201-3576
Fax: 440-232-2772

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 12/21/00
Amendment 03/21/01
Amendment 11/07/01
Micro Amendment 11/07/01
June 20, 2002 (New strength;2mg/200mL)
(originally submitted as new ANDA)
Amendment July 19, 2002 (response to 3/4/02 NA LTR)
August 26, 2002 (Collapse June submission into 76-087)

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL; 100 and 200 mL vials

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

17. COMMENTS
First Generic. Non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MINOR)

19. REVIEWER: A.Langowski

DATE COMPLETED: 11/12/02

APPEARS THIS WAY
ON ORIGINAL

Redacted 13 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 76-087
DIV FILE
Field Copy

Endorsements:

HFD-647/ALangowski/11/12/02 A. Langowski 1/16/03

HFD-647/GSmith/1/10/03 1/16/03

HFD-617/JMin/1/16/03 1/16/03

F/T by: jsm/1/16/03

V:\FIRMSAM\BEDFORD\LTRS&REV\76087C03..doc

TYPE OF LETTER: Not Approvable (MINOR)

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-087

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146
Tel: 440-201-3576
Fax: 440-232-2772

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Diflucan® manufactured by Pfizer. Patent 4404216 expires on January 29, 2004. There are 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 12/21/00
Amendment 03/21/01
Amendment 11/07/01
Micro Amendment 11/07/01
June 20, 2002 (New strength;2mg/200mL)
(originally submitted as new ANDA)
Amendment July 19, 2002 (response to 3/4/02 NA LTR)
August 26, 2002 (Collapse June submission into 76-087)
Amendment 01/21/03

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL; 100 and 200 mL vials

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

17. COMMENTS
Non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS
Approve.

19. REVIEWER: A.Langowski

DATE COMPLETED: June 03, 2003

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #4

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes _____

No ____x____

If no, explain reason(s) below:

Document room mistakenly codified the minor amendment as a major amendment resulting in a delay of the review process.

SPOT? Yes _____ No ___x_____

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA #XX-XXX REVIEW # 4**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	1	Adequate	12/11/02

Comments: Adequate

[redacted] III/[redacted] 4

Comments:

[redacted] III/[redacted] 4

Comments:

Comments:

Comments:

Comments:

APPEARS THIS WAY ON ORIGINAL

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 76-087
DIV FILE
Field Copy

Endorsements:

HFD-647/ALangowski/06/03/03 A. Langowski 6/23/03

HFD-647/GSmith/6/12/03 6/24/03

HFD-617/TPalat/6/20/03 6/24/03

F/T by: rad6/23/03

V:\FIRMSAM\BEDFORD\LTRS&REV\76087R04.AP

TYPE OF LETTER: Approval

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 76-087

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146
Tel: 440-201-3576
Fax: 440-232-2772

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Diflucan® manufactured by Pfizer. Patent 4404216 expires on January 29, 2004. RLD obtained pediatric exclusivity extending to 07/29/04.

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	12/21/00
Amendment	03/21/01
Amendment	11/07/01
Micro Amendment	11/07/01

June 20, 2002 (New strength;2mg/200mL)
(originally submitted as new ANDA)
Amendment July 19, 2002 (response to 3/4/02 NA LTR)
August 26, 2002 (Collapse June submission into 76-087)

Amendment	01/21/03	
TA	07/17/03	
Amendment	12/22/03	(Final approval requested)
Amendment	02/09/04	(Revised Patent Exclusivity)

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection (I.V.)

14. POTENCIES
2 mg/mL; 100 and 200 mL vials

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

17. COMMENTS
Non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS
Approve.

19. REVIEWER: A.Langowski

DATE COMPLETED: March 3, 2004

Addendum 03/03/04

The firm submitted an amendment dated 12/22/03 (60 day) prior to patent expiration and stated that there have been no CMC or labeling changes. The RLD has since received pediatric exclusivity extending to July 29, 2004. The ANDA sponsor amended this application 2/9/04 with a revised patent exclusivity statement.

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-087
Division File
Field Copy

Endorsement:
HFD-647/ALangowski/ A.J. Langowski 4/3/04
HFD-647/GSmith/3/12/04 4/6/04
HFD-617/TPalat/3/23/04 4/6/04

F/t by rad4/2/04
V:\Firmsam\Bedford\Ltrs&Rev\76087R5.AP

APPEARS THIS WAY
ON ORIGINAL

Full Approval Assessment

1. ANDA # 76-087

2. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly Rapp
300 Northfield Rd
Bedford, Ohio 44146

3. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan® Injection, 2mg/mL, (in Sodium Chloride 0.9% Injection) manufactured by Pfizer, Inc. 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	12/21/00
Tentatively Approved	04/09/04
Amendment	05/11/04

7. PHARMACOLOGICAL CATEGORY
Anti-fungal

8. Rx or OTC
Rx

9. RELATED DMF(s)

10. Samples and Results
N/A

11. LABELING STATUS - Acceptable 02/04/04

12. BIOEQUIVALENCY STATUS - Acceptable 10/15/02

13. MICROBIOLOGY STATUS - Acceptable 10/07/02

14. ESTABLISHMENT INSPECTION - Acceptable 07/11/03

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 05/11/04.

Recommend Approval.

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

cc: ANDA 76-087
Division File
Field Copy

Endorsements:

HFD-617\T.Palat\07/02/04 7/16/04
HFD-647\G.Smith\ 7/12/04

cmc OK RA 7/21/04

f/t by:

V:\FIRMSAM\BEDFORD\LTRS&REV\76087.Admin.AP.doc

Approval

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

BIOEQUIVALENCE REVIEW(S)

Fluconazole Injection
2 mg/ml; 100 ml per vial
ANDA #76-087
Reviewer: J. Lee
76087W.D00

Bedford Laboratories
Bedford, Ohio
Submission date:
December 21, 2000

Review of a Request for Waiver

The sponsor is submitting an application for fluconazole injection 2 mg/ml and is requesting a waiver of an in-vivo study. The sponsor claims that the drug product is intended for parenteral administration (IV infusion only) and is identical in formulation to the listed drug (Diflucan®).

Fluconazole is the first of a new subclass of synthetic triazole antifungal agents.

Presented below is a formulation comparison between the test/reference products:

	Bedford per ml	Diflucan® per ml
Fluconazole	2 mg	2 mg
NaCl	9 mg	9 mg
Water for Injection	q.s.	q.s.

Recommendation:

1. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that fluconazole 2 mg/ml injection 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. Bedford's test product is deemed bioequivalent to Diflucan® in sodium chloride 0.9% manufactured by Pfizer Inc.

R. Lee 3/2/01

J. Lee
Division of Bioequivalence
Review Branch II

for RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 3/2/01

Concur: Dale P. Conner Date: 3/8/01

Dale Conner, Pharm. D.

Director, Division of Bioequivalence

JLee/jl/03-02-01

cc: NDA #76-087 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-087
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\FIRMSam\Bedford\ltrs&rev\76087W.D00
Printed in final on 03/02/01

Endorsements: (Final with Dates)
HFD-655/ JLee E.J. 3/2/01
HFD-655/ Bio team Leader 3/2/01
HFD-650/ D. Conner 3/8/01

BIOEQUIVALENCY - ACCEPTABLE submission date: Dec 21, 2000

6. **WAIVER** (WAI) Strengths: 2 mg/ml
Outcome: AC

Outcome Decisions: **AC** - Acceptable

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-087 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fluconazole Injection 2 mg/ml; 100 ml per vial

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

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

Sincerely yours,

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-087 SPONSOR : Bedford Laboratories

DRUG AND DOSAGE FORM : Fluconazole injection

STRENGTH(S) : 2mg/ml; 100ml per vial

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

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

~~DISSOLUTION~~ : N/A

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 : R.S. DATE : 3/2/01

TEAM LEADER : SG Nerurkar BRANCH : II

INITIAL : [signature] DATE : 3/2/01

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

INITIAL : DPC DATE : 3/8/01

OCT 7 2002

Fluconazole Injection
2 mg/ml; 200 ml per vial
ANDA #76-087
Reviewer: J. Lee
76087W602.doc

Bedford Laboratories
Bedford, Ohio
Submission date:
June 20, 2002

Review of a Request for Waiver

The sponsor is amending their application for fluconazole injection 2 mg/ml to include an additional strength, a 2 mg/ml injection with 200 ml per vial. The sponsor has already received a waiver for a 2 mg/ml injection with 100 ml per vial [rev 8 Mar 01; JLee]. They are requesting waiver of an in-vivo study. The sponsor claims that the drug product is intended for parenteral administration (IV infusion only) and is identical in formulation to the listed drug (Diflucan®).

Fluconazole is the first of a new subclass of synthetic triazole antifungal agents.

A formulation comparison between the test/reference products is presented below:

	Bedford per ml	Diflucan® per ml
Fluconazole	2 mg	2 mg
NaCl	9 mg	9 mg
Water for Injection	q.s.	q.s.

Recommendation:

1. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that fluconazole 2 mg/ml injection; 200 ml per vial 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. Bedford's test product is deemed bioequivalent to Diflucan® in sodium chloride 0.9%; 200 ml per vial, manufactured by Pfizer Inc.

R. Lee 9/16/02

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR _____ 9/18/2002

Concur: _____ Date: 10/7/02

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

JLee/jl/09-16-02

cc: NDA #76-087 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-087
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\FIRMSam\Bedford\ltrs&rev\76087W602.doc
Printed in final on / /

9/18/02

Endorsements: (Final with Dates)
HFD-655/ JLee C.S. 9/16/02
HFD-655/ Bio team Leader
HFD-650/ D. Conner 10/7/02

BIOEQUIVALENCY - ACCEPTABLE

submission date: 20 June 02

6. **WAIVER** (WAI)

Strengths: 2 mg/ml; 200 ml per vial
Outcome: AC

Outcome Decisions: **AC** - Acceptable

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-087 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fluconazole Injection 2 mg/ml; 200 ml per vial

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

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

Sincerely yours,

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

(9)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-087 SPONSOR: Bedford Laboratories

DRUG AND DOSAGE FORM: Fluconazole injection

STRENGTH(S): 2mg/ml ; 200ml per vial

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: N/A

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-S DATE: 16 Sept 02

TEAM LEADER: SG Nerurkar BRANCH: II

INITIAL: [signature] DATE: 9/18/2002

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

INITIAL: [signature] DATE: 10/7/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-640

Microbiology Review #1

July 31, 2001

A. 1. **ANDA:** 76-087

APPLICANT: Bedford Laboratories
300 Northfield Rd.
Bedford, Ohio 44146

2. PRODUCT NAME: Fluconazole Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Fluconazole Injection is a sterile, aqueous solution that is packaged into 100 mL vials (3 mL fill) at a concentration of 2 mg/mL and administered by intravenous infusion.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Anti-fungal

B. 1. DATE OF INITIAL SUBMISSION: December 21, 2000
Subject of this Review (Received December 26, 2000)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS:
DMF [redacted]
DMF
DMF

4. ASSIGNED FOR REVIEW: July 20, 2001

C. REMARKS: Fluconazole Injection, 2 mg/mL is manufactured for Bedford Laboratories by Ben Venue Laboratories Inc. in Bedford, Ohio. The subject drug product is [redacted]

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

Marla Stevens-Riley 8/8/01
Marla Stevens-Riley, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by M. Stevens-Riley, HFD 600 v:microrev\76-087
Initialed by M. Fanning/A. High

8/9/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 13 page(s)

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confidential commercial

information from

MICROBIOLOGY REVIEW #1

Please clearly identify your amendment to this facsimile as RESPONSE TO MICROBIOLOGY DEFICIENCIES . The RESPONSE TO MICROBIOLOGY DEFICIENCIES should also be noted in your cover page/letter.

Sincerely yours,

Mary Hanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Product Quality Microbiology Review

January 16, 2002

ANDA: 76-087

Name of Drug: Fluconazole Injection

Review Number: 2

Submission Date: November 7, 2001

Applicant: Bedford Laboratories

Name of Reviewer: Marla Stevens-Riley

APPEARS THIS WAY
ON ORIGINAL

Product Quality Microbiology Data Sheet

A. 1. **ANDA:** 76-087

2. **REVIEW NUMBER:** 2

3. **REVIEW DATE:** January 16, 2002

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

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

6. **APPLICANT/SPONSOR:**

Name: Bedford Laboratories
300 Northfield Rd.
Bedford, Ohio 44146

Representative: Molly Rapp
Telephone: 440-201-3576

7. **MANUFACTURING SITE:** Ben Venue Laboratories of Bedford, Ohio

8. **DRUG PRODUCT NAME:**
Proprietary: None
Non-proprietary: Fluconazole Injection
Drug Priority Classification: N/A

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Fluconazole Injection is a sterile, aqueous solution that is packaged into 100 mL vials (3 mL fill) at a concentration of 2 mg/mL and is administered by intravenous infusion.

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

11. **PHARMACOLOGICAL CATEGORY:** Anti-fungal

B. 1. **DOCUMENT/LETTER DATE:** December 26, 2000
2. **RECEIPT DATE:** N/A
3. **CONSULT DATE:**N/A
4. **DATE OF AMENDMENTS:** November 7, 2001
(Subject of this review, November 8, 2001)
5. **ASSIGNED FOR REVIEW:** November 16, 2001
6. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** The subject amendment provides for the response to the Microbiological Deficiencies dated August 22, 2001. The applicant also provides data to validate the use of [redacted]

[redacted] The subject drug product is [redacted] at Ben Venue Laboratories in Bedford, Ohio. This review is prepared for HFD-640.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendation 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-None

C. Assessment of Risk Due to Microbiology Deficiencies-None

III. Administrative

A. Reviewer's Signature Marla Stevens-Riley 1/31/02

B. **Endorsement Block**
M. Stevens-Riley 1/31/02
L. Ensor/ L. Ensor 1/31/02
B. McNeal/

C. CC Block
cc:
Original ANDA 76-087
HFD-600 v:microrev\76-087a1.doc

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #2

Product Quality Microbiology Review
Review for HFD-640

1 October 2002

ANDA: 76-087

Drug Product Name
Proprietary: Diflucan
Non-proprietary: Fluconazole Injection
Drug Product Classification: N/A

Review Number: 3

Subject of this Review
Submission Date: June 20, 2002
Receipt Date: June 24, 2002
Consult Date: N/A
Date Assigned for Review: September 24, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): December 21, 2000
and November 7, 2001
Date(s) of Previous Micro Review(s): July 31, 2001
and January 16, 2002

Applicant/Sponsor
Name: Bedford Laboratories
Address: 300 Northfield Road
Bedford, Ohio 44146

Representative: Molly Rapp
Telephone: 440-201-3576

Name of Reviewer: Marla Stevens-Riley

Conclusion: 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:** Ben Venue Laboratories
270 Northfield Rd
Bedford, Ohio 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous injection, 2 mg/mL, 200 mL/vial

5. **METHOD(S) OF STERILIZATION:** ———————

6. **PHARMACOLOGICAL CATEGORY:** anti-fungal

B. **SUPPORTING/RELATED DOCUMENTS:**

C. **REMARKS:** The subject amendment provides for a new strength configuration for the subject drug product of 200 mL/vial at 2 mg/mL. The original submission is for a 100 mL/vial strength at 2 mg/mL. (In Microbiology Reviews #1 and #2, 3 mL fill/vial was inadvertently written.) This amendment was originally submitted as an original application, but it was collapsed into this application ANDA 76-087 as new strength amendment.

filename: v:\microrev\76-087a2.doc

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for approval on the basis of sterility assurance.

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 – [redacted]

B. Brief Description of Microbiology Deficiencies - none

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with this product is minimal.

III. Administrative

A. Reviewer's Signature Maula Stevens-Riley

B. Endorsement Block
M.Stevens-Riley, Ph.D. 10/4/02
N. Sweeney, Ph.D.
Neal Sweeney 10/7/02

C. CC Block
cc:
Original ANDA 76-087
Division file
Field Copy

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

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 25, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 25-JAN-2001

SUBJECT: Examination of the request for waiver submitted with an ANDA for Fluconazole Injection, 200 mg/100 mL (in Sodium Chloride 0.9%) to determine if the application is substantially complete for filing.

Bedford Laboratories has submitted ANDA 76-087 for Fluconazole Injection, 200 mg/100 mL (in Sodium Chloride 0.9%. 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 Bedford on December 21, 2000 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".

This is a waiver request; no bio study is requested

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
   (c) 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

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

1/29/01
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-087 DRUG NAME Fluconazole Injection FIRM Bedford Labs

DOSAGE FORM(s) 2 mg/mL; 100mL per vial

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol			N/A		
Assay Methodology			N/A		
Procedure SOP			N/A		
Methods Validation			N/A		
Study Results Ln/Lin			N/A		
Adverse Events			N/A		
IRB Approval			N/A		
Dissolution Data			N/A		
Pre-screening of patients			N/A		
Chromatograms			N/A		
Consent forms			N/A		
Composition	✓				
Summary of study			N/A		
Individual Data & Graphs, Linear & Ln			N/A		
PK/PD data disk			N/A		
Randomization Schedule			N/A		
Protocol Deviations			N/A		

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site			N/A		
Analytical site					
Study investigators					
Medical Records					
Clinical Raw Data					
Test Article Inventory					
BIO Batch Size					
Assay of active content drug					
Content uniformity					
Date of manufacture					
Exp. Date RLD					
Biostudy lot numbers					
Statistics					
Summary results provided by the firm indicate studies pass BE criteria					
Waiver requests for other strengths / supporting data			N/A		Waiver Request for 1 strength only

Additional comments:

Recommendation: COMPLETE / INCOMPLETE

concur 1/29/2001

Reviewed by Hoainhon Nguyen

Date 1/26/01

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

Telecon Record

Date: **August 8, 2002**

ANDA: **76-443**

Firm: **Bedford**

Drug: **Fluconazole Injection, 2 mg/mL, 200 mL vials**

FDA Participants: Martin Shimer

Industry Participants: **Molly Rapp**

Phone #: **(440) 201-3576**

Agenda: **Marty called Molly and asked that she provide 3 additional copies of the container label and an explanation of why the batch number for the accelerated stability in the upright position (pg 650) does not correlate to the executed batch record. Marty also discussed with Molly that in all probability this application would need to be submitted as a new strength amendment to their pending application 76-087.**

August 12, 2002

Marty called Molly to confirm that this submission would need to be submitted as a new strength amendment to their pending ANDA 76-087. OGD's rationale for this requirment is that the current submission meets all criteria of the "Variations" guidance and Bedford is submitting a PIII certification to patent number 4,404,216 which delays approval of the application until January 29, 2004. Therefore, submission of the new strength amendment will not effect the final approval of the strengths previously submitted in ANDA 76-087.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-087 Applicant Bedford ~~Laboratories~~ Laboratories
Drug Fluconazole Injection Strength 2 mg/mL; 100 mL and 200 mL vials

APPROVAL ~~XX~~ TENTATIVE APPROVAL X SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:		DRAFT Package	FINAL Package
1.	Project Manager, Team 9	Date 6/20/03	Date 6/25/03
	Review Support Branch Tech Point	Initials GM	Initials GM

Application Summary:

Original Rec'd date 12-21-2000
Date Acceptable for Filing 12-26-2000
Patent Certification (type) III
Date Patent/Exclus.expires Jan 29, 2004
Citizens' Petition/Legal Case Yes ☐ No X
(If YES, attach email from PM to CP coord)

EER Status Pending X Acceptable ☐ OAI ☐
Date of EER Status
Date of Office Bio Review 10-15-02
Date of Labeling Approv. Sum 10-15-02
Date of Sterility Assur. App. 10-7-02
Methods Val. Samples Pending Yes X No ☐
Commitment Rcd. from Firm Yes X No ☐

DA → First Generic Yes ☐ No X
-145 (If YES, Pediatric Exclusivity Tracking System (PETS)
P RLD =
4/15/03 Date checked NDA#
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

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:

P-III/yDhady 6/20/2003

2. Gregg Davis PPIV ANDAs Only Date 6/20/2003 Date 6/20/2003
Supv., Reg. Support Branch Initials [illegible] Initials [illegible]

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

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

OK for TA

3. Div. Dir./Deputy Dir. Date 7/1/03 Date 7/1/03
Chemistry Div. I or II Initials [illegible] Initials [illegible]
Comments:

one satisfactory

REVIEWER: FINAL ACTION

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

5. Peter Rickman
Acting Director, DLPS
Date 7/16/03 Initials [signature] Date 7/17/03 Initials [signature]
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐
Comments:
applicant made a P III cert. to the '216 patent which expires 1/29/04
NO exclusivity issues
2 vial sizes (strengths) 100 mL & 200 mL
micro acceptable 10/7/02
Office Level Bio 2 mg/mL - 100 mL vial acceptable 3/8/01 - 2mg/mL - 200mg to [redacted] acceptable 10/7/02
Labeling acceptable 10/15/02 OK TO TA
EER acceptable 7/11/2003

OR

5. Robert L. West
Acting Deputy Director, OGD
Date_____ Initials_____ Date_____ Initials_____

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

6. Gary Buehler
Director, OGD
Comments:
Date 7/17/03 Initials GB Date 7/17/03 Initials GB

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

7. Project Manager, Team 9
Review Support Branch
Date 7/17/03 Initials [signature] Date 7/17/03 Initials [signature]

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

Applicant notification:
4:15 pm Time notified of approval by phone 4:18 pm Time approval letter faxed

FDA Notification:
7/17/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/17/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V:\REPORTS\APPROVAL\Approvrou3.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-087 Applicant Bedford Laboratories
Drug Fluconazole Injection, 2mg/mL 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 24 March 2004 Initials MMS	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: '216 patent expired 1/29/2004. Bedford has AEX Pediat exp 7/29/2004
∴ Eligible for TA

2. Project Manager, Ted Pelt Team 9 Review Support Branch	Date 03/22/04 Initials	Date Initials

Original Rec'd date December 21, 2000
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing
Date of EER Status 3/28/03
Patent Certification (type) III
Date of Office Bio Review
Date Patent/Exclus.expires 7/29/04
Date of Labeling Approv. Sum
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App.
(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 7-17-2003
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:		Date 4/8/04 Initials

no CMC changes since TA dated 7/17/03

4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	**First Generics Only**	Date Initials

N/A

REVIEWER: FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS
Date ____
Initials ____

RLD=Diflucan in Sodium Chloride 0.9%
Pfizer Inc. 200mg/100mL NDA 19-950(001)

6. Peter Rickman
Director, DLPS
Date 4/9/04
Initials RW West for

Para.IV Patent Cert.: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable LES dated 7/11/03 (certified 4/9/04). No O.N.I. labels noted - Refer to the administrative sign-off form completed at the time of the first tentative approval issued on 7/17/03. On 12/22/03, Bedford submitted a minor amendment to request final approval based upon the expiration of the '216 patent on 1/29/04. See below. Bedford stated that no changes were made to the CMC section of the application, or to the labeling. FPL reviewed and found acceptable 2/4/04. CMC remains approvable 4/6/04.

6. Robert L. West
Deputy Director, OGD
Date 4/9/2004
Initials Robert West

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: Bedford made a paragraph III certification to the '216 patent which was to have expired on 1/29/04. However, Pfizer was awarded pediatric exclusivity for Diflucan. Pfizer's exclusivity expires on 7/29/04. On 2/9/04, Bedford addressed Pfizer's exclusivity.

Issue a second tentative approval letter to Bedford based upon the granting of pediatric exclusivity to Pfizer.

7. Gary Buehler
Director, OGD
Date 4/9/04
Initials GB

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

8. Project Manager, Team Ted Ralat
Review Support Branch
Date 4/12/04
Initials TR

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
4pm Time notified of approval by phone 4pm Time approval letter faxed
FDA Notification:
____ Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/12/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou6.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-087 Applicant Bedford Laboratories
Drug Fluconazole Injection ~~Bedford~~ 100ml, 200ml vials 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 1 July 2004 Date 7/22/04 for
Initials MS Initials Paul

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = NDA# 19-950
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked Previously granted
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: No changes from 4/9/2004 TA
Eligible for full approval on 7/24/2004

2. Project Manager, Ted Pelot Team 9
Review Support Branch
Date 6/25/04 Date
Initials [illegible] Initials

Original Rec'd date 12-21-00 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing Date of EER Status 7-11-03
Patent Certification (type) II Date of Office Bio Review 10-15-2002
Date Patent/Exclus.expires 7-29-04 Date of Labeling Approv. Sum 2-4-04
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. 10-7-02
(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 4-9-2004
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read (PP IVs Only) Pre-MMA Language included ☐ Date
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials
Comments:
N/A

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments: No CMC issues.
Date 7/21/04
Initials RCA

REVIEWER:

FINAL ACTION

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

NDA 19-950(001)

6. Vacant RLD=①; Eloxatin Injection 2mg/mL vs 0.9% Sodium Chloride Injection
Deputy Dir., DLPS
Date_____
Initials_____

7. Peter Rickman Pfizer Inc. 200mg/100mL and 400mg/200mL
Director, DLPS
Date 7/22/04
Initials Rickman for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 7/11/03 (Verified 7/22/04) No OA-I alerts noted
Refer to the administrative review forms completed at the time of the tentative approvals on 7/17/03 and 4/9/04. On 5/11/04 Bedford submitted a MINOR amendment to request final approval for the ANDA and stating that no changes had been made to the CMC section since the previous TA-FA remains acceptable (as endorsed 7/19/04). CMC remains acceptable for final approval 7/12/04.

8. Robert L. West
Deputy Director, OGD
Date 7/22/2004
Initials Robert West
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☒
Comments: Bedford made a paragraph III certification to the '216 patent that expired on 1/29/04. However the expiration of the '216 patent was effectively extended until 7/29/04 upon the granting of pediatric exclusivity to Pfizer. Bedford has changed its certification to a paragraph II certification and has also addressed Pfizer's period of exclusivity. This ANDA is recommended for final approval upon the expiration of Pfizer's exclusivity on 7/29/04.

9. Gary Buehler
Director, OGD
Date 7/22/04
Initials Rickman for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg Issue ☐

10. Project Manager, Team Ted Palat
Review Support Branch
Date_____
Initials_____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10A Time notified of approval by phone 1015 Time approval letter faxed
FDA Notification:
7/29 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/29 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

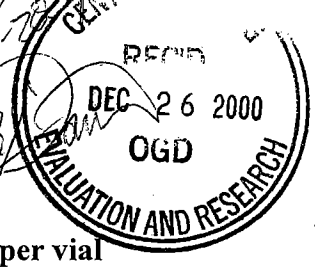
CORRESPONDENCE

BEDFORD
LABORATORIES™

December 21, 2000

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

505(b)(2)(A) OK
JOSAN-7-21



RE: Abbreviated New Drug Application
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Fluconazole Injection, 2 mg/mL; 100 mL per vial. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Pfizer Inc.'s DIFLUCAN®, NDA 19-950). The application consists of three volumes.

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of this application (Fluconazole Injection, 2 mg/mL; 100 mL per vials). The drug product is a solution intended solely for intravenous infusion and it contains the active ingredient and inactive ingredient in the same concentration as in the listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Bedford Laboratories commits to provide full cooperation to resolve any problem which may arise during the methods validation testing as part of the "Post-Approval" process for the above listed drug product.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

Two copies of analytical methods, which were used to test this product, as well as an analytical method validation package are enclosed separately along with this application.

Section XXII of this application, located in Volume 3, contains the Sterilization Assurance Data and Information as well as the following: a copy of the labeling and package insert, a summary of the manufacturing process including the components and composition statement, and ———— records. This product is ————.

This application will include a CMC ESD electronic submission. The diskettes will be sent as a New Correspondence within 30 days.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3333 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

ANDA 76-087

Bedford Laboratories
Attention: Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

Dear Sir:

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

NAME OF DRUG: Fluconazole in Sodium Chloride 0.9% Injection, 2 mg/mL, 100 mL vial

DATE OF APPLICATION: December 21, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 26, 2000

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) 827-5848

Sincerely yours,

Gregory S. Levin for

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

ANDA 76-087
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 30 JAN 2001 date
HFD-615/PPatel,CSO Paam Patel date 1/30/01
Word File V:\Firmsam\Bedford\ltrs&rev\76087.ACK
F/T EEH 01/30/01
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

1 disk
ND

BEDFORD LABORATORIES™

74-087

January 5, 2001

NEW CORRESPONDENCE

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

NEW CORRESP

RE: **CMC ESD Electronic Submission/New Correspondence**
Product: **Fluconazole Injection, 2 mg/mL; 100 mL vial**

Dear Sir/Madam,

As communicated in the December 21, 2000 Abbreviated New Drug Application for Fluconazole Injection, 2 mg/mL; 100 mL vial, Bedford Laboratories™ is submitting a diskette containing the CMC ESD Electronic Submission.

Bedford Laboratories™ certifies that the data contained in the files on the diskette is identical to the data found in the paper submission.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440) 201-3333 (direct) or (440) 232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN - 8 2001
OGD

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

January 26, 2001

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

NEW CORRESP
NC

RE: ANDA 76-087/Methods Validation Package
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

OK
P.M.P
1/31/01

Dear Sir/Madam:

We wish to supply the Agency with three copies of the Methods Validation Package for the above referenced ANDA, Fluconazole Injection, 2 mg/mL, 100 mL vials.

This is in response to the telephone conversation between Mr. Paras Patel of the Agency and Mr. Shahid Ahmed of Ben Venue Laboratories, Inc., on January 26, 2001.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3333 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 29 2001
OGD

BEDFORD
LABORATORIES™

March 21, 2001

CTO AMENDMENT
N/A

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

RE: ANDA 76-087/Amendment to Original Application
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

Dear Sir/Madam:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 100 mL per vial by providing corrected Finished Product Specifications and Stability Data Summary Sheets.

The Related Substances Specifications for Finished Product Specifications have been corrected by including Individual Known Impurities and revising Total Impurities Specifications. Also, typographical error for Total Impurities Specifications have been corrected for Stability Data Summary Sheets. Revised Finished Product Specifications (page 604 of the original Application) and Stability Data Summary Sheets (pages 671 and 672 of the original Application) are provided in this amendment.

I apologize for any inconvenience this may have caused.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3469 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel

Pratima Patel
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

3/26/01

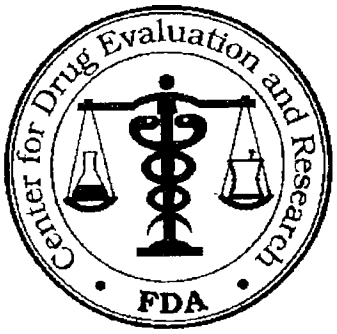
A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

R AMENDMENT

-087

JUN 22 2001

OF GENERIC DRUGS, CDER, FDA
nt Control Room, Metro Park North II
ndish Place, Room 150
e, MD 20855-2773 (301-594-0320)



PLICANT: Bedford Laboratories TEL: 440-201-3333

TN: Shahid Ahmed FAX: 440-232-2772

Jeen Min PROJECT MANAGER: 301-827-5849

imile is in reference to your abbreviated new drug application dated December 21, 2000, submitted to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL in 100

e is also made to your amendment(s) dated: March 21, 2001.

ication is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in hments (5 pages). This facsimile is to be regarded as an official FDA communication and unless d, a hard copy will not be mailed.

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

AL INSTRUCTIONS:

try and Labeling deficiencies with Bioequivalence comments.

B. Jnc
6/22/01

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by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, ion, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately by telephone and return it to us by mail at the above address.

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6/22/2001 FDA FAX

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

ANDA Number: 76-087 Date of Submission: December 21, 2000

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection

Labeling Deficiencies:

1. CONTAINER - 200 mg/100 mL

   The pictorial illustration on the hanging strip indicates that you will affix your label up side down. Please be advised that the statement of identity shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed. We ask that you affix your label parallel to the orientation of your bottle and make revisions accordingly in terms of the location of the hanging strip. Please ensure that when the vial is hung, the calibration reflects actual volume of the solution remaining in the container.

2. INSERT

   a. DESCRIPTION – Last paragraph, first sentence:

      ... solution of fluconazole in a sodium chloride diluent.

   b. PRECAUTIONS (Pediatric Use) – Penultimate paragraph:

      ...for 1 to 1,616 days.... ["1,616" rather than "1.616"]

   c. ADVERSE REACTIONS (In Patients Multiple... Candidiasis, Hepatobiliary) – Second paragraph, first sentence:

      ...levels from a baseline value of 30 IU/L to ... [add "value"]

   d. DOSAGE AND ADMINISTRATION

      i. Dosage and Administration in Adults – Multiple Dose:

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

         B) Add the following text as the first sentence of the first paragraph.

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

         C) Esophageal candidiasis – Last sentence:

            ...minimum of three weeks and for at least...

ii. Dosage in Patients With Impaired Renal Function – First paragraph:

Delete the second sentence " [redacted]".

iii. Administration

A) First sentence – Revise to read:

Fluconazole injection is administered by intravenous infusion.

B) Add the following as the second paragraph.

Fluconazole injection in glass container is intended only for intravenous administration using sterile equipment.

e. HOW SUPPLIED – Second sentence:

..glass vials, each containing 200 mg of fluconazole in 100 mL of sodium chloride solution.

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: 76-087 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fluconazole Injection 2 mg/ml; 100 ml per vial

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

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

Sincerely yours,

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

BEDFORD LABORATORIES™

November 7, 2001

Response to Minor Amendment/Chemistry and Labeling Deficiencies

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

N/AM

RE: ANDA 76-087
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

Dear Sir/Madam:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 100 mL per vial by responding to your letter dated June 22, 2001.

FDA 356h Form is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. Regarding the bulk drug substance specifications:

a, b. [redacted]

c. [redacted]

2. [redacted]

3. [redacted]

NOV 0 6 2001

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 FAX (440) 232-6264

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confidential commercial

information from

11/07/2001 BEDFORD LETTER

(Chemistry)

B. Please acknowledge that methods validation samples will be forwarded upon the Agency's request.

Labeling Deficiencies:

1. Container: We have revised the container label by removing the calibration marks. As we mentioned above, Ben Venue will use silk-screened containers (pre-marked with appropriate calibration marks) for commercial batches. Also, the pictorial illustration on the hanging strip has been amended.

2. Insert: We have revised our package insert labeling based on your comment.

3. Carton: Assumed satisfactory.

Please refer to Attachment VII for four copies of draft container vial label and draft package insert labeling for review. Also located in Attachment VII are annotated side-by-side comparisons of the draft container label and package insert with the previously submitted draft container label and package insert.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3469 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel for

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

November 7, 2001

BEDFORD LABORATORIES™

Response to Microbiology Deficiencies

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

N/As

ORIG AMENDMENT

RE: ANDA 76-087
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

Dear Sir/Madam:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 100 mL per vial by responding to your letter dated August 22, 2001.

FDA 356h Form is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

A. Microbiology Deficiencies:

1. [redacted]

2.

MW 11-14-01

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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11/7/2001 BEDFORD LETTER (Microbiology)

MINOR AMENDMENT

ANDA 76-087

MAR - 4 2002

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)

TO: APPLICANT: Bedford Laboratories

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-232-2772

FROM: Jeen Min

PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection 2 mg/mL in 100 mL vials.

Reference is also made to your amendment(s) dated: March 21 and November 7, 2001.

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

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

SPECIAL INSTRUCTIONS:

Chemistry Deficiencies.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

jm 3/4/02

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information from

3/4/2002 FDA FAX

3. Please provide data verifying the accuracy of the volumetric calibration marks indicated on the vial.

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

July 19, 2002

BEDFORD LABORATORIES™

Response to Chemistry Deficiencies/Minor Amendment

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

ORIG AMENDMENT
N/AM

RE: ANDA 76-087
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL per vial

Dear Sir/Madam:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 100 mL per vial by responding to your letter dated March 4, 2002.

FDA 356h Form is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. [redacted]

RECEIVED
JUL 22 2002
OGD / CDER

20-836 MA

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6244

BEDFORD LABORATORIES™

2. Material Safety Data Sheets are provided for the ink components for you review.

3. Bedford Laboratories commits to validate the accuracy of the volumetric calibration marks on the vial prior to commercial marketing of this drug product.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

August 9, 2002

BEDFORD LABORATORIES™

New Correspondence

Martin Shimer
Project Manager, Regulatory Affairs Support Branch, HFD-61
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

76-443

NEW CORRESP
NC

RE: Abbreviated New Drug Application
PRODUCT: Fluconazole Injection, 2 mg/mL; 200 mL per vial

Dear Mr. Shimer:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 200 mL per vial by responding to your telephone request, dated August 8, 2002.

FDA 356h Form is provided in this amendment.

Per your conversation, we have corrected the lot number on page 560of the original Application. Also, three copies of container label are provided for your review.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
AUG 13 2002
OGD / CDER

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

August 26, 2002

BEDFORD LABORATORIES™

Special Correspondence

Martin Shimer
Project Manager, Regulatory Affairs Support Branch, HFD-61
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: **ANDA 76-087**
Product: **Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL vials**

Dear Mr. Shimer:

This letter is in response to several telephone conversations with Mr. Martin Shimer of the Agency and Mrs. Molly Rapp of Ben Venue Laboratories, Inc. during the week of August 12, 2002.

Fluconazole Injection, 2 mg/mL, 200 mL vial, was submitted as an Abbreviated New Drug Application on June 20, 2002. Also, pending with the Agency is Bedford Laboratories' ANDA 76-087 for Fluconazole Injection, 2 mg/mL, 100 mL vial. Bedford Laboratories recognizes that the 200 mL dosage of Fluconazole Injection is eligible for inclusion in ANDA 76-087 (submitted for the 100 mL dosage) based on the Guidance for Industry, Variations in Drug Products that May be Included in a Single ANDA, December 1998. The 200 mL dosage was submitted as a separate ANDA in order to avoid any delay in approval of the ANDA 76-087, FLuconazole Injection, 2 mg/mL; 100 mL vial, which had reached the minor review status. After discussions with the Agency, it was determined that this additional dosage (200 mL per vial) should be submitted as an amendment to ANDA 76-087 instead of as a separate application.

Based on the above facts, Bedford Laboratories requests the withdrawal of the June 20, 2002 submission as a separate ANDA and also requests that the information provided in that submission be accepted as an amendment to ANDA 76-087, Fluconazole Injection, 2 mg/mL, 100 mL, for an additional dosage.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel for

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
AUG 27 2002
OGD / CDER

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: Bedford Laboratories — TEL: 440-201-3576

ATTN: Molly Rapp — FAX: 440-232-2772

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

Number of pages: 1
(excluding the cover sheet)

Comments:

Bioequivalence comments for ANDA 76-087 (Fluconazole Injection 2 mg/mL).

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Jen 10/27/05

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-087 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fluconazole Injection 2 mg/ml; 200 ml per vial

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

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

Sincerely yours,

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

MINOR AMENDMENT

ANDA 76-087

JAN 17 2003

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)

TO: APPLICANT: Bedford Laboratories

TEL: 440-201-3576

ATTN: Molly L. Rapp

FAX: 440-232-2772

FROM: Ted Palat

PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL vials.

Reference is also made to your amendment(s) dated: July ~~22~~ 19, 2002 and June ~~24~~ 20, 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.

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:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

jm 1/17/03

JAN 17 2003

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-087 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fluconazole Injection

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. We request that you revise the final product limit for the [redacted]

2. [redacted]

respectively.

Sincerely yours,

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

BEDFORD
LABORATORIES™

January 21, 2003

Response to Chemistry Deficiencies/Minor Amendment

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

ORIG AMENDMENT
N/Ac

RE: ANDA 76-087
PRODUCT: Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL per vials

Dear Sir/Madam:

We wish to amend our Abbreviated New Drug Application, Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL per vials by responding to your letter dated January 17, 2003.

FDA 356h Form is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. We have revised Finished Product Release Specifications by [redacted] respectively. Revised Finished Product Specifications are provided in this amendment.

2. [redacted] respectively. Revised Pre- and Post-Approval Stability Protocols are provided in this amendment.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

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JAN 22 2003
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BEDFORD LABORATORIES™

December 22, 2003

MINOR AMENDMENT-FINAL APPROVAL REQUESTED

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

ORIG AMENDMENT
N/A

RE: **ANDA 76-087/ Minor Amendment**
Product: **Fluconazole Injection; 2 mg/mL, 100 mL and 200 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-087, for Fluconazole Injection, 2 mg/mL, 100 mL and 200 mL per vial in order to receive the full approval. This is in reference to the Agency's letter, dated July 17, 2003 approving this Application tentatively. Form 356H is provided.

There have been no other changes to the Chemistry and Manufacturing Controls that were tentatively approved on July 17, 2003

There have also been no changes to the labels or labeling that was tentatively approved. Twelve final printed copies of the label and labeling are provided.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)201-3333, for any additional information.

Sincerely,
for Bedford Laboratories™

Molly Rapp
Manager, Regulatory Affairs
Ben Venue Laboratories, Inc.

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A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

February 9, 2004

BEDFORD LABORATORIES™

PATENT AMEDNMENT

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

N/ XP

NHI
Clubm
2/19/04
Ped Exc.

RE: **ANDA 76-087**
Product: **Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL vials**

Dear Sir/Madam:

We wish to amend our above listed Abbreviated New Drug Application, for Fluconazole Injection, 2 mg/mL; 100 mL and 200 mL per vial by providing revised Exclusivity Statement.

FDA 356h Form is provided in this amendment.

Bedford Laboratories™ acknowledges the assignment of the Pediatric Exclusivity for the "listed drug" Pfizer's DIFLUCAN® (NDA 19-950). Therefore, we have revised the Exclusivity Statement and provided in this amendment.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Molly Rapp
Manager, Regulatory Affairs
Ben Venue Laboratories, Inc.

FEB 11 2004

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

ORIGINAL

May 11, 2004

MINOR AMENDMENT-FINAL APPROVAL REQUESTED

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

ORIG AMENDMENT
N/am

RE: **ANDA 76-087/ Minor Amendment**
Product: **Fluconazole Injection; 2 mg/mL, 100 mL and 200 mL per vial**

Dear Sir/Madame:

We wish to amend our tentatively approved Abbreviated New Drug Application, ANDA 76-087, for Fluconazole Injection, 2 mg/mL, 100 mL and 200 mL per vial in order to receive the full approval. This is in reference to the Agency's letter, dated April 9, 2004 approving this Application tentatively (second time). Form 356H is provided.

There have been no other changes to the Chemistry and Manufacturing Controls that were tentatively approved on July 17, 2003

There have also been no changes to the labels or labeling that was sent to the Agency, dated December 22, 2003 for final approval request.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)201-3576, for any additional information.

Sincerely,
for Bedford Laboratories™

P. Patel for

Molly Rapp
Manager, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
MAY 1 2 2004
OGD/CDER