CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-145

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: American Pharmaceutical Partners, Inc.

Approval Date: July 29, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

APPROVAL LETTER

ANDA 76-145

JUL 29 2004

American Pharmaceutical Partners, Inc.
Attention: Dale Carlson
2045 North Cornell Avenue
Melrose Park, IL 60160-1002

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 27, 2001, 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 the Tentative Approval letters issued by this office on April 15, 2003, and April 12, 2004, and to your amendment dated May 12, 2004.

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

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

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

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

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

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

Sincerely yours,

Robert L. West / for 7/29/2004

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

cc: ANDA 76-145
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/M.Farahani/ 7/12/04
HFD-647/G.Smith/ 7/13/04
HFD-617/T.Palat/ 7/16/04
HFD-613/C.Park/7/8/04 7/16/04
HFD-613/L.Golson/ 7/15/04
HFD-600/N.Nath/ 7/20/04
HFD-600/N.Sweeney/ 7-20-04

CMC on 7/26/04 RCB

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F/T by rad7/12/04

APPROVAL

Robert Rudek
7/27/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

TENTATIVE APPROVAL LETTERS

ANDA 76-145

APR 15 2003

American Pharmaceutical Partners, Inc.
Attention: Leslie Sands
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 27, 2001, 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 your amendments dated November 15, 2002, and March 17, 2003.

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

The reference listed drug product (RLD) upon which you have based your application, Diflucan® (in 0.9% Sodium Chloride Injection) of Pfizer Inc., is currently subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book, U.S. patent 4,404,216 (the '216 patent) will expire on January 29, 2004). Your application contains a paragraph III certification to the '216 patent under Section 505(j)(2) (A)(vii)(III) of the Act stating that you will

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

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 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.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will <u>not</u> be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final

approval letter prior to January 29, 2004, you should amend your application accordingly.

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

Sincerely yours,

Gary Buehler 4/15/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-145
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-645/M.Farahani/ 2,4,03
HFD-647/G.Smith/ 2/4/03
HFD-617/J.Min/ for 2/5/03
HFD-600/N.Nath/ 2/5/03
HFD-600/N.Sweeney/ 2/5/03
HFD-613/C.Park/1/28/03 2/5/03
HFD-613/L.Golson/ 2/5/03

4/15/2003

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F/T by rad1/29/03

TENTATIVE APPROVAL

conc satisfactory

ANDA 76-145

APR 12 2004

American Pharmaceutical Partners, Inc.
Attention: ~~Leslie Sands~~ Ivy Chung
2045 North Cornell Avenue
Melrose Park, IL 60660

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 27, 2001, 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 April 13, 2003, granting tentative approval to this application, and to your amendments dated November 24, 2003; and January 23, and February 26, 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.

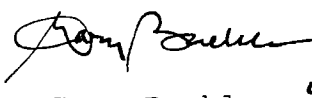
In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval 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 4/12/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-145
Division File
Field Copy
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HFD-617/T.Palat/ 4/5/04
HFD-613/C.Park/2/27/04 4/6/04
HFD-613/L.Golson 4/6/04

no cmc changes from TA dated 4/15/03
(b)(4) comments 4/8/04

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F/T by rad3/1/04

4/12/2004

TENTATIVE APPROVAL (2nd)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

LABELING

AMERICAN PHARMACEUTICAL PARTNERS, INC.

5940/Issued: November 2003

FLUCONAZOLE INJECTION

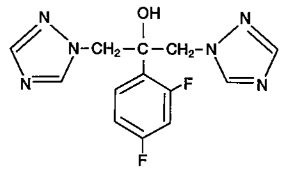
APPROVED

JUL 29 2004

FOR INTRAVENOUS INFUSION ONLY
Sterile Solution in 0.9% Sodium Chloride Injection

DESCRIPTION:
Fluconazole Injection, the first of a new subclass of synthetic triazole antifungal agents, is available as a sterile solution for intravenous use.

Fluconazole is designated chemically as 2,4-difluoro-α,α^1-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol. The structural formula is:



$C_{13}H_{12}F_2N_6O$ **M.W. 306.3**

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

Fluconazole Injection is an iso-osmotic, sterile, non-pyrogenic 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 diluent.

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

Pharmacokinetics and Metabolism
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

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

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

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

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. 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.

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)	C_{max} (mcg/mL)	Vdss (L/kg)
9 months to 13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25	2.9 (22%) N=16	–
9 months to 13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	–
5 to15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5 to15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5 to15 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 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 C_{max}. There was a mean ± SD decrease in fluconazole AUC of 13% ± 11% (range: –3.4 to –31%) and C_{max} 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 C_{max} compared to fluconazole given alone. There was a mean ± SD increase in fluconazole AUC and C_{max} 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 C_{max} 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, C_{max}, C_{min} (24 hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ± SD increase in AUC was 92% ± 43% (range: 18 to 147%). The C_{max} increased 60% ± 48% (range: -5 to 133%). The C_{min} 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, C_{max}, and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range: –5 to 48%). The C_{max} 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 C_{max} following the administration of fluconazole. There was a mean ± SD increase in tolbutamide AUC of 26% ± 9% (range: 12 to 39%). Tolbutamide C_{max} increased 11% ± 9% (range: –6 to 27%) (see **PRECAUTIONS**).

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

Glyburide: The AUC and C_{max} 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 C_{max} 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 C_{max} of cisapride both after single (AUC 102% and C_{max} 92% increases) and multiple (AUC 192% and C_{max} 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 adminstered orally and/or intravenously was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies in 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 (eg., *Candida krusei*). Such cases may require alternative antifungal therapy.

INDICATIONS AND USAGE:
Fluconazole Injection is indicated for the treatment of:

1. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.
2. Cryptococcal meningitis. Before prescribing fluconazole for AIDS patients with cryptococcal meningitis, please see **CLINICAL STUDIES** section. Studies comparing fluconazole to amphotericin B in non-HIV infected patients have not been conducted.

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

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

CLINICAL STUDIES:
Cryptococcal meningitis
In a multicenter study comparing fluconazole (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/mm^3. Mortality among high risk patients was 33% and 40% for amphotericin B and fluconazole patients, respectively (p=0.58), with overall deaths 14% (9 of 63 subjects) and 18% (24 of 131 subjects) for the 2 arms of the study (p=0.48). Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined. (Saag, *et al.* N Engl J Med 1992; 326:83-9.)

Pediatric Studies
Oropharyngeal candidiasis
An open-label, comparative study of the efficacy and safety of fluconazole (2 to 3 mg/kg/day) and oral nystatin (400,000 I.U. 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and mycological response rates were higher in the children treated with fluconazole.

Clinical cure at the end of treatment was reported for 86% of fluconazole treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.

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

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

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

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

WARNINGS:
(1) Hepatic injury
Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.

(2) Anaphylaxis
In rare cases, anaphylaxis has been reported.

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

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

Oral hypoglycemics	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 **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 7 times the recommended human dose. Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 mcg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 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 60 times the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20 to 60 times the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

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

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

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

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

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

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

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

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

ADVERSE REACTIONS:
In Patients Receiving Multiple Doses for Other Infections
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 transaminase 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	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 (TABLETS AND SUSPENSION) AND INTRAVENOUS ADMINISTRATION. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

The daily dose of fluconazole for the treatment of infections should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Fluconazole injections are intended only for intravenous administration using sterile equipment.

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

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

HOW SUPPLIED:

Product No.	NDC No.	
300861	63323-308-61	Fluconazole Injection in glass bottles, containing 200 mg of fluconazole in 100 mL of 0.9% sodium chloride injection, in trays of 10.
300863	63323-308-63	Fluconazole Injection in glass bottles, containing 400 mg of fluconazole in 200 mL of 0.9% sodium chloride injection, in trays of 10.

Vial stoppers do not contain natural rubber latex.

Store between 5°-30°C (41°-86°F).

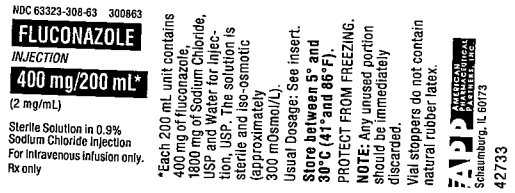
Protect from freezing.

NOTE: Any unused portion should be immediately discarded.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Schaumburg, IL 60173

45940
Issued: November 2003

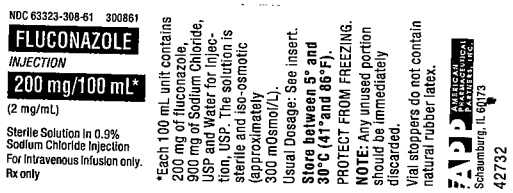
Final Printed Labeling – 200 mL Tray Label



ANDA 76-145
Fluconazole Injection

Minor Amendment
Final Approval Requested

Final Printed Labeling – 100 mL Tray Label



NDC 63323-308-61 308861
FLUCONAZOLE
INJECTION
200 mg/100 mL*
(2 mg/mL)
Sterile Solution in 0.9% Sodium Chloride Injection
For intravenous infusion only.
Rx only 100 mL
Approx. mL
63323-308-61 2
*Each 100 mL unit contains 200 mg of fluconazole, 900 mg of Sodium Chloride, USP and Water for Injection, USP. The solution is sterile and iso-osmotic (approximately 300 mOsmol/L).
Usual Dosage: See insert.
Store between 5° and 30°C (41° and 86°F)
PROTECT FROM FREEZING.
NOTE: Any unused portion should be immediately discarded.
Vial stoppers do not contain natural rubber latex.
Fluconazole Injection 200 mg/100 mL*
APPROVED
JUL 29 2004
American Pharmaceutical Partners, Inc.
Schaumburg, IL 60173
Patient Name
Date
Time
402058
Approx. mL

NDC 63323-308-63 308863
FLUCONAZOLE
INJECTION
400 mg/200 mL*
(2 mg/mL)
Sterile Solution in 0.9% Sodium Chloride Injection
For intravenous infusion only.
Rx only 200 mL
Approx. mL
63323-308-63 6
*Each 200 mL unit contains 400 mg of fluconazole, 1800 mg of Sodium Chloride, USP and Water for Injection, USP. The solution is sterile and iso-osmotic (approximately 300 mOsmol/L).
Usual Dosage: See insert.
Store between 5° and 30°C (41° and 86°F)
PROTECT FROM FREEZING.
NOTE: Any unused portion should be immediately discarded.
Vial stoppers do not contain natural rubber latex.
Fluconazole Injection 400 mg/200 mL*
APPROVED
JUL 29 2004
American Pharmaceutical Partners, Inc.
Schaumburg, IL 60173
Patient Name
Date
Time
LIFT HERE
402059
Approx. mL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

LABELING REVIEWS

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

ANDA Number: 76-145 Date of Submission: March 27, 2001

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Fluconazole Injection , 2 mg/mL

Labeling Deficiencies:

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

   a. We believe that your products are designed to be hung for intravenous infusion. Please explain how the bottles will be hung and submit information regarding your hanging devices.

   b. We ask that you relocate the phrase "Sterile Solution in 0.9% Sodium Chloride Injection" to appear immediately beneath the established name.

   c. Relocate the route of administration to appear immediately beneath the expression of strength.

2. INSERT

   a. TITLE

      Include "Sterile Solution in 0.9% Sodium Chloride Injection" beneath the statement "FOR INTRAVENOUS INFUSION ONLY" as found on your container labels.

   b. CLINICAL PHARMACOLOGY (Drug Interaction Studies)

      i. Cyclosporine - Second sentence:

         ...following the administration of fluconazole. [add "the"]

      ii. Terfenadine - Last sentence:

         ...at 400 mg and 800 mg daily... [delete a hyphen]

   c. INDICATIONS AND USAGE

      i. First sentence:

         Fluconazole injection is... [add "injection"]

      ii. Item #3

         ...please see CLINICAL STUDIES section. [add "section"]

d. PRECAUTIONS

i. Use the term "times" rather than the symbol "x" throughout this section.

ii. Delete the subsection " [redacted] " in its entirety.

iii. Drug Interactions - Tacrolimus - Last sentence:

...in the CLINICAL PHARMACOLOGY section have not... [add "section"]

iv. Pregnancy (Teratogenic Effects, Pregnancy Category C) - Last paragraph, second sentence:

...with high dose (400 to 800 mg/day) fluconazole... [use "to" rather than a hyphen]

e. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults

a. Delete the sub-subsection heading " [redacted] ".

b. Prophylaxis inpatients undergoing bone marrow transplantation - Last sentence:

Revise to read "cu mm^3" rather than "cu mm". [2 places]

ii. Dosage and Administration in Children (Esophageal candidiasis) - Last sentence:

Patients with... [delete an apostrophe]

iii. Dosage in Patients with Impaired Renal Function (Administration) - First sentence:

Fluconazole injection has... [add "injection"]

f. HOW SUPPLIED

i. Revise to read as follows:

Fluconazole Injection in glass bottles, containing 200 mg of fluconazole in 100 mL of 0.9% sodium chloride injection, in packages of [redacted]

Fluconazole Injection in glass bottles, containing 400 mg of fluconazole in 200 mL of 0.9% sodium chloride injection, in packages of [redacted]

ii. We encourage that you increase the prominence of the statement "Protect from freezing.".

iii. We ask that you include the following statement as found on your container labels.

NOTE: Any unused portion should be immediately discarded.

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

NOTE/QUESTION TO THE CHEMIST

1. **See the comment under CONTAINER.**

2. **The sponsor claims that vial stoppers do not contain natural rubber latex. Is this an accurate statement?**

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	

FOR THE RECORD:

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

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. 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.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

6. PACKAGING CONFIGURATIONS

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

7. CONTAINER/CLOSURE

Container: Type I USP glass, Flint, Molded vial
Closure: 28 mm Rubber Piggyback Stopper
Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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

11. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product when reviewing ANDA 76-087. The e-mail correspondences can be found in the file folder. Until the innovator changes the name or USP lists this as "fluconazole in

sodium chloride injection", the generics will be the same as the innovator regarding established name (i.e., fluconazole injection). This is not the subject of a USP monograph, yet.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (~~20-690~~). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

12. We decided to revisit the name issue and seek for opinion from Yana Mille.

Date of Review: 8/22/01 **Date of Submission: 3/27/01**

Primary Reviewer: Chan Park C Park **Date:** 9/10/01

Team Leader: **Date:**

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cc: for Angela Payne

ANDA: 76-145
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Review

sodium chloride injection", the generics will be the same as the innovator regarding established name (i.e., fluconazole injection). This is not the subject of a USP monograph, yet.

folks,

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

Chan

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

Hi Matthew:

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

[redacted]

Chan

Date of Review: 8/22/01 **Date of Submission: 3/27/01**

Primary Reviewer: Chan Park **Date:** 9/10/01

Team Leader: **Date:**

9/10/01

cc:

ANDA: 76-145
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Review

A2.1

Medical Officer

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

ANDA Number: 76-145 Date of Submission: October 30, 2001

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Fluconazole Injection , 2 mg/mL

Labeling Deficiencies:

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

   On principal display panel, relocate expression of strength, 200 mg/100 mL* (2 mg/mL) to immediately follow the established name, Fluconazole Injection.

2. INSERT

   1. GENERAL

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

   2. PRECAUTIONS (Carcinogenesis...Fertility) - Third paragraph, second sentence:

      Use the term "times" rather than the symbol "x" . ["15 times" rather than "15x"]

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

NOTE/QUESTION TO THE CHEMIST

The sponsor claims that vial stoppers do not contain natural rubber latex. Is this an accurate statement?

FOR THE RECORD:

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

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. 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.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

6. PACKAGING CONFIGURATIONS

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

7. CONTAINER/CLOSURE

   Container: Type I USP glass, Flint, Molded vial
   Closure: 28 mm Rubber Piggyback Stopper
   Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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

have the generic sponsors silent on all information specifically associated with "Vaginal Candidiasis"

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

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

Chan

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

Hi Matthew:

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

[redacted]

Chan

13. The sponsor proposed a clear, plastic hanging "sling" to hang the bottle. We find the proposal acceptable.

Date of Review: 12/12/01 **Date of Submission: October 30, 2001**

Primary Reviewer: Chan Park **Date:** 12/18/01

Team Leader: **Date:** 12/18/01

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cc:

ANDA: 76-145
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Review

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

ANDA Number: 76-145 Date of Submission: January 15, 2002

Applicant's Name: American Pharmaceutical Partners, Inc.

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

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

   a. We note that the expression of strength on the principal display panel does not appear sufficiently prominent, the white print on the dark blue or orange background. Please increase the prominence of the text by changing the background color and/or any other means.

   b. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. INSERT (DOSAGE AND ADMINISTRATION, Dosage and Administration in Adults, Prophylaxis in...transplantation)

   Revise to read "per cu mm" or "per mm^3". [2 instances]

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.

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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

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

Do you have 12 Final Printed Labels and Labeling? No

Submitted in draft labels and labeling

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

PROFESSIONAL PACKAGE INSERT LABELING:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

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

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request.

FOR THE RECORD:

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

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. Patent Data

019950	001	4404216	JAN 29,2004
019950	001	4416682	JUN 02,2001

Exclusivity Data

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

6. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
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7. CONTAINER/CLOSURE

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Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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Chan

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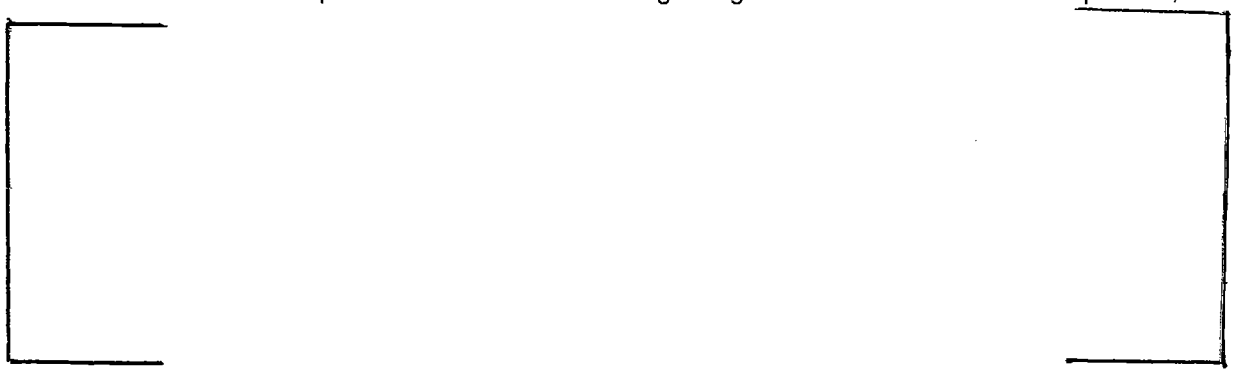
Hi Matthew:

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



Chan

13. The sponsor proposed a clear, plastic hanging "sling" to hang the bottle. We find the proposal acceptable.

14. The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

Date of Review: 1/22/02 **Date of Submission: 1/15/02**

Primary Reviewer: Chan Park C Park **Date:** 1/30/02

Team Leader: **Date:**

1/30/02

cc:

ANDA: 76-145
DUP/DIVISION FILE
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Review

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

ANDA Number: 76-145 Date of Submission: March 7, 2002

Applicant's Name: American Pharmaceutical Partners, Inc.

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

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

Do you have 12 Final Printed Labels and Labeling? No (4 copies of draft)

Submitted in draft labels and labeling

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

Satisfactory in draft as of 3/7/02 submission (vol. 3.1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of 3/7/02 submission (vol. 3.1)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

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

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request.

FOR THE RECORD:

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

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. 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.**

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

6. PACKAGING CONFIGURATIONS

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

7. CONTAINER/CLOSURE

Container: Type I USP glass, Flint, Molded vial
Closure: 28 mm Rubber Piggyback Stopper
Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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

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

folks,

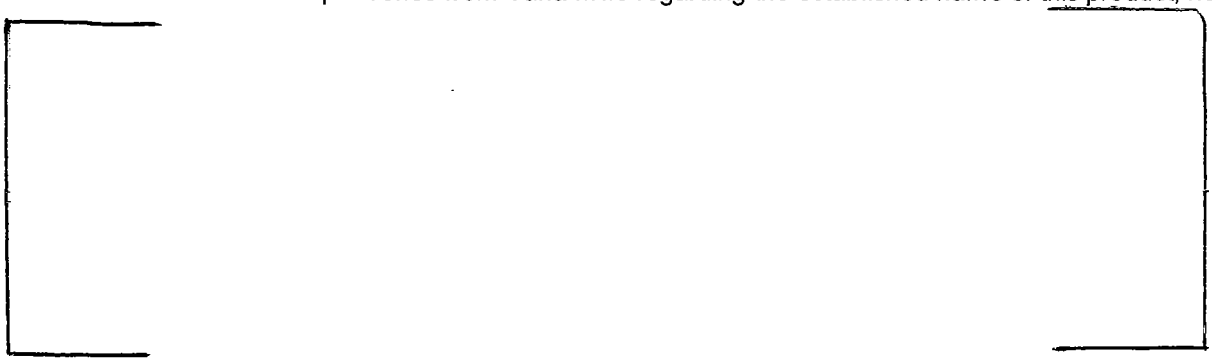
This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (19-950). I can't image having two established names for one product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

Chan

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

Hi Matthew:

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



Chan

13. The sponsor proposed a clear, plastic hanging "sling" to hang the bottle. We find the proposal acceptable.

14. The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request. This indication is specifically associated with Single administration of Diflucan tablet, 150 mg.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

Date of Review: 3/13/02 **Date of Submission: 3/7/02**

Primary Reviewer: Chan Park C Park **Date:** 3/18/02

Team Leader: **Date:**

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cc: 3/15/02

ANDA: 76-145
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSAM\APP\LTRS&REV\76145TAP.LABELING.doc

Review

APPEARS THIS WAY
ON ORIGINAL

(This TAP2 summary supersedes the TAP prepared on 3/13/02)
(TENTATIVE APPROVAL SUMMARY #2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-145 **Date of Submission: November 24, 2003 & January 23, 2004**

Applicant's Name: American Pharmaceutical Partners, Inc.

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

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

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

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

Satisfactory in FPL as of **1/23/04** submission (T90529)

TRAY LABELS - 10 vials x 100 mL, 10 vials x 200 mL

Satisfactory in FPL as of 11/24/03 submission (vol. 4.1, Attachment 1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 11/24/03 submission (vol. 4.1, Attachment 1, Rev. 11/03, Code # - 45940)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

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

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request.

2. The FPL contains minor editorial changes from the draft labels found acceptable for the tentative approval #1.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. S-034 approved 8/7/02 is specifically related to the approval of PPI for the 150 mg tablets.

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. Patent Data

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

Please note that the "4404216" patent has effectively been extended by an additional 6 months of marketing exclusivity under Section III of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) per Mary Ann Holovac. This has not been posted in the OB as of 2/4/04.

Exclusivity Data

There is no unexpired exclusivity for this product.

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store between 5° to 30°C (41° to 86°F). Protect from freezing.

6. PACKAGING CONFIGURATIONS

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

7. CONTAINER/CLOSURE

   Container: Type I USP glass, Flint, Molded vial
   Closure: 28 mm Rubber Piggyback Stopper
   Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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

10. The sponsor proposed a clear, plastic hanging "sling" to hang the bottle. We find the proposal

acceptable.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

13. We contacted the innovator , Pfizer (Ms. [redacted] on 1/7/04 to fine out the the Diflucan solution bottle still ahs graduation, which may net be necessary. She stated that the bottle still has the graduation. For this reason, we will have the applicant to retain the graduation on their proposed container labels.

14. The sponsor's container labels for the 400 mg/200 mL do not include the 200 mL graduation line while the innovator's bottle product has the 200 mL line marked on the bottle. However, we will accept the sponsor's proposal for the following reasons:

    a. This drug product also available in plastic bags, which do not have graduation at all.

    b. The whole contents is administered to the patient usually over one hour (100 mL) or two hours (200 mL) using the piggy back administration set. It is standard procedure to give this volume over these time periods unless the product causes burning sensation if given too fast (e.g., Vancomycin). They rarely monitor the infusion rate for the piggy back (small bags), not like the primary infusion bags/bottles (e.g. TPN, KCL, Sodium Bicarbonate, etc.)

    c. If the patient needs an adjusted dosage due to renal impairment (usually they decrease the frequency rather than making a dose adjustment), they use vials containing powder to make the exact dosage. However, we are not sure the powder in vial is available for Diflucan.

15. The sponsor's proposed tray labels do not contain the net quantity, i.e., 10 vials. However, the bar code tray labels containing the net quantity statement will be also affixed to the trays. We (Lillie and Chan) found this acceptable.

Date of Review: 2/4/04 **Date of Submission: 11/24/03 & 1/23/04**

Primary Reviewer: Chan Park **Date:** 2/10/04

Team Leader: **Date:** 2/10/04

(This AP#2 summary supersedes the TAP#2 prepared on 2/4/04)
(APPROVAL SUMMARY #2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-145 **Date of Submission: November 24, 2003 & January 23, 2004**

Applicant's Name: American Pharmaceutical Partners, Inc.

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

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

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

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

Satisfactory in FPL as of **1/23/04** submission (T90529)

TRAY LABELS - 10 vials x 100 mL, 10 vials x 200 mL

Satisfactory in FPL as of 11/24/03 submission (vol. 4.1, Attachment 1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 11/24/03 submission (vol. 4.1, Attachment 1, Rev. 11/03, Code # - 45940)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan® Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #:

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

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

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. The insert does not contain any information specifically associated with "Vaginal Candidiasis" throughout the text per Agency's request.

2. The FPL contains minor editorial changes from the draft labels found acceptable for the tentative approval #1.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. S-039 approved 3/24/04 is specifically related to the approval of the revised PPI for the 150 mg tablets.

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

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 126 (Volume B.1.1).

4. Patent Data

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

Please note that the "4404216" patent has effectively been extended by an additional 6 months of marketing exclusivity under Section III of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

Exclusivity Data

There is no unexpired exclusivity for this product.

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store between 5° to 30°C (41° to 86°F). Protect from freezing.

6. PACKAGING CONFIGURATIONS

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

7. CONTAINER/CLOSURE

   Container: Type I USP glass, Flint, Molded vial
   Closure: 28 mm Rubber Piggyback Stopper
   Seal: Flip-cap Tear-off Aluminum Crimp Seal (p.761, B.1.3)

8. This drug product is manufactured by American Pharmaceutical Partners, Inc. (p.186, B.1.1)

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

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

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

10. The sponsor proposed a clear, plastic hanging "sling" to hang the bottle. We find the proposal acceptable.

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

13. We contacted the innovator , Pfizer (Ms. [redacted]) on 1/7/04 to fine out the the Diflucan solution bottle still ahs graduation, which may net be necessary. She stated that the bottle still has the graduation. For this reason, we will have the applicant to retain the graduation on their proposed container labels.

14. The sponsor's container labels for the 400 mg/200 mL do not include the 200 mL graduation line while the innovator's bottle product has the 200 mL line marked on the bottle. However, we will accept the sponsor's proposal for the following reasons:

    a. This drug product also available in plastic bags, which do not have graduation at all.

    b. The whole contents is administered to the patient usually over one hour (100 mL) or two hours (200 mL) using the piggy back administration set. It is standard procedure to give this volume over these time periods unless the product causes burning sensation if given too fast (e.g., Vancomycin). They rarely monitor the infusion rate for the piggy back (small bags), not like the primary infusion bags/bottles (e.g. TPN, KCL, Sodium Bicarbonate, etc.)

    c. If the patient needs an adjusted dosage due to renal impairment (usually they decrease the frequency rather than making a dose adjustment), they use vials containing powder to make the exact dosage. However, we are not sure the powder in vial is available for Diflucan.

15. The sponsor's proposed tray labels do not contain the net quantity, i.e., 10 vials. However, the bar code tray labels containing the net quantity statement will be also affixed to the trays. We (Lillie and Chan) found this acceptable.

Date of Review: 7/8/04 **Date of Submission: 11/24/03 & 1/23/04**

Primary Reviewer: Chan Park **Date:** 7/8/04

Team Leader: **Date:** 7/19/04

cc:

ANDA: 76-145
DUP/DIVISION FILE
HFD-613/Cpark/LGolson (no cc)
V:\FIRMSAM\APP\LTRS&REV\76145AP#2.LABELING.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1 2. ANDA # 76145

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Lincy Michael
2045 North Cornell Avenue
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION
RLD Is DIFLUCAN sterile solution in 0.9% sodium chloride injection) manufactured by Pfizer Inc. The strength of the Reference Listed Drug is 2 mg/mL, 200 mg in a 100-mL vial and 400 mg and 200 mL vial. The patent expiration date is listed as 01/29/04 (patent No. 4404216) for application No. 19950. The patent expiration date is listed as 06/02/01 (patent No. 4416682) for application No. 19950.

Exclusivity Data:
There is no unexpired exclusivity for this product.

Paragraph III Certification:
APP, Inc. hereby certifies in accordance with section 505 (j)(2)(A)(vii)(III) of the FDA that: patent 4416682 held by imperial Chemical Industries, PLC will expire June 2, 2001; and (b) patent 4404216 held by Pfizer Inc. will expire January 29,2004.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
3/27 01- Original submission
4/19/01- New Correspondent
7/13/01- Amendment

FDA:

4/26/00 - Acknowledgement receipt

10. PHARMACOLOGICAL CATEGORY
Vaginal Candidiasis; oropharyngeal and esophageal candidiasis; Cryptococcal meningitis.

11. Rx or OTC
Rx

12. RELATED DMFs

[redacted]

13. DOSAGE FORM
Injectable

14. POTENCY
200 mg in 100 ml vial & 400 mg in 200 ml vial

15. CHEMICAL NAME AND STRUCTURE
2,4-diflororo-α,α-bis (1 H-1,2,4-triazol-1-yl methyl) benzyl alcohol

16. RECORDS AND REPORTS
Bio review date 5/15/01 (by M Gokhale)
Labeling is pending

17. COMMENTS
Methods validation by FDA Laboratory is requested.
Bio is adequate dated 5/15/01
DMF is adequate per review date 8/1/01 by Mahnaz Farahani
Deficiency noted:
1. Labeling is pending
2. Chemistry is not adequate

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approvable letter to issue.

19. REVIEWER: Mahnaz Farahani Ph.D.

DATE COMPLETED: July 25, 2001 & September 5, 2001

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

35. ENVIRONMENTAL IMPACT/CATEGORICAL EXCLUSION:
Pursuant to 21 CFR §25.31 (a), APP, Inc. claims a categorical exclusion from the requirements of an environmental impact analysis statement.

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

xYes

SPOT
☐No

APPEARS THIS WAY ON ORIGINAL

37. DMF Checklist for ANDA 76-145 REVIEW # 1

DMF #	TYPE/SUBJECT/HOLDER	DMF CODE	ACTION REVIEW	DATE RESULT OF COMPLETED
[redacted]	II/ [redacted]		1	8/1/01
	Comments: inadequate			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	

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

APPEARS THIS WAY ON ORIGINAL

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 76-145 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL in 100 ml vial & 200 ml vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

Regarding raw material control, we have the following comments:

A. Please submit a ———— specification for Fluconazole.

B. The limits for ——— specifications for the drug substance and drug product appear ———— ———— by the submitted data. Please revise the limits based on data accrued to date.

C. DMF ——— was found to be inadequate. The holder has been notified of the deficiencies.

Sincerely yours,

9/12/01

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

cc: ANDA 76-145
Dup
Field Copy

Endorsements:
HFD-645/MFarahani/07/27/01, 9/4/01 Mahmoud Farahani 9,10,01
HFD-647/GSmith/9/6/01 9/10/01
HFD-617/JMin 9/12/01
F/T by rad9/7/01

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CHEMISTRY REVIEW -Not Approved

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 76-145

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Genny Cruz
2045 North Cornell Avenue
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION
RLD Is DIFLUCAN sterile solution in 0.9% sodium chloride injection) manufactured by Pfizer Inc. The strength of the Reference Listed Drug is 2 mg/mL, 200 mg in a 100-mL vial and 400 mg and 200 mL vial. The patent expiration date is listed as 01/29/04 (patent No. 4404216) for application No. 19950. The patent expiration date is listed as 06/02/01 (patent No. 4416682) for application No. 19950.

Exclusivity Data:
There is no unexpired exclusivity for this product.

Paragraph III Certification:
APP, Inc. hereby certifies in accordance with section 505 (j)(2)(A)(vii)(III) of the FDA that: patent 4416682 held by imperial Chemical Industries, PLC will expire June 2, 2001; and (b) patent 4404216 held by Pfizer Inc. will expire January 29,2004.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
3/27 01- Original submission
4/19/01- New Correspondent
7/13/01- Amendment
10/30/01- Amendment
1/15/02 - Amendment

FDA:

4/26/00 - Acknowledgement receipt
9/04/01- Deficiency letter
11/16/01- Approval letter

10. PHARMACOLOGICAL CATEGORY
Vaginal Candidiasis; oropharyngeal and esophageal candidiasis; Cryptococcal meningitis.

11. Rx or OTC
Rx

12. RELATED DMFs

[redacted]

13. DOSAGE FORM
Injectable

14. POTENCY
200 mg in 100 ml vial & 400 mg in 200 ml vial

15. CHEMICAL NAME AND STRUCTURE
2,4-diflororo-α,α-bis (1 H-1,2,4-triazol-1-y1 methyl) benzyl alcohol

16. RECORDS AND REPORTS
Bio review date 5/15/01 (by M Gokhale).
Labeling is unsatisfactory per Chan Park 1/30/02

17. COMMENTS
Methods validation by FDA Laboratory is requested.
Bio is adequate dated 5/15/01
DMF is adequate per review date 9/16/01 by Mahnaz Farahani
Micro Deficiency noted.
Labeling is unsatisfactory per Chan Park 1/30/02

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval - pending Micro & Labeling.

19. REVIEWER:
Mahnaz Farahani Ph.D.

DATE COMPLETED:
November 15, 2001

Redacted 16 page(s)

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information from

CHEMISTRY REVIEW #2

32. LABELING
Deficient per Chan Park 1/30/02

33. ESTABLISHMENT INSPECTION
Acceptable 12/17/01

34. BIOEQUIVALENCY STATUS
Bio is adequate dated 5/15/01

35. ENVIRONMENTAL IMPACT/CATEGORICAL EXCLUSION:
Pursuant to 21 CFR §25.31 (a), APP, Inc. claims a categorical exclusion from the requirements of an environmental impact analysis statement.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
xYes

SPOT
☐No

APPEARS THIS WAY
ON ORIGINAL

37. DMF Checklist for ANDA 76-145 REVIEW # 2

DMF #	TYPE/SUBJECT/HOLDER	DMF CODE	ACTION REVIEW	DATE RESULT OF COMPLETED
[redacted]	II/[redacted]		1	11/18/01
	Comments: adequate			
[redacted]	III/[redacted]		4	
	Comments:			
[redacted]	III/[redacted]		4	
	Comments:			
[redacted]	III/[redacted]		4	
	Comments:			
[redacted]	III/[redacted]		4	

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 _____

APPEARS THIS WAY
ON ORIGINAL

38. Chemistry Comments to be Provided to the Applicant

ANDA 76-145 Applicant: American Pharmaceutical Partners, Inc.

Drug Product: Fluconazole Injection, 2 mg/mL in 100 mL vial & 200 mL vial

The deficiency presented below represent a Minor deficiency.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated January 18, 2002 regarding deficiencies in the microbiology section of your application and the accompanying labeling deficiencies. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding microbiology deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

2/1/02

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

cc: ANDA 76-145
Division File
Field Copy

Endorsements:
HFD-645/MFarahani/11/16/01 Mahnaz Farahani 1,31,02
HFD-647/GSmith/1/17/02 11/31/02
HFD-617/JMin/1/18/02 Jean Min 1/31/02

F/T by jsm/1/30/02

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CHEMISTRY REVIEW - NA Minor - Micro & Labeling pending

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 76-145

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Leslie Sands
2045 North Cornell Avenue
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION
RLD Is DIFLUCAN sterile solution in 0.9% sodium chloride injection) manufactured by Pfizer Inc. The strength of the Reference Listed Drug is 2 mg/mL, 200 mg in a 100-mL vial and 400 mg and 200 mL vial. The patent expiration date is listed as 01/29/04 (patent No. 4404216) for application No. 19950. The patent expiration date is listed as 06/02/01 (patent No. 4416682) for application No. 19950.

Exclusivity Data:
There is no unexpired exclusivity for this product.

Paragraph III Certification:
APP, Inc. hereby certifies in accordance with section 505 (j)(2)(A)(vii)(III) of the FDA that: patent 4416682 held by imperial Chemical Industries, PLC will expire June 2, 2001; and (b) patent 4404216 held by Pfizer Inc. will expire January 29,2004.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
3/27 01- Original submission
4/19/01- New Correspondent
7/13/01- Amendment
10/30/01- Amendment
1/15/02 - Amendment

2/11/02- Micro Amendment
3/7/02- Amendment
6/5/02- Micro Amendment

FDA:

4/26/00 - Acknowledgement receipt
9/04/01- Deficiency letter
8/13/02-Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Vaginal Candidiasis; oropharyngeal and esophageal candidiasis; Cryptococcal meningitis.

11. Rx or OTC
Rx

12. RELATED DMFs

13. DOSAGE FORM
Injectable

14. POTENCY
200 mg in 100 ml vial & 400 mg in 200 ml vial

15. CHEMICAL NAME AND STRUCTURE
2,4-diflororo-α,α-bis (1 H-1,2,4-triazol-1-yl methyl) benzyl alcohol

16. RECORDS AND REPORTS
Bio review date 5/15/01 (by M Gokhale)
Labeling is satisfactory 3/15/02

17. COMMENTS
Methods validation by FDA Laboratory is requested.
Bio is adequate dated 5/15/01
DMF is inadequate.
Micro adequate dated 8/2/02
Labeling is satisfactory 3/15/02

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable - pending chemistry is deficient.

19. REVIEWER:
Mahnaz Farahani Ph.D.

DATE COMPLETED:
April 23, 2002
and August 13, 2002

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #3

30. CONTROL NUMBERS
Field function.

31. SAMPLES AND RESULTS
Available for FDA use. Drug substance and drug products are not compendial. Method validation has been requested on August 1, 2001.

32. LABELING
Acceptable 3/15/02

33. ESTABLISHMENT INSPECTION
Acceptable 12/17/01

34. BIOEQUIVALENCY STATUS
Bio is adequate dated 5/15/01

35. ENVIRONMENTAL IMPACT/CATEGORICAL EXCLUSION:
Pursuant to 21 CFR §25.31 (a), APP, Inc. claims a categorical exclusion from the requirements of an environmental impact analysis statement.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
xYes

SPOT
☐No

APPEARS THIS WAY
ON ORIGINAL

37. DMF Checklist for ANDA 76-145 REVIEW # 2

DMF # TYPE/SUBJECT/HOLDER	DMF CODE	ACTION REVIEW	DATE RESULT OF COMPLETED
[redacted] II/ [redacted]		1	11/18/01 and 8/13/02
Comments: inadequate			
[redacted] III/ [redacted]		4	
Comments:			
[redacted] III/ [redacted]		4	
Comments:			
[redacted] III/ [redacted]		4	
Comments:			
[redacted] III/ [redacted]		4	

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 _____

APPEARS THIS WAY
ON ORIGINAL

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 76-145 APPLICANT: American Pharmaceutical Partners, Inc.
DRUG PRODUCT: Fluconazole Injection 200 mg in 100-ml vial & 400 mg in 200-ml vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. [redacted]

2. DMF # ——— as revised is deficient. Please contact the DMF holder for possible changes in ——————— specifications.

Sincerely yours,

8/23/02

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

cc: ANDA 76-145
Division File
Field Copy

Endorsements:
HFD-645/MFarahani/4/23/02 and 8/13/02 8,23,02
HFD-647/GSmith/8/14/02 8/23/02
HFD-617/JMin/8/22/02 8/23/02

F/T by rad8/23/02

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CHEMISTRY REVIEW - not approvable

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4 2. ANDA # 76-145

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Leslie Sands
2045 North Cornell Avenue
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION
RLD Is DIFLUCAN sterile solution in 0.9% sodium chloride injection) manufactured by Pfizer Inc. The strength of the Reference Listed Drug is 2 mg/mL, 200 mg in a 100 mL vial and 400 mg in a 200 mL vial. The patent expiration date is listed as 01/29/04 (patent No. 4404216) for application No. 19950. The patent expiration date is listed as 06/02/01 (patent No. 4416682) for application No. 19950.

Exclusivity Data:
There is no unexpired exclusivity for this product.

Paragraph III Certification:
APP, Inc. hereby certifies in accordance with section 505 (j)(2)(A)(vii)(III) of the FDA that: patent 4416682 held by imperial Chemical Industries, PLC will expire June 2, 2001; and (b) patent 4404216 held by Pfizer Inc. will expire January 29,2004.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
03/27/01- Original submission
04/19/01- New Correspondent
07/13/01- Amendment
10/30/01- Amendment
01/15/02 - Amendment

02/11/02- Micro Amendment
03/7/02- Amendment
06/5/02- Micro Amendment
11/15/02-Minor Amendment
3/17/03-Response to Telephone Amendment

FDA:

4/26/00 - Acknowledgement receipt
9/04/01- Deficiency letter
8/13/02-Deficiency letter
12/03/02- Approval letter
3/17/03-Telephone Amendment

10. PHARMACOLOGICAL CATEGORY
Vaginal Candidiasis; oropharyngeal and esophageal candidiasis; Cryptococcal meningitis.

11. Rx or OTC
Rx

12. RELATED DMFs

[redacted]

13. DOSAGE FORM
Injectable

14. POTENCY
200 mg in 100 ml vial & 400 mg in 200 ml vial

15. CHEMICAL NAME AND STRUCTURE
2,4-diflororo-α,α-bis (1 H-1,2,4-triazol-1-y1 methyl) benzyl alcohol

16. RECORDS AND REPORTS
Bio review date 5/24/01 (by M Gokhale)
Labeling is satisfactory 3/15/02

17. COMMENTS
Methods validation by FDA Laboratory is requested.
Bio is adequate dated 5/24/01
DMF is adequate.
Micro adequate dated 8/2/02
Labeling is satisfactory 3/15/02

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable -

19. REVIEWER:
Mahnaz Farahani Ph.D.

DATE COMPLETED:
December 4, 2002
and March 18, 2003

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CHEMISTRY REVIEW #4

[ ]

30. CONTROL NUMBERS
Field function.

31. SAMPLES AND RESULTS
Available for FDA use. Drug substance and drug products are not compendial. Method validation has been requested on August 1, 2001.

32. LABELING
Acceptable 3/15/02

33. ESTABLISHMENT INSPECTION
Acceptable 12/17/01

34. BIOEQUIVALENCY STATUS
Bio is adequate dated 5/24/01

35. ENVIRONMENTAL IMPACT/CATEGORICAL EXCLUSION:
Pursuant to 21 CFR §25.31 (a), APP, Inc. claims a categorical exclusion from the requirements of an environmental impact analysis statement.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
xYes

SPOT
☐No

37. DMF Checklist for ANDA 76-145 REVIEW # 4

DMF # TYPE/SUBJECT/HOLDER	DMF CODE	ACTION REVIEW	DATE RESULT OF COMPLETED
[redacted] II/ [redacted]		1	12/04/02
Comments: adequate			
[redacted] III/ [redacted]		4	
Comments:			
[redacted] III/ [redacted]		4	
Comments:			
[redacted] III [redacted]		4	
Comments:			
[redacted] III/ [redacted]		4	

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 76-145
Division File
Field Copy

Endorsements:
HFD-645/MFarahani/12/05/02 and 3/18/03 Mahnaz Farhani 3,25,03
HFD-647/GSmith/1/24/03 3/25/03
HFD-617/JMin/1/28/03 for 3/25/03

F/T by rad1/29/03

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CHEMISTRY REVIEW - Approvable

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 15 2. ANDA # 76-145

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Leslie Sands
2045 North Cornell Avenue
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION
RLD Is DIFLUCAN sterile solution in 0.9% sodium chloride injection) manufactured by Pfizer Inc. The strength of the Reference Listed Drug is 2 mg/mL, 200 mg in a 100 mL vial and 400 mg in a 200 mL vial. The patent expiration date is listed as 01/29/04 (patent No. 4404216) for application No. 19950. The patent expiration date is listed as 06/02/01 (patent No. 4416682) for application No. 19950.

Exclusivity Data:
There is no unexpired exclusivity for this product.

Paragraph III Certification:
APP, Inc. hereby certifies in accordance with section 505 (j)(2)(A)(vii)(III) of the FDA that: patent 4416682 held by imperial Chemical Industries, PLC will expire June 2, 2001; and (b) patent 4404216 held by Pfizer Inc. will expire January 29,2004.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fluconazole injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
03/27/01- Original submission
04/19/01- New Correspondent
07/13/01- Amendment
10/30/01- Amendment
01/15/02 - Amendment

02/11/02- Micro Amendment
03/7/02- Amendment
06/5/02- Micro Amendment
11/15/02-Minor Amendment
3/17/03-Response to Telephone Amendment
11/24/03-Amendment and request final approval for this ANDA

FDA:

4/26/00 - Acknowledgement receipt
9/04/01- Deficiency letter
8/13/02-Deficiency letter
12/03/02- Approval letter
3/17/03-Telephone Amendment
1/13/04- Approval letter

10. PHARMACOLOGICAL CATEGORY
Vaginal Candidiasis; oropharyngeal and esophageal candidiasis; Cryptococcal meningitis.

11. Rx or OTC
Rx

12. RELATED DMFs

[redacted]

13. DOSAGE FORM
Injectable

14. POTENCY
200 mg in 100 ml vial & 400 mg in 200 ml vial

15. CHEMICAL NAME AND STRUCTURE
2,4-diflororo-α,α-bis (1 H-1,2,4-triazol-1-yl methyl) benzyl alcohol

16. RECORDS AND REPORTS
Bio review date 5/24/01 (by M Gokhale)
Labeling is satisfactory ~~3/15/02~~ 2/27/04 JS

17. COMMENTS
Methods validation by FDA Laboratory is requested.
Method validation satisfactory May 2, 2002.
Bio is adequate dated 5/24/01

DMF is adequate.
Micro adequate dated 8/2/02
Labeling is satisfactory 3/15/02
Chemistry is satisfactory and the firm certifies that there is no change in chemistry and manufacturing dated 1/13/04

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable -

19. REVIEWER:
Mahnaz Farahani Ph.D.

DATE COMPLETED:
December 4, 2002,
March 18, 2003 and
January 13, 2004

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #5

30. CONTROL NUMBERS
Field function.

31. SAMPLES AND RESULTS
Available for FDA use. Drug substance and drug products are not compendial. Method validation has been requested on August 1, 2001. Method validation satisfactory May 2, 2002.

32. LABELING
Acceptable ~~3/15/02~~ 2/27/04 rs

33. ESTABLISHMENT INSPECTION
Acceptable 12/17/01

34. BIOEQUIVALENCY STATUS
Bio is adequate dated 5/24/01

35. ENVIRONMENTAL IMPACT/CATEGORICAL EXCLUSION:
Pursuant to 21 CFR §25.31 (a), APP, Inc. claims a categorical exclusion from the requirements of an environmental impact analysis statement.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
xYes

SPOT
☐No

APPEARS THIS WAY
ON ORIGINAL

37. DMF Checklist for ANDA 76-145 REVIEW # 4

DMF #	TYPE/SUBJECT/HOLDER	DMF CODE	ACTION REVIEW	DATE RESULT OF COMPLETED
[redacted]	II/ [redacted]		1	12/04/02
	Comments: adequate			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	
	Comments:			
[redacted]	III/ [redacted]		4	

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 76-145
Division File
Field Copy

Endorsements:
HFD-645/MFarahani/12/05/02, 3/18/03 and 1/13/04 3/29/04
HFD-647/GSmith/1/24/03 4/5/04
HFD-617/TPalat/ 4/5/04

F/T by rad3/1/04

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CHEMISTRY REVIEW - Approvable

APPEARS THIS WAY
ON ORIGINAL

Full Approval Assessment

1. ANDA # 76-145

2. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
Attention: Ivy Chung
2045 North Central Ave.
Melrose Park, IL 60660

3. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan® (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	03/27/01
Tentatively Approved	04/12/04
Amendment	05/12/04

7. PHARMACOLOGICAL CATEGORY
Anti-fungal

8. Rx or OTC
Rx

9. RELATED DMF(s)

10. Samples and Results
N/A

11. LABELING STATUS - Acceptable 03/15/02

12. BIOEQUIVALENCY STATUS - Acceptable 05/24/03

13. MICROBIOLOGY STATUS - Acceptable 08/02/02

14. ESTABLISHMENT INSPECTION - Acceptable 02/09/04

15. CONCLUSIONS AND RECOMMENDATIONS - The firm submitted certification that no changes have been made to the Chemistry, Manufacturing and Controls Sections of the application since receiving Tentative Approval on 05/12/04.

Recommend Approval.

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

cc: ANDA 76-145
Division File
Field Copy

Endorsements:

HFD-617\T.Palat\07/02/04 7/16/04
HFD-647\G.Smith\ 7/13/04

f/t by:

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Approval

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

BIOEQUIVALENCE REVIEW(S)

Fluconazole 2 mg/mL
Sterile Solution in 0.9% NaCl Injection
100 mL fill in 100 mL vial
200 mL fill in 200 mL vial
ANDA # 76-145
v:\firmsam\app\ltrs&rev\76145WAI.301.doc

American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park
IL 60160
Reviewer: Mamata S. Gokhale
Submission Date: March ~~29~~ 27, 2001

Review of a Waiver Request

Background

1) The firm has submitted a request for the waiver of in vivo bioavailability/bioequivalance study requirements based on 21 CFR 320.22(b) for its proposed product, Fluconazole, 2 mg/mL Sterile Solution in 0.9% Sodium Chloride Injection, 100 mL fill in 100 mL vial and 200 mL fill in 200 mL vial. The RLD is Diflucan® Sterile Solution in 0.9% Sodium Chloride Injection, 2 mg/mL, 100 mL and 200 mL vials, manufactured by Pfizer Inc.

2) Fluconazole is a synthetic triazole antifungal agent indicated for *Candida* and *Cryptococcal* infections. It acts by selective inhibition of fungal cell demethylation.

3) Diflucan® injection, 2 mg/mL is an iso-osmotic sterile solution of fluconazole in a sodium chloride diluent, pH 4.0-8.0, to be administered by intravenous infusion. The test product is proposed to be administered by a similar route under similar conditions.

Formulation Comparison

Ingredient	[1]**Reference Product** (per mL)	[1,2]**Test Product** (per mL)
[3]Fluconazole	2	2
[4]Sodium Chloride, USP	9	9
Water for Injection, USP	q. s. to 1 mL	q. s. to 1 mL

[1]pH range of 4.0-8.0
[2]Theoretically scaled up to exhibit batch size of ——— and commercial batch size of ——— for each fill size, i.e. 100 mL and 200 mL vials.
[3]Active ingredient
[4]Inactive ingredient, within FDA approved safety limits (IIG, January 1996).

Comments

1) The proposed product is a parenteral solution intended for administration solely by injection by the intravenous route.

2) The active ingredients, route of administration, dosage form and strength of the test product are the same as those of the reference listed product.

3) The inactive ingredients in the test and reference products are qualitatively and quantitatively the same.

Recommendations

The Division of Bioequivalence agrees that the information submitted by American Pharmaceutical Partners, Inc. demonstrates that Fluconazole Injection, 2 mg/mL Sterile Solution in 0.9% Sodium Chloride injection, 100 mL fill in 100 mL vial and 200 mL fill in 200 mL vial falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for Fluconazole, 2 mg/mL Sterile Solution in 0.9% Sodium Chloride Injection, 100 mL fill in 100 mL vial and 200 mL fill in 200 mL vial, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Diflucan® Sterile Solution in 0.9% Sodium Chloride Injection, 2 mg/mL, 100 mL and 200 mL vials, manufactured by Pfizer Inc.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 5/15/01
Review Branch III
Division of Bioequivalence

BMD 5/15/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M. Davit Date 5/15/01

Concur: [signature] Date 5/25/2001
fw Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 76-145 (original, duplicate), Gokhale, HFD-658, Davit, HFD-658, Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-145

APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Fluconazole in Sodium Chloride 0.9%
2 mg/mL, 100 and 200 mL vials

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

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

Sincerely yours,

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

CC: ANDA # 76-145
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale

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Printed in final on 5/15/01

Endorsments: (Final with Dates)
HFD-658/ M. Gokhale MSK 5/15/01
HFD-658/ B. Davit BMD 5/15/01
HFD-650/ D. Conner for Rep 5/29/2001
HFD-617/ S. Mazzella

Bioequivalency- Acceptable

Submission Date: ~~29~~ 27 March, 2001

Waiver (WAI)

Strength: 2 mg/mL; 100 mL and 200 mL vials
Outcome: AC

Outcome Decisions: AC- Acceptable
Winbio comments: Waiver is granted

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-145 SPONSOR : American Pharmaceutical Partners, Inc.

DRUG AND DOSAGE FORM : Fluconazole ~~Injection~~ Sterile Solution
in 0.9% Sodium Chloride Injection
100 mL fill in 100 mL vial, 200 mL fill in 200 mL vial

STRENGTH(S) : 2 mg/mL

TYPES OF STUDIES : SD SDF MULT [OTHER]

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A

DISSOLUTION : N/A Waiver of in vivo BE is granted.

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 : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSG DATE : 5/15/01

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : BMD DATE : 5/15/01

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

for INITIAL : N Balwait DATE : 5/24/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

20 December 2001

ANDA: 76-145

Name of Drug: Fluconzole Injection

Review Number: 1

Submission Date: 27 March 2001

Applicant: American Pharmaceutical Partners, Inc

Name of Reviewer: Nrapendra Nath

Product Quality Microbiology Data Sheet

A. 1. **ANDA:** 76-145

2. **REVIEW NUMBER: 1**

3. **REVIEW DATE: 20 December 2001**

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

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

6. **APPLICANT/SPONSOR:**
Name:
American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

Representative: Lincy Michael
Telephone: 708-547-3617

7. **MANUFACTURING SITE:**
American Pharmaceutical Partners, Inc.
2020 Ruby Street
Melrose Park, IL 60160

8. **DRUG PRODUCT NAME:**
Proprietary: Diflucan
Non-proprietary: Fluconazole Injection
Drug Priority Classification: N/A

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY**: 2mg/mL filled as 100mL and 200mL per vials. I/V

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

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

B. 1. **DOCUMENT/LETTER DATE:** March 27, 2001
2. **RECEIPT DATE:** March 29, 2001
3. **CONSULT DATE: N/A**
4. **DATE OF AMENDMENTS:** N/A
5. **ASSIGNED FOR REVIEW:** December 13, 2001
6. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The subject drug product is manufactured using ——— ——— in a facility located in Melrose Park, IL. The subject drug product is filled in single dose glass vials. The review was prepared for HFD-640

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the ——— ——— process are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

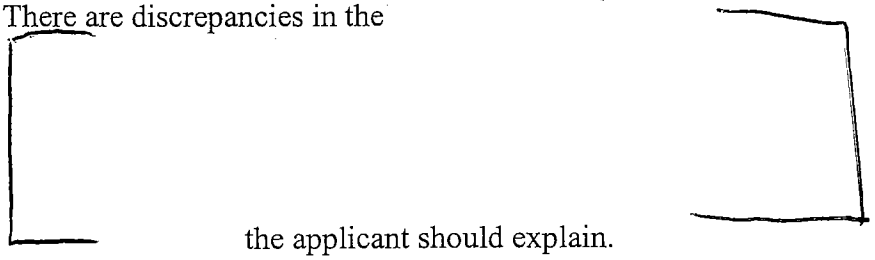
B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology
The subject drug product is manufactured using ———

——— The subject drug product is filled as single dose in 100mL and 200mL glass vials. The recommended storage temperature for the unopened vials is 5-30°C.

B. Brief Description of Microbiology Deficiencies
There are discrepancies in the



the applicant should explain.

C. Assessment of Risk Due to Microbiology Deficiencies- Significant.

III. Administrative

A. Reviewer's Signature Nrakendra Nath 12/20/01
Nrapendra Nath, Ph.D

B. **Endorsement Block** L. Ensor 1/14/02
N. Nath /Date
L. Ensor/Date
McNeal/Date

CC Block
cc:
Original ANDA 76-145
HFD-600; V:\Microrev\76-145.doc

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

7. [ ]

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 Fanning, 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
Review for HFD-620

16 April 2002

ANDA: 76-145

Drug Product Name
Proprietary: N/A
Non-proprietary: Fluconzole Injection
Drug Product Classification: Anti-infective

Review Number: 2

Subject of this Review
Submission Date: February 11, 2002
Receipt Date: February 12, 2002
Consult Date: N/A
Date Assigned for Review: April 4, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): March 27, 2001
Date(s) of Previous Micro Review(s): December 20, 2001

Applicant/Sponsor
Name: American Pharmaceutical Partners, Inc
Address: 2045 North Cornell Avenue
Melrose Park, IL 60160
Representative: Leslie Sands
Telephone: 708-486-2117

Name of Reviewer: Nrapendra Nath

Conclusion: The subject amendment is **not 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:**
American Pharmaceutical Partners, Inc.
2020 Ruby Street
Melrose Park, IL 60160

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 2mg/mL filled as 100mL and 200mL per vials. I/V

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

6. **PHARMACOLOGICAL CATEGORY:** Anti- infective

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

C. **REMARKS:** The subject amendment provides for the response to microbiology deficiencies in the correspondence dated January 18, 2001.

filename: HFD-600; V:\Microrev\76-145a1.doc

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The subject drug product is manufactured [redacted]

B. Brief Description of Microbiology Deficiencies -
Response to deficiencies is inadequate and further explanations are needed.

C. Assessment of Risk Due to Microbiology Deficiencies -
High

III. Administrative

A. Reviewer's Signature Nrapendra Nath

B. Endorsement Block L. Ensor 4/19/02
Microbiologist / Nrapendra Nath
Microbiology Supervisor/Lynne Ensor

C. CC Block
cc:
Original ANDA 76-145
HFD- 600/Division File

filename: HFD-600; V:\Microrev\76-145a1.doc

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of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #2

Product Quality Microbiology Review
Review for HFD-640

31 July 2002

ANDA: 76-145

Drug Product Name
Proprietary: N/A
Non-proprietary: Fluconzole Injection
Drug Product Classification: Anti-infective

Review Number: 3

Subject of this Review
Submission Date: June 5, 2002
Receipt Date: June 6, 2002
Consult Date: N/A
Date Assigned for Review: July 30, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): Initial—March 27, 2001;
Amendment-February 11, 2002
Date(s) of Previous Micro Review(s): December 20, 2001;
April 16, 2002

Applicant/Sponsor
Name: American Pharmaceutical Partners, Inc
Address: 2045 North Cornell Avenue
Melrose Park, IL 60160
Representative: Leslie Sands
Telephone: 708-486-2117

Name of Reviewer: Nrapendra Nath

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

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: N/A

2. SUPPLEMENT PROVIDES FOR: N/A

3. MANUFACTURING SITE:
American Pharmaceutical Partners, Inc.
2020 Ruby Street
Melrose Park, IL 60160

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 2mg/mL filled as 100mL and 200mL per vials. I/V

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

6. PHARMACOLOGICAL CATEGORY: Anti- infective

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: None.

filename: HFD-600; V:\Microrev\76-145a2.doc

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. Specific comments are provided in the "Product Quality Microbiology Assessment" section.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The subject drug product is manufactured [redacted]

B. Brief Description of Microbiology Deficiencies -

Response to deficiencies is adequate.

C. Assessment of Risk Due to Microbiology Deficiencies -

N/A

III. Administrative

A. Reviewer's Signature

Nrapendra Nath 8/2/02
Neal Sweeney 8/2/02

B. Endorsement Block

Microbiology Reviewer: Nrapendra Nath
Microbiology Team Leader: Neal J. Sweeney

C. CC Block

cc:
Original ANDA 76-145
HFD- 600/Division File
Field Copy

filename: HFD-600; V:\Microrev\76-145a2.doc

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of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Called the firm after they requested a teleconference to discuss Deficiency #3 of their Micro deficiency letter issued on 4/22/02. It is shown below:

[redacted]

Filename: V:\FIRMSAM\APP\TELECONS\76145May9-02.doc

DATE:
MAY 9, 2002

ANDA NUMBER
76-145

TELECON INITIATED BY APPLICANT

PRODUCT NAME:
Fluconazole Injection 2 mg/mL

FIRM NAME:
American Pharmaceutical Partners, Inc.

FIRM REPRESENTATIVES:
Leslie Sands, Sr. Regulatory Affairs Director; [redacted], Microbiology Manager

TELEPHONE NUMBER:
708-486-2071 (Dale Carleson's office)

FDA REPRESENTATIVES
Nrapendra Nath N Nath 6/4/02
Lynne Ensor L Ensor 6/4/02
Bonnie McNeal B McNeal 6/4/02

SIGNATURES:

Orig: ANDA 76-145
Cc: Division File

Telecon Record

Date: February 24, 2004

NC

ANDA: 76-145

Firm: APP

Drug: Fluconazole Injection 2 mg/mL, 100 mL and 200 mL

FDA Participants: Martin Shimer

Industry Participants: Dale Carlson

Phone #: (708) 486-2071

Agenda: Marty called Mr. Carlson and asked that he provide a revised Patent certification and exclusivity statement to acknowledge the pediatric exclusivity that was granted on 1/21/2004. Specifically Marty asked that Mr. Carlson provide a PII to the '216 patent(exp 1/29/2004) and acknowledge that APP would not be eligible for final approval until such a time that the ped exclusivity has expired on 7/29/2004.

200mg/100mL vial
400mg/200mL vial

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-145 Applicant APP
Drug Fluconazole Inj (0.9% NaCl) Strength 2 mg/mL

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

REVIEWER:

	DRAFT Package	FINAL Package
1. Project Manager, Team Jeen Min Review Support Br Team 9	Date 1/28/03 Initials JM	Date 2-5-03 Initials GT

Application Summary:

Original Rec'd date 3/29/01
Date Acceptable for Filing 3/29/01 ✓
Patent Certification (type) III
Date Patent/Exclus.expires 1/29/2004
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic ~~Unk~~ ☐ No ☑
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked N/A NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 12/17/2001
Date of Office Bio Review 5/24/2001
Date of Labeling Approv. Sum _____
Date of Sterility Assur. App. 8/2/2002
Methods Val. Samples Pending Yes ☑ No ☐
Commitment Rcd. from Firm Yes ☐ No ☑
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

76-303
76-304
1st generic

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

2. Gregg Davis **PPIV ANDAs Only** Date 4/15/03 Date 4/15/03
Supv., Reg. Support Branch Initials _____ Initials _____

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

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked 4/15/2003
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

4P III
N/A

RLD-Diflucan in Sodium Chloride 0.9% Pfizer Inc. 200mg/100mL NDA 19-950, 400mg/200mL

Comments: APP made a paragraph III certification to the '216 patent due to expire on 1/29/04. There is no unexpired exclusivity listed in the Orange Book for this drug product.

3. Div. Dir./Deputy Dir. 2/10/03
Chemistry Div. I or II
Comments:

Date 3/25/03
Initials

OMC Satisfactory

REVIEWER:

FINAL ACTION

4 Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review) satisfactory
Date 4/10/03
Initials FH

this is the first generic tentative approval for the injectable dosage form of this drug product.

5. Peter Rickman
~~Acting~~ Director, DLPS
Date 4/15/03
Initials PR for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable CES dated 12/7/01 (verified 4/15/03) NDO AI - all acts noted - Bioequivalence waiver granted under 21CFR 320.22(b)(1). Dose product is QHQ to the RLD. Office-level bio endorsed 5/24/01. Labeling found acceptable for TA 3/5/02 (as endorsed 2/5/03). Microbiology / sterility assurance found acceptable 8/2/02. CMC found acceptable 3/25/03. Methods validation is pending.

~~OR~~

5. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 4/15/2003
Initials (dad for west
Para.IV Patent Cert: Yes☐ No☒ Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments:

This ANDA is recommended for tentative approval (pending expiration of the '216 patent on 1/29/04).

6. Gary Buehler
Director, OGD
Date 4/15/03
Initials GB
Comments: tentative for Injection

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

7. Project Manager, Team Review Support Branch Ted Falat
Date
Initials

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

4/15/03
Applicant notification:
4pm Time notified of approval by phone 4pm Time approval letter faxed

FDA Notification:
4/15/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/15/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

\reports\approval\approvrou2.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-145 Applicant American Pharmaceutical Partners, Inc.
Drug Fluconazole Injection Strength(s) 2mg/mL

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

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

1. Martin Shimer
Chief, Reg. Support Branch
Date 2/24 Initials MS
Date 4/12/04 Initials for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
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: Eligible for TA
Comments:

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

Original Rec'd date March 27, 2001
Date Acceptable for Filing March 29, 2001
Patent Certification (type) III
Date Patent/Exclus.expires 02-29-04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabled Yes ☑ No ☐
EER Status Pending ☒ Acceptable ☒ OAI ☐
Date of EER Status ~~12-17-2003~~ 2-9-04
Date of Office Bio Review 5-24-2003
Date of Labeling Approv. Sum 3-15-2002
Date of Sterility Assur. App. 8-02-2002
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./NA Minor issued ☐ Date _____
Comments:

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:
Date 4/6/04 Initials CSL

No CMC changes from TA dated 4/15/03

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

N/A

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date_____
Initials_____

RLD = Diflucan Injection (in Sodium Chloride 0.9%)
200mg/100mL; 400mg/200mL
Pfizer Inc. NDA 19-950 (001)

6. Peter Rickman
Director, DLPS
Date 4/12/04 /for
Initials

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable ES dated 2/9/04 (Verified 4/9/04). No OAI alerts noted. Refer to the administrative sign-off form completed at the time of the tentative approval issued on 4/15/03. On 11/24/03 APP submitted a minor amendment OR to request final approval effective 1/29/04. APP submitted updated final printed labeling and stated that no CMC changes had been made since the TA. Updated PI para telephone request was submitted on 1/23/04. PI found acceptable 2/10/04. CMC found acceptable 3/29/04. Methods validation completed and acceptable per chemistry review #4.

6. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 4/12/2004
Initials /Robert L. West

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: At the time of filing APP made a paragraph III certification to the '216 patent that was due to expire on 1/29/04. Pediatric exclusivity was subsequently awarded to Pfizer for Diflucan, the RLD. On 2/26/04, APP submitted correspondence to acknowledge the expiration of the '216 patent on 1/29/04 and Pfizer's exclusivity due to expire on 7/29/04.

Plan: Issue a second tentative approval letter to APP. Final approval may be granted upon the expiration of Pfizer's pediatric exclusivity on 7/29/04.

7. Gary Buehler
Director, OGD
Date 4/12/04
Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Ted Palat
Review Support Branch
Date 4/12/04
Initials
NA Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
4:30p Time notified of approval by phone 4:30p 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/approvrou5.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-145 Applicant APP
Drug Fluvastatin Injection - Vials 100mL of 200mL 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 Initials MS	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: PII to '216 patent & has ped exclusivity exp 7/29/2004
Comments: Eligible for Full Approval on 7/29/2004

2. Project Manager, Ted Pratt Team 9 Review Support Branch	Date 06/29/04 Initials GO	Date Initials

Original Rec'd date 3-27-01
Date Acceptable for Filing 3-29-01
Patent Certification (type) II
Date Patent/Exclus.expires 7-29-04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☐ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 2-9-04
Date of Office Bio Review 5-24-03
Date of Labeling Approv. Sum 3-15-02
Date of Sterility Assur. App. 8-2-02
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☒ Date 4-12-04
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

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

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments:	w CMC review beyond below comments	Date 7/28/04 Initials RCR

REVIEWER: FINAL ACTION

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

Date__________
Initials_______

RLD=Diflucan Injection (in Sodium Chloride 0.9%) NDA 19-950(001)
Pfizer Inc.
200mg/100mL and 400mg/200mL
single-dose vials

6. Vacant
Deputy Dir., DLPS

Date__________
Initials_______

7. Peter Rickman
Director, DLPS

Date 7/27/04 for
Initials [signature]

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 2/9/04 (verified 7/27/04). No OAI alerts noted. Refer to the administrative sign-off forms completed at the time of the tentative approvals issued on 4/15/03 and 4/12/04. On 5/12/04 APP submitted a minor amendment to request final approval effective 7/29/04. APP stated that no changes were made to the CMC section or FPL since the prior tentative approval. FPL acceptable for final approval 7/19/04. CMC acceptable for approval 1/16/04. Methods validation has been completed and found acceptable.

8. Robert L. West
Deputy Director, OGD

Date 7/27/2004
Initials Robert West

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments: APP made a paragraph II certification to the '216 patent that expired on 1/29/04. However, the '216 patent was effectively extended until 7/29/04 upon the granting of pediatric exclusivity to Pfizer. APP revised its patent certification to a paragraph II certification and has acknowledged Pfizer's period of pediatric exclusivity. This ANDA is recommended for final approval upon the expiration of Pfizer's exclusivity on 7/29/04.

9. Gary Buehler
Director, OGD
Comments:

Date 7/29/04
Initials [signature] for

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

10. Project Manager, Team Ed Rabt
Review Support Branch

Date 7/29/04
Initials [initials]

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10am Time notified of approval by phone 10am Time approval letter faxed
FDA Notification:
7/29 10am Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/29 10am Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-145

CORRESPONDENCE

AMERICAN PHARMACEUTICAL PARTNERS, INC.

4/3/01 Ack for filing! Middleton

Concur. 25-APR-2001

March 27, 2001

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

CENTER FOR DRUGS RECEIVED MAR 29 2001 OGD EVALUATION AND RESEARCH

Re: Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200-mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL
Number of Volumes: 5 Volumes

ORIGINAL ANDA

Dear Mr. Buehler:

This Abbreviated New Drug Application is submitted in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Fluconazole Injection. The reference listed drug is DIFLUCAN®, manufactured by Pfizer Inc.

American Pharmaceutical Partners, Inc. will manufacture this product in manufacturing facilities located at 2020 Ruby Street, Melrose Park, IL 60160. This application contains all the information required describing the chemistry, manufacturing and control of Fluconazole Injection. This application contains a request for the waiver of *in vivo* bioequivalence studies. **This application also contains microbiology and sterility assurance information, which is provided in Section XXII.**

The application has been formatted according to the information in the Guidance for Industry: Organization of an ANDA, dated February 1999. An Executive Summary explaining the organization of this application is included after the cover letter. The application consists of 5 volumes.

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

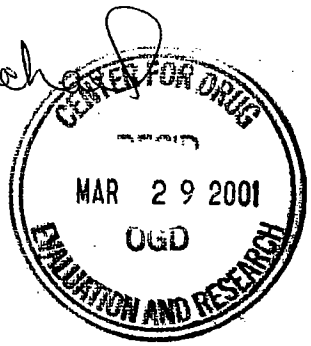
American Pharmaceutical Partners Inc. is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the ANDA, and a technical review copy (in a red folder) which contains all of the information in the archival copy with the exception of the bioequivalence section (Section VI). Three copies of the analytical methods validation section are included in red folders. Four copies of the draft labeling are included in both the archival and the review copies. A separate copy of the bioequivalence section is provided in an orange folder. The bioequivalence section consists of a request for a waiver from the need to conduct a bioequivalence study.

Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this Abbreviated New Drug Application is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606. We certify that the Field Copy is a true and complete copy of this Abbreviated New Drug Application.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(708) 547-3617** or Dale Carlson, Associate Director, Regulatory Affairs, at **(708) 547-2373**.

Sincerely,

Lincy Michael
Senior Regulatory Scientist



AMERICAN PHARMACEUTICAL PARTNERS, INC.

April 19, 2001

ARCHIVAL

NEW CORRESP
NC

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

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200-mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to the April 19, 2001 telephone discussion between Ms. Saundra Middleton of the FDA and Ms. Lincy Michael of American Pharmaceutical Partners, Inc. (APP). As discussed during the telephone conversion, we have revised the Form FDA 356h to clarify the name of the reference listed drug product from DIFLUCAN® to DIFLUCAN® in Sodium Chloride 0.9%. The revised 356h Form is included in this submission.

In compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this submission is being provided to Mr. Raymond V. Mlecko, District Director, FDA Chicago District Office. We certify that the Field Copy is a true and complete copy of this submission.

Should you have any questions or require additional information concerning this submission, please contact the undersigned at **(708) 547-3617** or Dale Carlson, Associate Director, Regulatory Affairs, at **(708) 547-2373**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 2 0 2001
OGD

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

ANDA 76-145

American Pharmaceutical Partners, Inc.
Attention: Lincy Michael
2045 North Cornell Avenue
Melrose Park, IL 60160

APR 26 2001

Dear Madam:

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

Reference is also made to the telephone conversation dated April 19, 2001 and your correspondence dated April 19, 2001.

NAME OF DRUG: Fluconazole in Sodium Chloride 0.9% Injection, 2 mg/mL, 100 mL and 200 mL vials

DATE OF APPLICATION: March 27, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 29, 2001

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

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

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-145
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 date 25-APR-2001
HFD-615/SMiddleton, CSO date 4/23/01
Word File
V:\FIRMSAM\APP\LTRS&REV\76145.ACK
F/T EEH 04/23/01
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

AMERICAN PHARMACEUTICAL PARTNERS, INC.

July 13, 2001

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

N/AA
ORIG AMENDMENT

ARCHIVAL

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 17 2001
OGD

Re: **ANDA 76-145**
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

AMENDMENT TO THE ORIGINAL APPLICATION

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment to make minor revisions to the Active Pharmaceutical Ingredient (API) specifications for Fluconazole, and to provide the correct sample chromatogram for the finished product impurity analysis.

APP identified the above issues while addressing questions from the FDA Field Inspector during the May, 2001 pre-approval inspection of the Fluconazole Injection ANDA. The following changes are made to the Fluconazole API specifications:

- [redacted]
- [redacted]

and is included in **Attachment 1**.

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

Redacted 1 page(s)

of trade secret and/or

confidential commercial

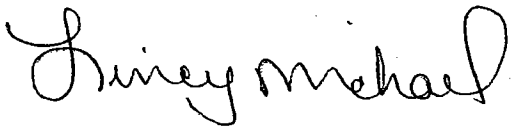
information from

7/13/2001 APP LETTER

In compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 547-3617** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 547-2373**.

Sincerely,



Lincy Michael
Sr. Regulatory Scientist

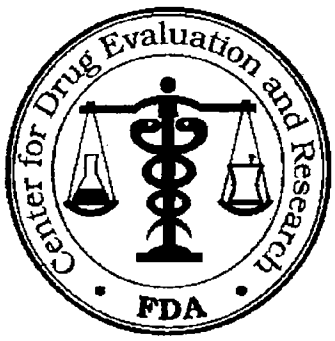
**APPEARS THIS WAY
ON ORIGINAL**

MINOR AMENDMENT

ANDA 76-145

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)

SEP 17 2001



TO: APPLICANT: American Pharmaceutical Partners, Inc.

ATTN: Lincy Michael

TEL: 708-547-3617

FAX: 708-343-4269

PROJECT MANAGER: 301-827-5849

FROM: Jeen Min

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL.

Reference is also made to your amendment(s) dated: July 13, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 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 & Labeling deficiencies with Bio comments.

jm 9/14/01

SEP 17 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 76-145 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL in 100 ml vial & 200 ml vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

Regarding raw material control, we have the following comments:

A. Please submit a [redacted] specification for Fluconazole.

B. The limits for [redacted] specifications for the drug substance and drug product appear [redacted] by the submitted data. Please revise the limits based on data accrued to date.

C. DMF [redacted] was found to be inadequate. The holder has been notified of the deficiencies.

Sincerely yours,

Yolayat Bayiw

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

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

ANDA Number: 76-145 Date of Submission: March 27, 2001

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Fluconazole Injection , 2 mg/mL

Labeling Deficiencies:

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

   a. We believe that your products are designed to be hung for intravenous infusion. Please explain how the bottles will be hung and submit information regarding your hanging devices.

   b. We ask that you relocate the phrase "Sterile Solution in 0.9% Sodium Chloride Injection" to appear immediately beneath the established name.

   c. Relocate the route of administration to appear immediately beneath the expression of strength.

2. INSERT

   a. TITLE

      Include "Sterile Solution in 0.9% Sodium Chloride Injection" beneath the statement "FOR INTRAVENOUS INFUSION ONLY" as found on your container labels.

   b. CLINICAL PHARMACOLOGY (Drug Interaction Studies)

      i. Cyclosporine - Second sentence:

         ...following the administration of fluconazole. [add "the"]

      ii. Terfenadine - Last sentence:

         ...at 400 mg and 800 mg daily... [delete a hyphen]

   c. INDICATIONS AND USAGE

      i. First sentence:

         Fluconazole injection is... [add "injection"]

      ii. Item #3

         ...please see CLINICAL STUDIES section. [add "section"]

d. PRECAUTIONS

i. Use the term "times" rather than the symbol "x" throughout this section.

ii. Delete the subsection " [redacted] " in its entirety.

iii. Drug Interactions - Tacrolimus - Last sentence:

...in the CLINICAL PHARMACOLOGY section have not... [add "section"]

iv. Pregnancy (Teratogenic Effects, Pregnancy Category C) - Last paragraph, second sentence:

...with high dose (400 to 800 mg/day) fluconazole... [use "to" rather than a hyphen]

e. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults

a. Delete the sub-subsection heading " [redacted] ".

b. Prophylaxis inpatients undergoing bone marrow transplantation - Last sentence:

Revise to read "cu mm^3" rather than "cu mm". [2 places]

ii. Dosage and Administration in Children (Esophageal candidiasis) - Last sentence:

Patients with... [delete an apostrophe]

iii. Dosage in Patients with Impaired Renal Function (Administration) - First sentence:

Fluconazole injection has... [add "injection"]

f. HOW SUPPLIED

i. Revise to read as follows:

Fluconazole Injection in glass bottles, containing 200 mg of fluconazole in 100 mL of 0.9% sodium chloride injection, in packages of –.

Fluconazole Injection in glass bottles, containing 400 mg of fluconazole in 200 mL of 0.9% sodium chloride injection, in packages of –

ii. We encourage that you increase the prominence of the statement "Protect from freezing.".

iii. We ask that you include the following statement as found on your container labels.

NOTE: Any unused portion should be immediately discarded.

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 # 76-145 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Fluconazole in Sodium Chloride 0.9%
2 mg/mL, 100 and 200 mL vials

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

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

Sincerely yours,

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

BIOAVAILABILITY

October 30, 2001

ORIG AMENDMENT

ARCHIVAL

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

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

MINOR AMENDMENT

Response to Chemistry, Labeling and Bioequivalence Comments

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to the attached September 17, 2001 Minor Deficiency to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to each of the comments made in the minor deficiency. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

In compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, FDA Chicago District Office.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 07 2001
RECEIVED

11-9-01

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

********** -COMM. JOURNAL- ********** DATE DEC-18-2001 ***** TIME 11:06 *********

MODE = MEMORY TRANSMISSION START=DEC-18 11:05 END=DEC-18 11:06

FILE NO.=002

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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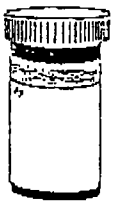
Fax Cover Sheet



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

Date: Dec 18, 01

To: Lincy Michael

Phone: 708-486-2117 Fax: 708-343-4269

From: Chon Park

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments: ANDA 76-145
Labeling comments per telecon,
Thanks

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

ANDA Number: 76-145 Date of Submission: October 30, 2001

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Fluconazole Injection , 2 mg/mL

Labeling Deficiencies:

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

   On principal display panel, relocate expression of strength, 200 mg/100 mL* (2 mg/mL) to immediately follow the established name, Fluconazole Injection.

2. INSERT

   1. GENERAL

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

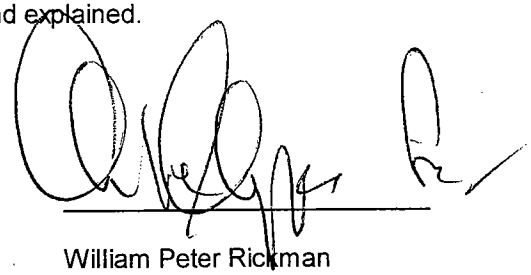
   2. PRECAUTIONS (Carcinogenesis...Fertility) - Third paragraph, second sentence:

      Use the term "times" rather than the symbol "x" . ["15 times" rather than "15x"]

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

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



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

APPEARS THIS WAY
ON ORIGINAL

AMERICAN PHARMACEUTICAL PARTNERS, INC.

January 15, 2002

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

N/A

CMC AMENDMENT

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL
Number of Volumes: 1 Volume

LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to our October 30, 2001 response to the FDA's Minor Chemistry, Labeling and Bioequivalence deficiency letter dated September 17, 2001. Further reference is made to the attached December 18, 2001 FDA labeling comments to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to the labeling comments made in the December 18, 2001 FDA communication. Provided in **Attachment 1** are four (4) draft copies of the revised container labels and package insert. A detailed, annotated side-by-side comparison between the proposed and the existing labels and labeling is included in **Attachment 2**.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2115** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 16 2002

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

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: APP

ATTN: ~~Jonathan Dohnalek~~ Gerry Cruz

FROM: Jeen Min

TEL: 708-486-2115

FAX: 708-343-4269

PROJECT MANAGER: 301-594-0338

Number of pages: 2
(excluding the cover sheet)

Comments:

Microbiology deficiencies for ANDA 76-145 (Fluconazole Injection).

1/18/02

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

1/18/2002 FDA FAX

7. [ ]

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

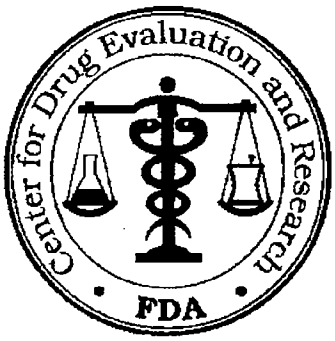
APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 76-145

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)

FEB - 1 2002



486-2115

TO: APPLICANT: American Pharmaceutical Partners, Inc.

TEL: 708-~~547-3617~~

FAX: 708-343-4269

ATTN: Genny Cruz

PROJECT MANAGER: 301-827-5849

FROM: Jeen Min

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection).

Reference is also made to your amendment(s) dated: July 13 and October 30, 2001; and January 15, 2002.

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:

Enclosed are Chemistry and Labeling Deficiencies.

Jm 2/1/02

FEB - 1 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA 76-145 Applicant: American Pharmaceutical Partners, Inc.

Drug Product: Fluconazole Injection, 2 mg/mL in 100 mL vial & 200 mL vial

The deficiency presented below represent a Minor deficiency.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated January 18, 2002 regarding deficiencies in the microbiology section of your application and the accompanying labeling deficiencies. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding microbiology deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

for

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

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

ANDA Number: 76-145 Date of Submission: January 15, 2002

Applicant's Name: American Pharmaceutical Partners, Inc.

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

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

   a. We note that the expression of strength on the principal display panel does not appear sufficiently prominent, the white print on the dark blue or orange background. Please increase the prominence of the text by changing the background color and/or any other means.

   b. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. INSERT (DOSAGE AND ADMINISTRATION, Dosage and Administration in Adults, Prophylaxis in...transplantation)

   Revise to read "per cu mm" or "per mm^3". [2 instances]

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

February 11, 2002

N/AS
ORIG AMENDMENT
ARCHIVAL

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

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Further reference is made to the attached January 18, 2002 Microbiology Deficiency to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to each of the comments made in the microbiology deficiency. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

In compliance with 21 CFR § 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to the acting District Director, FDA Chicago District Office.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 12 2002
OGD

Sincerely,

Leslie Sands

Leslie Sands
Senior Regulatory Scientist

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

March 7, 2002

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

ORIG AMENDMENT

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL
Number of Volumes: 1 Volume

MINOR AMENDMENT

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to the attached February 1, 2002 FDA labeling comments to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to the labeling comments made in the February 1, 2002 FDA communication. Provided in **Attachment 1** are four (4) draft copies of the revised container labels and package insert. A detailed, annotated side-by-side comparison between the proposed and the existing labels and labeling is included in **Attachment 2**.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Leslie Sands
Senior Regulatory Scientist

RECEIVED
MAR 1 1 2002
OGD / CDER

3/11/02

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

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AMERICAN PHARMACEUTICAL PARTNERS, INC.

2002

March 17, 2002

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

ARCHIVAL

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

TELEPHONE AMENDMENT

DRUG AMENDMENT
N/AM

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Further reference is made to telephone conversations between APP and FDA on 3/4/03 and on 3/06/03 regarding chemistry comments to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this telephone amendment in response to each of the comments made in the conversations. For ease of review, each of the reviewer's comments are provided in bold, followed by APP's response.

In compliance with 21 CFR § 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to the acting District Director, FDA Chicago District Office.

Should you have any questions or require additional information concerning this telephone amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Leslie Sands

Leslie Sands
Senior Regulatory Scientist

RECEIVED
MAR 18 2003
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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: APP

TEL: 708-486-2117

ATTN: Leslie Sands

FAX: 708-343-4269

FROM: Jeen Min

PROJECT MANAGER: 301-594-0338

Number of pages: 1
(excluding the cover sheet)

Comments:

Microbiology deficiencies for ANDA 76-145 (Fluconazole Injection).

Jm 4/22/02

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

4/22/2002 FDA FAX

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

June 5, 2002

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

N/AS

ORIG AMENDMENT

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Further reference is made to the attached April 22, 2002 Microbiology Deficiency letter to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to each of the comments made in the microbiology deficiency. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

In compliance with 21 CFR § 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to the acting District Director, FDA Chicago District Office.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Leslie Sands
Senior Regulatory Scientist

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JUN 0 6 2002
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MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
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MINOR AMENDMENT

ANDA 76-145

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)

AUG 27 2002

TO: APPLICANT: American Pharmaceutical Partners, Inc.

TEL: 708-486-2117

FAX: 708-343-4269

ATTN: Leslie Sands

PROJECT MANAGER: 301-827-5849

FROM: Jeen Min

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole Injection, 2 mg/mL (in 0.9% Sodium Chloride Injection).

Reference is also made to your amendment(s) dated: February 11, March 7, and June 5, 2002.

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

Jm 8/27/02

AUG 27 2002

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 76-145 APPLICANT: American Pharmaceutical Partners, Inc.
DRUG PRODUCT: Fluconazole Injection 200 mg in 100-ml vial & 400 mg in 200-ml vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. [redacted]

2. DMF # [redacted] as revised is deficient. Please contact the DMF holder for possible changes in [redacted] specifications.

Sincerely yours,

for Silayat Fang

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

November 15, 2002

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

ARCHIVAL

ORIG AMENDMENT

N/am

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

MINOR AMENDMENT

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Further reference is made to the attached August 27, 2002 Chemistry Deficiency letter to this application.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to each of the comments made in the chemistry deficiency. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

In compliance with 21 CFR § 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to the acting District Director, FDA Chicago District Office.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2117** or Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-2071**.

Sincerely,

Leslie Sands
Senior Regulatory Scientist

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NOV 1 8 2002
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11-19

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

Sent to label
12/12/03

AMERICAN PHARMACEUTICAL PARTNERS, INC.

November 24, 2003

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

ARCHIVAL

ORIG AMENDMENT
N/AM

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

MINOR AMENDMENT
FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to the attached April 15, 2003 tentative approval letter received for this ANDA.

ANDA 76-145 contains a paragraph III certification to the U.S. patent 4,404,216 (the '216 patent) under section 505(j) (2) (A) (vii) of the Act stating that American Pharmaceutical Partners (APP) will not market this drug product prior to the January 29, 2004 expiration of the '216 patent. Therefore APP requests final approval of the application on January 29, 2004, pursuant to 21 U.S.C. 355 (j) (5) (B) (ii) of the Act.

As described in the tentative approval letter, APP hereby submits this minor amendment to inform the Agency that APP has made no changes related to the Chemistry, Manufacturing and Controls data for ANDA 76-145, and to request final approval for this ANDA.

APP has made the following minor changes in the final printed labeling for Fluconazole Injection:

Vial label: The positioning of the volume graduation lines has been adjusted for increased accuracy.

Tray label: A new tray label has been added for use on tray packs of ten vials. The tray label contains the same information as the vial label except for the graduation lines, bar code and patient information, which are not present in the tray label.

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NOV 25 2003
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MELROSE PARK, IL 60160-1002

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www.appdrugs.com

Package insert: The How Supplied section has been revised to indicate the new tray pack of ten vials.

In addition, all labeling has been revised to indicate APP's change in corporate address from Los Angeles, CA to Schaumburg, IL.

Final Printed Labeling (FPL) is provided in **Attachment 1** for the revised vial label, tray label and package insert. Twelve (12) copies of the FPL are provided in the FDA review copy of the submission. A detailed annotation of the differences between the proposed labeling and the existing labeling is provided in **Attachment 2**.

Furthermore, in compliance with 21 CFR 314.96 (b), a true and complete copy (the Field Copy) of this amendment is being provided to Arlyn Baumgarten, Director, Chicago District, Food and Drug Administration, 550 W. Jackson, Suite 1500, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2071** or Ivy Chung, Supervisor, Regulatory Affairs at **(708) 486-2137**.

Sincerely,

Dale Carlson

Dale Carlson
Associate Director, Regulatory Affairs

AMERICAN PHARMACEUTICAL PARTNERS, INC.

January 23, 2004

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

TELEPHONE AMENDMENT
Labeling Deficiency

ORIG AMENDMENT
N/AF
ARCHIVAL

Re: ANDA 76-145
Fluconazole Injection, 2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145 and to our Minor Amendment – Final Approval Requested, dated November 24, 2003.

Reference is also made to the telephone conversations between Mr. Chan Park of FDA and Ms. Ivy Chung of American Pharmaceutical Partners Inc. (APP), during which Mr. Park requested APP to submit a Telephone Amendment for minor labeling deficiencies:
1) Container labels need to have net quantity, 100 mL or 200 mL
2) Tray labels need to have net quantity, 10 vials/tray or 10x100 mL per tray
Twelve (12) copies of the Final Printed Labeling (FPL) should be submitted.

American Pharmaceutical Inc. (APP) has added the net quantities to its vial labels.

Twelve (12) copies of FPL for the revised vial label: with the net quantity at the bottom right-hand corner of the label's main panel, are provided in **Attachment 1.**

A copy of the tray label's drawings with packaged quantity are provided in **Attachment 2.** Per agreement with Mr. Park, the Tray Labels submitted in our Minor Amendment dated November 24, 2003, remain the same. The drawings (bar code tray labels) are printed on-line by a bar code software system, which does not allow for text or layout changes. The trays will be labeled with both the bar code tray labels and the pre-printed tray labels.

RECEIVED
JAN 27 2004
OGD/CDER

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

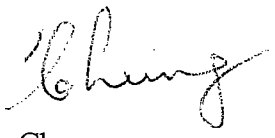
MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

An annotation of the differences between the proposed labeling and the submitted labeling is provided in **Attachment 3.**

In compliance with 21 CFR 314.96 (b), a true and complete copy (Field Copy) of this amendment is being provided to Arlyn Baumgarten, Director, Chicago District, Food and Drug Administration, 550 W. Jackson, Suite 1500, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2137** or Mr. Dale Carlson, Associate Director, Regulatory Affairs at **(708) 486-207**1.

Sincerely,



Ivy Chung
American Pharmaceutical Partners Inc.,
Regulatory Affairs Department
Supervisor

APPEARS THIS WAY
ON ORIGINAL

AMERICAN PHARMACEUTICAL PARTNERS, INC.

per FED addressed to 21/6 for S. Middleton

February 26, 2004

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

ARCHIVAL

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

PATENT AMENDMENT

NEW CORRESP

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Further reference is made to the telephone communication from Martin Shimer, FDA, to Dale Carlson, APP, dated February 24 , 2004.

As advised by FDA during the February 24, 2004 telephone communication, American Pharmaceutical Partners, Inc. hereby amends the patent certification to include recognition of the expiration of patent 4404216 and the pediatric exclusivity granted to the reference listed drug holder. The revised patent certification is provided in **Attachment 1**.

In compliance with 21 CFR § 314.96(b), a true and complete copy of this amendment is being provided to the Chicago District Office, FDA.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2071** or Kathleen Dungan, Senior Regulatory Scientist, at **(708) 486-2024**.

Sincerely,

RECEIVED
FEB 27 2004
OGD/CDER

Dale Carlson
Associate Director, Regulatory Affairs

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

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AMERICAN PHARMACEUTICAL PARTNERS, INC.

ORIGINAL

May 12, 2004

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

NIAM

ARCHIVAL

Re: ANDA 76-145
Fluconazole Injection
2 mg/mL
100 mL fill in 100 mL vial (Code 300861)
200 mL fill in 200 mL vial (Code 300863)
Manufacturing Site: Melrose Park, IL

MINOR AMENDMENT
FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Reference is made to our March 27, 2001 submission of an original Abbreviated New Drug Application (ANDA) for Fluconazole Injection, ANDA # 76-145. Reference is also made to the attached April 12, 2004 tentative approval letter received for this ANDA.

ANDA 76-145 originally contained a paragraph III certification to the U.S. patent 4,404,216 (the '216 patent) under section 505(j) (2) (A) (vii) of the Act stating that American Pharmaceutical Partners (APP) would not market this drug product prior to the January 29, 2004 expiration of the '216 patent. At the Agency's request, APP amended its patent certification on February 26, 2004 to include recognition of the expiration of the '216 patent and the pediatric exclusivity granted to the reference listed drug holder. Therefore APP now requests final approval of the application on July 29, 2004, pursuant to 21 U.S.C. 355 (j) (5) (B) (ii) of the Act.

As described in the tentative approval letter, APP hereby submits this minor amendment to inform the Agency that APP has made no changes related to the Chemistry, Manufacturing and Controls data for ANDA 76-145. APP also has not made any changes to the final-printed labeling that was submitted in amendments dated November 24, 2003 and January 23, 2004.

RECEIVED
MAY 13 2004
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MELROSE PARK, IL 60160-1002

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Furthermore, in compliance with 21 CFR 314.96 (b), a true and complete copy (the Field Copy) of this amendment is being provided to the Acting Director, Chicago District, Food and Drug Administration, 550 W. Jackson, Suite 1500, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 486-2071** or Ivy Chung, Supervisor, Regulatory Affairs at **(708) 486-2137**.

Sincerely,

Dale Carlson

Dale Carlson
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL