CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-653

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letters	X
Labeling	X
Labeling Reviews	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Review	X
Statistical Review(s)	
Microbiology Review	X
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

APPROVAL LETTER

ANDA 76-653

JUL 29 2004

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to the tentative approval letters issued by this office on December 24, 2003, and May 24, 2004, and to your amendment dated May 24, 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® (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 Lewis for 1/29/2004

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

cc: ANDA 76-653
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/A.Basak/ 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 OK
7/20/04
R.C. Adams

\\CDSNAS\OGDS11\FIRMSNZ\SICOR\LTRS&REV\76653.AP.DOC

F/T by rad7/12/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

TENTATIVE APPROVAL LETTERS

ANDA 76-653

DEC 24 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to your amendments dated July 31 (2 submissions), and August 22, 2003.

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

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

stating that you will not market this drug product prior to the expiration of the '216 patent.

Please note that the expiration of the '216 patent may be effectively 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 holder submits requested information relating to the use of the drug in the pediatric population. In this case, the NDA holder, Pfizer Inc., has submitted such information to the agency. The agency is in the process of determining whether the submitted information meets the criteria stated in the statute. If the agency concludes that the submitted information does meet the criteria, the '216 patent will be granted a 6-month extension. Please contact the project manager, Ted Palat, for an update on the status of this determination.

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., currently January 29, 2004. However, the expiration of the '216 patent could be effectively extended until July 29, 2004 as noted above.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 60 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

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

status of your application, or may result in a delay in the issuance of the final approval letter.

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

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will 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 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, Project Manager, (301) 827-5849.

Sincerely yours,

Gary Buehler 12/24/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-653
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/A.Basak/ 12/16/03
HFD-647/G.Smith/ for 12/17/03 12/18/03
HFD-617/T.Palat/ 12/18/03
HFD-600/N.Nath/ 12/17/03
HFD-600/N.Sweeney/ 12-19-03
HFD-613/C.Park/12/10/03 12/19/03
HFD-613/L.Golson 12/19/03

Robert Levy 12/24/2003

V:\FIRMSNZ\SICOR\LTRS&REV\76653.TA.doc

F/T by rad12/11/03

TENTATIVE APPROVAL

cmc satisfactory 12/23/03

ANDA 76-653

MAY 24 2004

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to our letter dated December 24, 2003 granting tentative approval to this application, and to your amendment dated January 5, 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,

Robert Lee Test /for/ 5/24/2004

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

cc: ANDA 76-653
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-647/A.Basak/ 5/5/04
HFD-647/G.Smith/ 5/5/04
HFD-617/T.Palat/ 5/5/04
HFD-600/N.Nath 5/5/04
HFD-600/N.Sweeney 5-5-04
HFD-613/C.Park/4/26/04 5/6/04
HFD-613/L.Golson 5/6/04
R. C. adams 5/13/04

\\Cdsnas\OGDS11\FIRMSNZ\SICOR\LTRS&REV\76653.2ndTA.doc

F/T by rad4/30/04

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

LABELING

Package Insert

℞only

Fluconazole Injection

sicor™

Y36-000-74A

Package Insert

℞only

Fluconazole Injection

sicor™

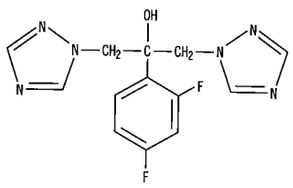
JUL 29 2004

APPROVED

DESCRIPTION

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

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



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

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

CLINICAL PHARMACOLOGY

Mode of Action

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

Pharmacokinetics and Metabolism

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

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

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

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

*Relative to concurrent concentrations in plasma in subjects with normal renal function.

† Independent of degree of meningeal inflammation.

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

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

In normal volunteers, fluconazole administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the ACTH-simulated 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)	V_{dss} (L/kg)
9 months–13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	—
9 months–13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	—
5–15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5–15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5–15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

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

In premature newborns (gestational age 26 to 29 weeks), the mean (%cv) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

Drug Interaction Studies

Oral contraceptives: Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of 50 mg of fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

In a second study, twenty-five normal females received daily doses of both 200 mg fluconazole tablets or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.

Cimetidine: Fluconazole 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC and 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 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 for 5 days. (See **CONTRAINDICATIONS** and **PRECAUTIONS.**)

Microbiology

Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*.

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. Fluconazole administered orally and/or intravenously was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies is unknown.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cr. neoformans*, and antagonism of the two drugs in systemic infection with *Asp. fumigatus*. The clinical significance of results obtained in these studies is unknown.

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

INDICATIONS AND USAGE

Fluconazole injection is indicated for the treatment of:

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

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

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

CLINICAL STUDIES

Cryptococcal meningitis: In a multicenter study comparing fluconazole (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/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 study (p=0.48). Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined (Saag, *et al.* N Engl J Med 1992; 326:83–9).

Pediatric Studies

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

PRECAUTIONS

Drug Interactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See **CLINICAL PHARMACOLOGY.**)

Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

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

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

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

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

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

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

ADVERSE REACTIONS

In Patients Receiving Multiple Doses 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 transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Immunologic: In rare cases, anaphylaxis has been reported.

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

Central Nervous System: Seizures.

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

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

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Adverse Reactions in Children

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

Percentage of Patients With Treatment-Related Side Effects

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

OVERDOSAGE

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

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

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

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

DOSAGE AND ADMINISTRATION

Dosage and Administration in Adults

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

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

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

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

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

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

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

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

Dosage and Administration in Children

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

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

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

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

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

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

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

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

Dosage In Patients With Impaired Renal Function

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

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

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

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

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

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

Fluconazole injections in glass vials 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.

DO NOT ADD SUPPLEMENTARY MEDICATION.

HOW SUPPLIED

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

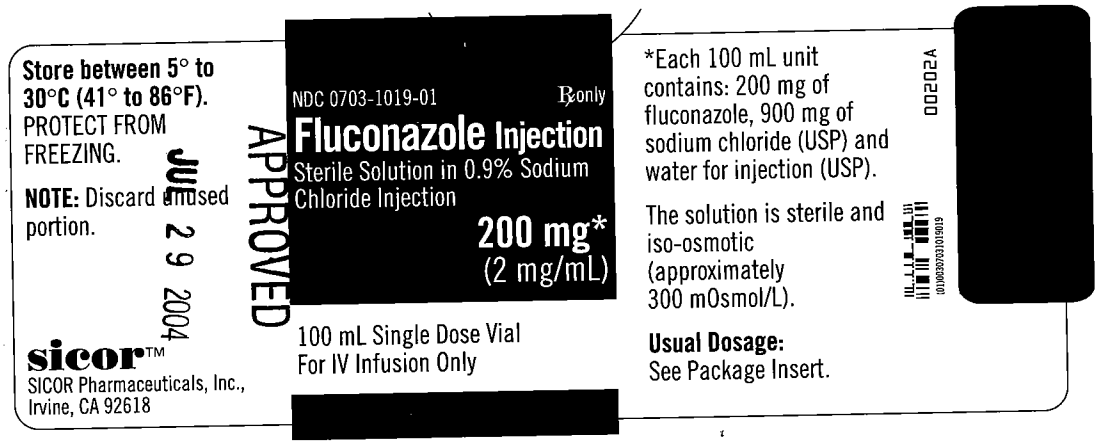
NDC Number	Contents	Package Size
0703-1019-09	200 mg	100 mL vial packaged 6 per shelf pack
0703-1010-09	400 mg	200 mL vial packaged 6 per shelf pack

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

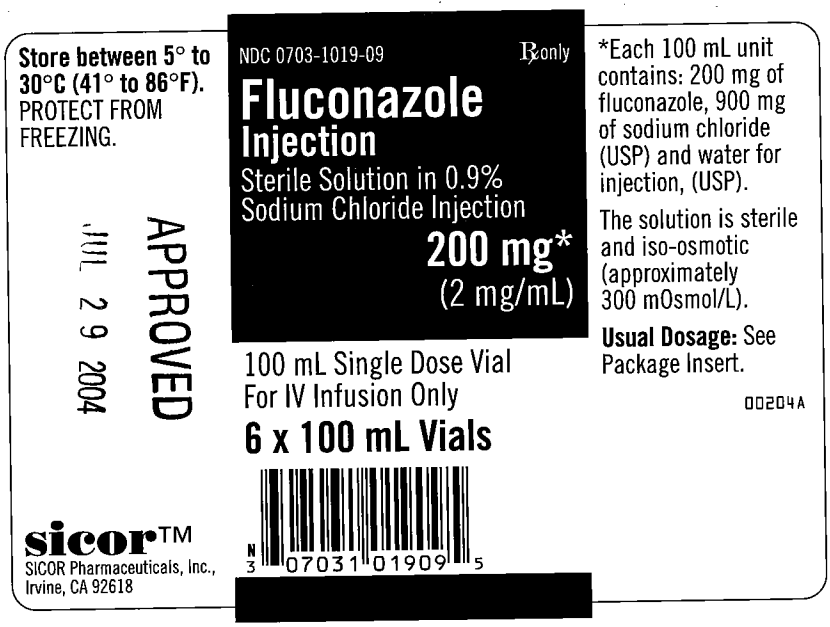
Issued: July 2003

sicor™
SICOR Pharmaceuticals, Inc.
Irvine, CA 92618

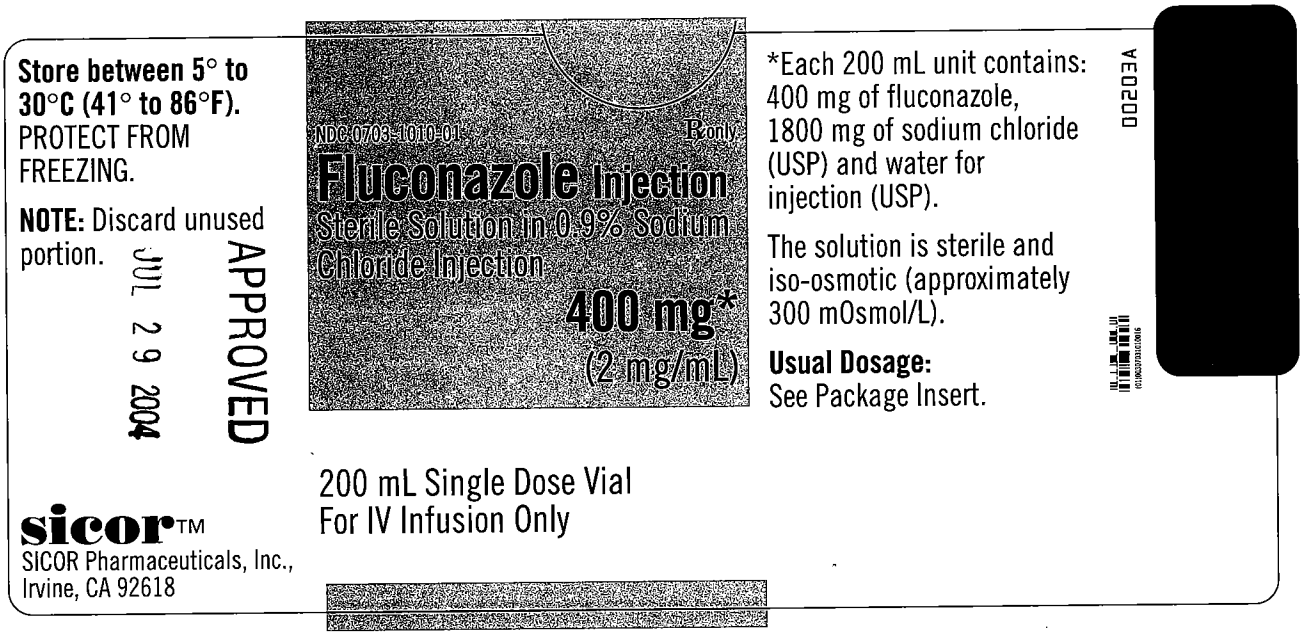
100 mL Vial Label
(Part No. Y29-002-02A)



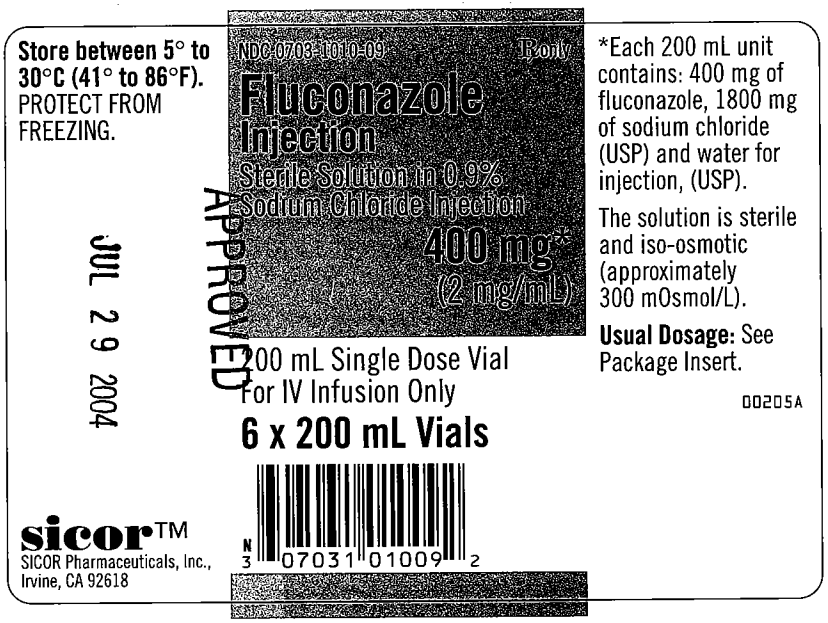
100 mL Shelf Pack Label
(Part No. Y29-002-04A)



200 mL Vial Label (Part No. Y29-002-03A)



200 mL Shelf Pack Label (Part No. Y29-002-05A)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

LABELING REVIEWS

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

ANDA Number: 76-653 Date of Submission: January 31, 2003

Applicant's Name: GensiaSicor Pharmaceuticals, Inc.

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

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

   a. Relocate the text "Sterile... Injection" to appear immediately below the established name of your drug product.

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

   c. Revise to read "Single-dose Vial".

   d. You may revise "**NOTE**: Any..." statement to read "**NOTE**: Discard unused portion.".

   e. 200 mg/100 mL

      We ask you to increase the readability of the name and place of the manufacturer by increasing the background contrast and/or any other means. The ——— print on the ——— background does not render a sufficient contrast.

2. CARTON

   See comments under CONTAINER, where applicable.

3. INSERT

   a. General

      i. Although the print size may meet the minimum requirement, we encourage you to increase this to enhance the readability of your labeling.

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

      iii. It appears that the efficacy and safety profile of the oral and injection form of fluconazole are similar to each other as the pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. Therefore, we ask that you include information related to the oral form although your drug product is injection. See comments below.

      iv. We acknowledge that you carved out all information associated with vaginal candidiasis as this is the indication specific to the 150 mg tablet only. We find this acceptable.

   b. DESCRIPTION - Second paragraph:

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

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics in Children

Relocate "(36%)", (33%), and (37%)" in the first column to the last one.

ii. Drug Interaction Studies

A) Antacid:

Please include a disclaimer for Maalox®.

B) Phenytoin - First sentence:

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

iii. Microbiology

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

d. INDICATIONS AND USAGE

Revise to read "Fluconazole injection is ...

e. PRECAUTIONS

1. Delete the subsection heading "———— ".

ii. Drug Interactions - Tacrolimus:

Retain the second paragraph "Fluconazole tablets... is presently unknown." appearing in the innovator's labeling.

iii. Carcinogenesis, Mutagenesis and Impairment of Fertility

A) Retain the first paragraph "Fluconazole showed no... hepatocellular adenomas." appearing in the innovator's labeling.

B) Include the following as the second sentence to the first paragraph you proposed:

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.

C) Second paragraph, first sentence:

...rates treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral...

f. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults:

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

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

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

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

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

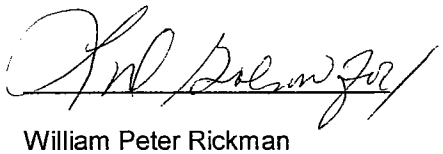
ii. Administration - First paragraph:
Fluconazole injection may be administered... [add "injection"]

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

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

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

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



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

NOTE/QUESTION TO THE CHEMIST (The following question was forwarded to the chemist via e-mail on 7/11/03)

The sponsor proposed that post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH and 5°C±3°C up to 36 months. (p.2454, B. 1.3). Considering this proposal, the firm's storage temperature statement, "Store between 86°F (30°C) and 41°F (5°C). Protect from freezing." is acceptable? This statement is identical to the one for the RLD.

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 1051 (Volume B 1.1).

4. Patent Data

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

Exclusivity Data

There is no unexpired exclusivity for this product.

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

ANDA: Same as RLD. Post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH & 5°C±3°C up to 36 months. (p.2454, B. 1.3)

6. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL & 200 mg/200 mL (in glass bottle in 0.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.1404 B. 1.1)

Vials - Flint Glass Molded 28 mm Finish USP Type I
Stopper - Gray ——— 28 mm Finish
Overseal - Aluminum Seal Flip-off Cap 28 mm Finish

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

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

Candidiasis"

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

folks,

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

Chan

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

Hi Matthew:

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

Chan

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by GensiaSicor Pharmaceuticals, Inc. (p.1098, Vol.B.1.1)

13. This drug product is packaged in the glass bottle. Consequently, it is not required to include information specifically associated with the special packaging of plastic piggy bags, *i.e.,* information on the stability of the plastic bag, Do not use in serial connections, some storage requirement specific to the plastic bag, etc.

Date of Review: 6/6/03 **Date of Submission: 1/31/03**

Primary Reviewer: Chan Park Chan Park **Date:** 7/11/03

Team Leader: [signature] **Date:** 7/16/03

---

cc:

ANDA: 76-653
DUP/DIVISION FILE
HFD-613/Cpark/Lgolson

V:\FIRMSAM\GENSIA\LTRS&REV\76653NA1.LABELING.doc
Review

APPEARS THIS WAY
ON ORIGINAL

(Superseded by the AP Summary #2 prepared 4/26/04)

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

ANDA Number: 76-653 Date of Submission: July 31, 2003

Applicant's Name: Sicor Pharmaceuticals, Inc.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes

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

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

SHELF-PACK LABEL - 6 x 100 mL & 6 x 200 mL

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1, Issued July, 2003, Code - Y36-000-74A

REVISIONS NEEDED POST-APPROVAL - INSERT:

Add the text "For Intravenous Use Only" beneath the title.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer, Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

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

OTHER COMMENTS:

NOTE/QUESTION TO THE CHEMIST (The following question was forwarded to the chemist via e-mail on 7/11/03 and 10/7/03)

The sponsor proposed that post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH and 5°C±3°C up to 36 months. (p.2454, B. 1.3). Considering this proposal, the firm's storage temperature statement, "Store between 86°F (30°C) and 41°F (5°C). Protect from freezing." is acceptable? This statement is identical to the one for the RLD.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. S-034, approved 8/4/02 is for the PPI for the 150 mg tablets only. The package insert is the combined one for the tablets, injection and oral solution.

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 1051 (Volume B 1.1).

4. Patent Data

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

Exclusivity Data

There is no unexpired exclusivity for this product.

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

   ANDA: Same as RLD. Post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH & 5°C±3°C up to 36 months. (p.2454, B. 1.3). See the comments to chemist.

6. PACKAGING CONFIGURATIONS

   RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
   ANDA – 200 mg/100 mL & 200 mg/200 mL (in glass bottle in 0.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.1404 B. 1.1)

   Vials - Flint Glass Molded 28 mm Finish USP Type I
   Stopper - Gray ——— 28 mm Finish
   Overseal - Aluminum Seal Flip-off Cap 28 mm Finish

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

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

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

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

folks,

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

Chan

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

Hi Matthew:

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

Chan

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by SICOR (formerly "GensiaSicor") Pharmaceuticals, Inc. (p.1098, Vol.B.1.1)

13. This drug product is packaged in the glass bottle. Consequently, it is not required to include information specifically associated with the special packaging of plastic piggy bags, *i.e.,* information on the stability of the plastic bag, Do not use in serial connections, some storage requirement specific to the plastic bag, etc.

14. The sponsor has changed the name to "SICOR Pharmaceuticals, Inc.".

Date of Review: 10/7/03 **Date of Submission: 7/31/03**

Primary Reviewer: Chan Park C Park **Date:** 10/8/03

Team Leader: [signature] **Date:** 10/8/03

---

cc:

ANDA: 76-653
DUP/DIVISION FILE
HFD-613/Cpark/Lgolson

V:\FIRMSNZ\SICOR\LTRS&REV\76653AP.LABELING.doc
Review

(This AP summary #2 supersedes the AP summary prepared 10/7/03)
(APPROVAL SUMMARY #2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-653 Date of Submission: July 31, 2003

Applicant's Name: Sicor Pharmaceuticals, Inc.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes

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

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

SHELF PACK LABEL - 6 x 100 mL & 6 x 200 mL

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1, Issued July, 2003, Code - Y36-000-74A

REVISIONS NEEDED POST-APPROVAL - INSERT:

Add the text "For Intravenous Use Only" beneath the title.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer, Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

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

OTHER COMMENTS:

NOTE/QUESTION TO THE CHEMIST (The following question was forwarded to the chemist via e-mail on 7/11/03 and 10/7/03)

The sponsor proposed that post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH and 5°C±3°C up to 36 months. (p.2454, B. 1.3). Considering this proposal, the firm's storage temperature statement, "Store between 86°F (30°C) and 41°F (5°C). Protect from freezing." is acceptable? This statement is identical to the one for the RLD.

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 revised PPI for the 150 mg tablets. The revision is associated with the warning on co-administration of Seldane® with fluconazole 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 1051 (Volume B 1.1).

4. Patent Data

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

Exclusivity Data

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

   ANDA: Same as RLD. Post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH & 5°C±3°C up to 36 months. (p.2454, B. 1.3). See the comments to chemist.

6. PACKAGING CONFIGURATIONS

   RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
   ANDA – 200 mg/100 mL & 200 mg/200 mL (in glass bottle in 0.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.1404 B. 1.1)

   Vials - Flint Glass Molded 28 mm Finish USP Type I
   Stopper - Gray——— 28 mm Finish
   Overseal - Aluminum Seal Flip-off Cap 28 mm Finish

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

   The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration."

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

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

folks,

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

Chan

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

Hi Matthew:

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

Chan

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by SICOR (formerly "GensiaSicor") Pharmaceuticals, Inc. (p.1098, Vol.B.1.1)

13. This drug product is packaged in the glass bottle. Consequently, it is not required to include information specifically associated with the special packaging of plastic piggy bags, *i.e.,* information on the stability of the plastic bag, Do not use in serial connections, some storage requirement specific to the plastic bag, etc.

14. The sponsor has changed the name to "SICOR Pharmaceuticals, Inc.".

Date of Review: 4/29/04 **Date of Submission: 7/31/03**

Primary Reviewer: Chan Park **Date:** 5/4/04

Team Leader: **Date:** 5/6/04

---

cc:

ANDA: 76-653
DUP/DIVISION FILE
HFD-613/Cpark/Lgolson

V:\FIRMSAM\GENSIA\LTRS&REV\76653AP#2.LABELING.doc
Review

(This AP #2 summary supersedes the AP summary prepared on 10/7/03)
(APPROVAL SUMMARY #2)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-653 Date of Submission: July 31, 2003

Applicant's Name: Sicor Pharmaceuticals, Inc.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes

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

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

SHELF PACK LABEL - 6 x 100 mL & 6 x 200 mL

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/31/03 submission (vol. 2.1, Issued July, 2003, Code - Y36-000-74A

REVISIONS NEEDED POST-APPROVAL - INSERT:

Add the text "For Intravenous Use Only" beneath the title.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer, Inc.

Date of Approval of NDA Insert and supplement #: S-028/Approved February 22, 1999.
S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.

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

Was this approval based upon an OGD labeling guidance? No

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

OTHER COMMENTS:

NOTE/QUESTION TO THE CHEMIST (The following question was forwarded to the chemist via e-mail on 7/11/03 and 10/7/03)

The sponsor proposed that post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH and 5°C±3°C up to 36 months. (p.2454, B. 1.3). Considering this proposal, the firm's storage temperature statement, "Store between 86°F (30°C) and 41°F (5°C). Protect from freezing." is acceptable? This statement is identical to the one for the RLD.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-039 approved 3/24/04 is specifically related to the approval of revised PPI for the 150 mg tablets.

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

3. 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 1051 (Volume B 1.1).

4. Patent Data

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

Exclusivity Data

There is no unexpired exclusivity for this product.

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

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

   ANDA: Same as RLD. Post-approval stability test will be performed at 27.5°C ± 2.5°C/40% ± 5% RH & 5°C±3°C up to 36 months. (p.2454, B. 1.3). See the comments to chemist.

6. PACKAGING CONFIGURATIONS

   RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
   ANDA – 200 mg/100 mL & 200 mg/200 mL (in glass bottle in 0.9% Sodium Chloride injection)

7. CONTAINER/CLOSURE (P.1404 B. 1.1)

   Vials - Flint Glass Molded 28 mm Finish USP Type I
   Stopper - Gray ——— 28 mm Finish
   Overseal - Aluminum Seal Flip-off Cap 28 mm Finish

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

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

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

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

folks,

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

Chan

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

Hi Matthew:

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

Chan

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

Question:

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

Chan

Answer:

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

Imo (Ibia, Ekopino)

12. This drug product is solely manufactured by SICOR (formerly "GensiaSicor") Pharmaceuticals, Inc. (p.1098, Vol.B.1.1)

13. This drug product is packaged in the glass bottle. Consequently, it is not required to include information specifically associated with the special packaging of plastic piggy bags, *i.e.,* information on the stability of the plastic bag, Do not use in serial connections, some storage requirement specific to the plastic bag, etc.

14. The sponsor has changed the name to "SICOR Pharmaceuticals, Inc.".

Date of Review: 7/8/04 **Date of Submission: 7/31/03**

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

Team Leader: **Date:** 7/15/04

---

cc:

ANDA: 76-653
DUP/DIVISION FILE
HFD-613/Cpark/Lgolson

V:\FIRMSNZ\SICOR\LTRS&REV\76653AP#2.LABELING.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

CHEMISTRY REVIEWS

ANDA 76-653

Fluconazole Injection
2 mg/mL

Gensia Sicor Pharmaceuticals, Inc.

Arup K. Basak, Ph. D.
OGD - Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-653

2. REVIEW #: 1

3. REVIEW DATE: June 13, 2003

4. REVIEWER: Arup K. Basak, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date

7. NAME & ADDRESS OF APPLICANT:

Name:	Gensia Sicor Pharmaceuticals, Inc.
Address:	19 Hughes Irvine CA 92618 – 1902 USA
Representative:	Rosalie A. Lowe, Director, Regulatory Affairs
Telephone:	949-457-2808 949- 583 - 7351 (Fax)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Diflucan® in 0.9% Sodium Chloride
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Diflucan® in Sodium Chloride 0.9%, manufactured by Pfizer.
Applicant: Pfizer Laboratories NDA # 19-950 (001)
Approval Date: January 29, 1990

There is unexpired patent for this product. US Patent No. 4,404,216 will expire on January 29, 2004. Paragraph III certification is appended on page 1012. There is no unexpired exclusivity for this product in electronic orange book (page 1012).

10. PHARMACOL. CATEGORY:

Antifungal; Indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis.

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 2 mg/mL (200 mg/100 mL and 400 mg /200 mL)

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

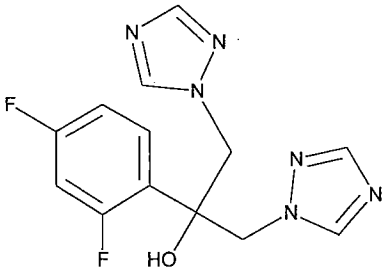
_____SPOTS product – Form Completed

__X___Not a SPOTS product

Chemistry Review Data Sheet

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

FLUCONAZOLE: $C_{13}H_{12}F_2N_6O$: **M.W. 306.28:** **CAS No: 86386-73-4**



Chemical Name: 1) 2,4-Difluoro-α,α-bis(1H-1,2,4,triazol-1-yl)methyl)benzyl alcohol
α-(2,4-difluorophenyl)- α-(1H-1,2,4-Triazol-1-yl)methyl)1H-1,2,4-Triazole-1-ethanol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: **NOT SATISFACTORY**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	**Inadequate** as per Rajagopalan, R	5/23/03	LOA & appointment of RS Rep. p.1055-1056
[redacted]	III			3	Adequate		LOA p.# 1561

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	6/18/03	
Methods Validation	To be initiated		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-653

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

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

N/A

II. Summary of Chemistry Assessments

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

Fluconazole is a synthetic broad-spectrum fluorinated bis-triazole antifungal agent. It may exist in three anhydrous polymorphic forms and a monohydrate form. The monohydrate form is formed when the DS is exposed to Relative Humidity higher than 70%. The water solubility is 0.5%. There is no USP monograph for the drug substance. In addition, the drug substance is dissolved in water for injection, polymorphs should not be a concerns for this ANDA.

The drug substance is manufactured and supplied by ——— , whose parent company is ——— located at ———. The drug substance appears as a white crystalline powder as reported in the Certificate of Analysis.

The drug product is manufactured by compounding Fluconazole and Sodium Chloride in water for injection (WFI). Besides API, the compounding ingredients are either USP or NF. The finished drug product is packaged in 100 mL and 200 mL vials

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

Upon review of this ANDA, deficiencies regarding updated specification and release report of API, in-process control specifications, and controls for release and stability and other missing regulatory documentation were identified. MINOR.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-647/AKBasak/6/28/03

HFD-647/GJSmith/7/1/03

HFD-617/TPalat/

C. CC Block

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

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

1. Please note that using the same Lot Number for the "Compounded Lot" and for "100 mL Fill/100 mL Vial" is confusing. We recommend using different identification number for all future production/validation batches.

2. A method validation request will be sent to an FDA laboratory. Once samples have been requested, any modification to the method in response to any of the deficiencies listed above should also be communicated to the laboratory.

Sincerely yours,

7/8/03

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/AKBasak/6/28/03

HFD-647/GJSmith/7/1/03 7/3/03

HFD-617/TPalat/ 7/3/03

F/T by rad7/2/03

V:\FIRMSAM\GENSIA\LTRS&REV\76653Ncr1.RAB

TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-653

Fluconazole Injection
2 mg/mL

Gensia Sicor Pharmaceuticals, Inc.

Arup K. Basak, Ph. D.
OGD - Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-653

2. REVIEW #: 2

3. REVIEW DATE: November 4, 2003 and December 1, 2003

4. REVIEWER: Arup K. Basak, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
General Correspondence: Change of Corporate Company Name.	July 2, 2003
Original Amendment	July 31, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Sicor Pharmaceuticals, Inc.
Address:	19 Hughes Irvine CA 92618 – 1902 USA
Representative:	Rosalie A. Lowe, Director, Regulatory Affairs
Telephone:	949-457-2808 949- 583 - 7351 (Fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Diflucan® in 0.9% Sodium Chloride
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Diflucan® in Sodium Chloride 0.9%, manufactured by Pfizer.
Applicant: Pfizer Laboratories NDA # 19-950 (001)
Approval Date: January 29, 1990

There is unexpired patent for this product. US Patent No. 4,404,216 will expire on January 29, 2004. Paragraph III certification is appended on page 1012. There is no unexpired exclusivity for this product in electronic orange book (page 1012).

10. PHARMACOL. CATEGORY:

Antifungal; Indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis.

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 2 mg/mL (200 mg/100 mL and 400 mg /200 mL)

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X__Rx ___OTC

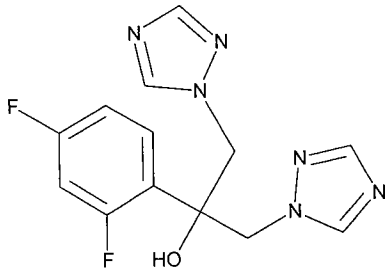
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

FLUCONAZOLE: $C_{13}H_{12}F_2N_6O$: **M.W. 306.28:** **CAS No: 86386-73-4**



Chemical Name: 1) 2,4-Difluoro-α,α-bis(1H-1,2,4,triazol-1-yl)methyl)benzyl alcohol
α-(2,4-difluorophenyl)- α-(1H-1,2,4-Triazol-1-yl)methyl)1H-1,2,4-Triazole-1-ethanol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: **NOT SATISFACTORY**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	**Adequate** as per Rajagopalan, R	09/17/03	LOA & appointment of RS Rep. p.1055-1056
	III			3	Adequate		LOA p.# 1561

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	08/28/03	Nrapendra Nath
EES	Acceptable	06/18/2003	
Methods Validation	New Method Validation procedure was followed.		
Labeling	Acceptable	10/8/03	
Bioequivalence	Bio Waiver Granted	09/03/03	S. P. Shrivastava
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-653

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE .

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

N/A

II. Summary of Chemistry Assessments

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

Fluconazole is a synthetic broad-spectrum fluorinated bis-triazole antifungal agent. It may exist in three anhydrous polymorphic forms and a monohydrate form. The monohydrate form is formed when the DS is exposed to Relative Humidity higher than 70%. The water solubility is 0.5%. There is no USP monograph for the drug substance. In addition, the drug substance is dissolved in water for injection, polymorphs should not be a concerns for this ANDA.

The drug substance is manufactured and supplied by ———— , whose parent company is ———— located at ————The drug substance appears as a white crystalline powder as reported in the Certificate of Analysis.

The drug product is manufactured by compounding Fluconazole and Sodium Chloride in water for injection (WFI). Besides API, the compounding ingredients are either USP or NF. The finished drug product is packaged in 100 mL and 200 mL vials

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

Upon review of this ANDA, deficiencies regarding updated specification and release report of API, in-process control specifications, and controls for release and stability and other missing regulatory documentation were identified. MINOR.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

AKBasak/12/1/03
GJSmith/12/2/03 D Roselle for 12/17/03

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

32. LABELING

Acceptable 10/8/03

33. ESTABLISHMENT INSPECTION

Overall acceptable as of March 28, 2003.

34. BIOEQUIVALENCE

A request for a waiver of *In-vivo* studies is included in page 1047.

The waiver of Bioequivalence study requirement is granted as of September 3, 2003.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm seeks categorical exclusion under 21 CFR § 25.31 (a) and (b). The firm also states that they are in compliance with applicable Federal, State and local environmental laws (p. 2515).

cc: ANDA 76-653
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/AKBasak/12/1/03

HFD-647/GJSmith/12/2/03 D Roselle for 12/17/03 12/18/03

HFD-615/TPalat/12/5/03 12/18/03

F/T by rad12/11/03

V:\FIRMSAM\GENSIA\LTRS&REV\76653Ncr2.RAB

TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-653

Fluconazole Injection
2 mg/mL

Gensia Sicor Pharmaceuticals, Inc.

Arup K. Basak, Ph. D.
OGD - Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-653

2. REVIEW #: 3

3. REVIEW DATE: April 7, 2004

4. REVIEWER: Arup K. Basak, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
General Correspondence: Change of Corporate Company Name.	July 2, 2003
Original Amendment	July 31, 2003
Minor Amendment – Request for Final Approval	January 5, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Sicor Pharmaceuticals, Inc.
Address:	19 Hughes Irvine CA 92618 – 1902 USA
Representative:	Rosalie A. Lowe, Director, Regulatory Affairs
Telephone:	949-457-2808 949- 583 - 7351 (Fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Diflucan® in 0.9% Sodium Chloride
b) Non-Proprietary Name (USAN): Fluconazole and Sodium Chloride in Water for Injection

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Diflucan® in Sodium Chloride 0.9%, manufactured by Pfizer.
Applicant: Pfizer Laboratories NDA # 19-950 (001)
Approval Date: January 29, 1990

There is unexpired patent for this product. US Patent No. 4,404,216 will expire on January 29, 2004. Paragraph III certification is appended on page 1012. There is no unexpired exclusivity for this product in electronic orange book (page 1012).

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

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 2 mg/mL
(200 mg/100 mL and 400 mg /200 mL)

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X__Rx ___OTC

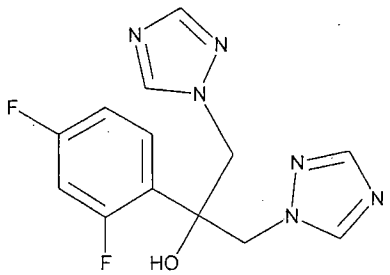
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

FLUCONAZOLE: $C_{13}H_{12}F_2N_6O$: M.W. 306.28: CAS No: 86386-73-4



Chemical Name: 1) 2,4-Difluoro-α,α-bis(1H-1,2,4,triazol-1-yl)methyl)benzyl alcohol
α-(2,4-difluorophenyl)- α-(1H-1,2,4-Triazol-1-yl)methyl)1H-1,2,4-Triazole-1-ethanol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: **SATISFACTORY**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	**Adequate** as per Rajagopalan, R	09/17/03	LOA & appointment of RS Rep. p.1055-1056
	III			3	Adequate		LOA p.# 1561

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	08/28/03	Nrapendra Nath
EES	Acceptable	06/18/2003	
Methods Validation	New Method Validation procedure was followed.		
Labeling	Acceptable	10/8/03	
Bioequivalence	Bio Waiver Granted	09/03/03	S. P. Shrivastava
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-653

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE .

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

N/A

II. Summary of Chemistry Assessments

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

Fluconazole is a synthetic broad-spectrum fluorinated bis-triazole antifungal agent. It may exist in three anhydrous polymorphic forms and a monohydrate form. The monohydrate form is formed when the DS is exposed to Relative Humidity higher than 70%. The water solubility is 0.5%. There is no USP monograph for the drug substance. In addition, the drug substance is dissolved in water for injection, polymorphs should not be a concerns for this ANDA.

The drug substance is manufactured and supplied by ——— whose parent company is ——— located at ———. The drug substance appears as a white crystalline powder as reported in the Certificate of Analysis.

The drug product is manufactured by compounding Fluconazole and Sodium Chloride in water for injection (WFI). Besides API, the compounding ingredients are either USP or NF. The finished drug product is packaged in 100 mL and 200 mL vials

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

Tentative Approval letter was issued from the Agency on November 12, 2003 with the clause that Final Approval of the application may not be made until the US Patent No. 4,404,216 has expired *i. e.* January 29, 2004. Through the January 5, 2004 amendment, the applicant informed that there is no revision to the labeling and no change in CMC section, based on which the application was approved.

Pediatric Exclusivity has been granted for Fluconazole prior to patent expiry date. This pushes the approval date out to July 29, 2004.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

AKBasak/04/07/04
GJSmith/04/14/04
TPalat/04/14/04

C. CC Block

ANDA 76-653
Field Copy
Division File

V:\FIRMSNZ\SICOR\LTRS&REV\76653Ncr2ta.RAB.doc

This review is also saved under Gensia with the same file name. Please see Gensia for prior reviews.

Tentative Approval – 2nd TA

APPEARS THIS WAY
ON ORIGINAL

Full Approval Assessment

1. ANDA # 76-653

2. NAME AND ADDRESS OF APPLICANT
SICOR Pharmaceuticals, Inc.
Attention: Rosalie Lowe
19 Hughes
Irvine, CA 92618-1902

3. LEGAL BASIS FOR SUBMISSION
The reference-listed drug is Diflucan® Injection (in 0.9% Sodium Chloride 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	01/31/03
Tentatively Approved	05/24/03
Amendment	05/24/04

7. PHARMACOLOGICAL CATEGORY
Anti-fungal

8. Rx or OTC
Rx

9. RELATED DMF(s)
—

10. Samples and Results
N/A

11. LABELING STATUS - Acceptable 10/08/03

12. BIOEQUIVALENCY STATUS - Acceptable 09/05/03

13. MICROBIOLOGY STATUS - Acceptable 09/04/03

14. ESTABLISHMENT INSPECTION - Acceptable 06/18/03

15. CONCLUSIONS AND RECOMMENDATIONS - The firm submitted certification that no changes have been made to the Chemistry, Manufacturing and Controls Sections of the application since receiving Tentative Approval on 05/24/04.

Recommend Approval.

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

cc: ANDA 76-653
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:

V:\FIRMSNZ\SICOR\LTRS&REV\76653.Admin.AP.doc

Approval

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

BIOEQUIVALENCE REVIEW

1c1

Bioeq

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	**76-653**
Drug Product Name	**Fluconazole Injection in Sodium Chloride, 0.9%**
Strength	**2 mg/mL; 200 mg/100 mL and 400 mg/200 mL vials**
Applicant Name	**Gensia Sicor Pharmaceuticals, Inc.**
Address	**Irvine, CA**
Submission Date(s)	**January 31, 2003**
Amendment Date(s)	**N/A**
Reviewer	**S. P. Shrivastava**
First Generic	**No**
File Location	**V:\firmsam\Gensia\ltrs&rev\76653w0103**

I. Executive Summary

The firm has submitted a request for waiver of *in vivo* bioavailability/bioequivalance study requirements based on 21 CFR 320.22(b)(1) for its proposed product fluconazole Injection, 2 mg/mL in 0.9% sodium chloride, in 200 mg/100 mL and 400 mg/200 mL vials. The Test product, supplied in vials as 2 mg/mL (200 mg/100 mL and 400 mg/200 mL fill/vial) is bioequivalent to 2 mg/mL Diflucan® Injection in 0.9% sodium chloride (NDA #N19950, 1/29/90), manufactured by Pfizer Inc. The waiver of bioequivalence study requirements is granted.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	2 mg/mL fluconazole injection in 0.9%sodium chloride
Reference Product	2 mg/mL Diflucan® Injection in 0.9% sodium chloride
RLD Manufacturer	Pfizer Inc.
NDA No.	019297
RLD Approval Date	1/29/90
Indication	Fluconazole is indicated for the treatment of vaginal oropharyngeal and oesophageal candidiasis.

B. PK/PD Information

Bioavailability	IV - 100%, oral – 90%
Food Effect	N/A
Tmax, Hrs.	Oral - 1-2
Metabolism	N/A
Excretion	Oral – Primarily renal, 80% of dose excreted in urine as parent drug, 11% as metabolite.
Half-life (Terminal)	Oral - Approx. 30 Hrs. (range 20-50 hrs)
Relevant OGD or DBE History	ANDAs: 76-087, 76-145, 76-303, and 76-617 Protocols: None CD 02-620: Inquiry on pH Specification
Agency Guidance	None
Drug Specific Issues (if any)	None

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation---N/A

E. In Vivo Studies----N/A

1. Single-dose Fasting Bioequivalence Study ----N/A

2. Single-dose Fed Bioequivalence Study----N/A

F. Formulation (Not For Release Under FOI)

Location	**See below**
Inactive ingredients within IIG Limits (yes or no)	**Yes, identical to the RLD**
If yes, list ingredients outside of limits	**None**
If a tablet, is the product scored? (yes or no)	**N/A**
If yes, which strengths are scored?	**N/A**
Is scoring of RLD the same as test? (yes or no)	**N/A**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	**N/A**

Components and composition of the test and the reference products are given in Table 1.

Table 1. Comparative Composition of Test* and Reference Products, 2mg/mL Injection in 0.9% Sodium Chloride

Ingredient	Test Mg/100 mL Fill	Reference Mg/100 mL Fill	Test Mg/200 mL Fill	Referen Mg/200 ml
Fluconazole	200.0	200.0	400.0	400.0
Sodium Chloride, USP	900.0	900.0	1800.0	1800.0
Water for Injection	q.s. to 100 mL	q.s. to 100 mL	q.s. to 200 mL	q.s. to 200 n
[redacted]	**		**	

* Exhibit Batch Size = [redacted] Proposed Production Batch Size = [redacted]

** [redacted]

COMMENTS

1. The test drug product contains the same active and inactive ingredients.
2. The test drug product has the same route of administration (i.e., intravenous injection) and the same indications for use as that of the RLD.

G. In Vitro Dissolution ---N/A

H. Waiver Request(s)

The Applicant requests a waiver of *in vivo* bioequivalence testing under 21 CFR 320.22(b)(1) for the following strength(s): 2 mg/mL, in 200 mg/100 mL and 400 mg/200 mL vials

I. Deficiency Comments ---- None

J. Recommendations

The Division of Bioequivalence agrees that the information submitted by Gensia Sicor Pharmaceuticals, Inc. demonstrates that fluconazole injection, 2 mg/mL in sodium chloride, 0.9%, in 200 mg/100 mL and 400 mg/200 mL vials, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for fluconazole injection, 2 mg/mL in sodium chloride, 0.9%, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Diflucan® Injection, 2 mg/mL in Sodium Chloride, 0.9%, manufactured by Pfizer Inc.

The firm should be informed of the recommendation.

Surendra P. Shrivastava, Ph.D.

9/3/2003

Shriniwas Nerurkar, Ph.D.

SPS/sps/8-26-03/76653n0103

cc: ANDA #76-653 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

BIOEQUIVALENCY COMMENTS

ANDA: 76-653 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL in Sodium Chloride, 0.9%, in 200 mg/100 mL and 400 mg/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,

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ SShrivastava

V:\FIRMSAM\GENSIA SICOR\ltrs&rev\76653w0103
Printed in final on 8/26/03

9/3/03

Endorsements: (Final with Dates)
HFD-655/ SShrivastava 9/3/03
HFD-655/ SNerurkar
HFD-650/ D. Conner 9/4/03

BIOEQUIVALENCY - ACCEPTABLE

1. WAIVER (WAI) Submission date: 1/31/03

Strengths: 2 mg/mL in Sodium Chloride, 0.9%, in 200 mg/100 mL and 400 mg/200 mL vials
Outcome: AC

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-653	SPONSOR: Gensia Sicor Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM :	Fluconazole Injection in 0.9% Sodium Chloride
STRENGTH(S) :	2 mg/mL, in 200 mg/100 mL and 400 mg/200 mL Vials
TYPES OF STUDIES:	N/A
CINICAL STUDY SITE(S):	N/A
ANALYTICAL SITE(S):	N/A
STUDY SUMMARY:	N/A
DISSOLUTION:	N/A.
WAIVER REQUEST:	Acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No	Inspection requested: (date)	
New facility No	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER: S. P. Shrivastava BRANCH: II
INITIAL: _____ DATE: 9/3/03

TEAM LEADER: SNerurkar BRANCH: II
INITIAL: _____ DATE: 9/3/2003

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

INITIAL: _____ DATE: 9/5/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-640

August 28, 2003

ANDA: 76-653

Drug Product Name
Proprietary: N/A
Non-proprietary: Fluconazole Injection
Drug Product Classification: Antifungal Agent
Review Number: #1

Subject of this Review
Submission Date: January 31, 2003
Receipt Date: February 3, 2003
Amendment: August 22, 2003 (Response to telecon 8/15/2003)
Consult Date: N/A
Date Assigned for Review: August 12, 2003

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

Applicant/Sponsor
Name: Gensia Sicor Pharmaceuticals, Inc.
Address: 19 Hughes, Irvine, CA 92618-1902
Representative: Rosalie A. Lowe, Director, Regulatory Affairs
Telephone: 949-457-2808

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:**
Gensia Sicor Pharmaceuticals
19 Huges
Irvine, CA 92618

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

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

6. **PHARMACOLOGICAL CATEGORY:** Antifungal agent.

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

C. **REMARKS:** Parts of the subject ANDA are similar to ANDA 40-454, which was reviewed by the subject reviewer in June 2002 for its sterility assurance content.

The subject reviewer requested (Telecon August 15, 2003) the applicant to provide data in support of validation of [redacted] of the subject drug product filled in 100mL and 200mL containers. The response contained in the amendment dated 8/22/03 has been incorporated in the subject review.

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 ———————

B. Brief Description of Microbiology Deficiencies -
None.

C. Assessment of Risk Due to Microbiology Deficiencies -
None.

III. Administrative

A. Reviewer's Signature Daniel C Ollis 9/4/03
for Nagendra Nath

B. Endorsement Block
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney

Neal J Sweeney 9-4-03

C. CC Block
cc:
Original ANDA
HFD- 600
Division File
V:\MICROREV\76-653.doc

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

ADMINISTRATIVE DOCUMENTS

To File:
Nrapendra Nath
Date: August 15, 2003. Time: 11:45AM

ANDA # 76-653

Drug: Fluconazole

Firm: Gensia Sicor

Contact Person: Rosalie A. Lowe, Director, Regulatory Affairs

Telephone: 949- 457-2808

Questions:
Regarding validation of ——— —— data provided is for 2mL and 50mL vials (volume 3, p. 3088); the vial size for the drug product are 100mL and 200mL. Please explain.

Response:
She will look into it and send in the amendment as soon as possible.

CC: ANDA 76-653
DN File

APPEARS THIS WAY
ON ORIGINAL

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-653 Applicant SICOR Pharmaceuticals
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 10/7/2003 Initials MMS	Date Initials

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

2. Project Manager, Ted Palat Team 9 Review Support Branch	Date 12/9/03 Initials CP	Date 12/22/03 Initials

Original Rec'd date January 31, 2003
Date Acceptable for Filing February 3, 2003
Patent Certification (type) III
Date Patent/Exclus.expires Jan 29, 2004
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
Acceptable Bio reviews tabled Yes ☑ No ☐
EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status June 18, 2003
Date of Office Bio Review September 5, 2003
Date of Labeling Approv. Sum Oct 8, 2003
Date of Sterility Assur. App. September 4, 2003
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. Gregg Davis Deputy Dir., DLPS	Date Initials	Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:	12/19/03 JCB	Date 12/23/03 Initials

one satisfactory.

RLD = Diflucan Injection 2mg/mL; 200mg/100mL and 400mg/200mL Pfizer Central Research NDA 19-950/001

REVIEWER: **FINAL ACTION**

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

N/A Multiple ANDAs have been tentatively approved for this drug product (Abbott, Bedford, HPP, Faulding)

6. Peter Rickman Date 12/24/03 for
Director, DLPS Initials JM
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 6/18/03 (Verified 12/24/03). No OAI. Alerts noted. Bioequivalence waiver granted under 21 CFR 320.22(b)(1). Drug product is "Q1Q" to the RLD. Office level biowaiver 9/5/03. Labeling found acceptable 10/8/03. Microbiology/sterility assurance found acceptable 9/4/03. CMC found acceptable 12/2/03. Methods validation status to be determined.

6. Robert L. West Date 12/24/2003
~~Acting~~ Deputy Director, OGD Initials RLW for the dir
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Sicor made a paragraph III certification to the '216 patent scheduled to expire on 1/29/04. However, Pfizer has submitted a pediatric study in response to a written request from the new drugs group. The granting of pediatric exclusivity is pending.

This ANDA is recommended for tentative approval.

7. Gary Buehler Date 12/24/03
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Ted Palat Date _____
Review Support Branch 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 10:55am Time approval letter faxed
FDA Notification:
12/24/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/24/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-653 Applicant SICOR Pharmaceuticals, Inc.
Drug Fluvastatin Injection Strength(s) 2 mg/mL

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

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

1. Martin Shimer
Chief, Reg. Support Branch
Date 27 April 2004 Initials MS
Date 5/21/04 Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 19-950 (001) previously granted
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: PII to '216 patent that exp. 1/29/2004 } Eligible for TA only
NCE Ped EXCL exp. 7/29/2004

2. Project Manager, Ted Pilot Team 9
Review Support Branch
Date 4/14/04 Initials GO
Date Initials

Original Rec'd date 1-31-03
Date Acceptable for Filing 2-3-03
Patent Certification (type) III
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 6/18/2003
Date of Office Bio Review 9/5/03
Date of Labeling Approv. Sum 10/8/03
Date of Sterility Assur. App. 9/4/03
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☑ Date 12/24/03
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments: No changes in cmc or labeling.
Date 5/13/04 Initials RGA

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

REVIEWER: FINAL ACTION

5. Gregg Davis (in 0.9% Sodium Chloride Inj.)
Deputy Dir., DLPS Date _____
Initials _____

RLD= Diflucan Injection, 2mg/mL; 200mg/100mL and 400mg/200mL
Pfizer Central Research
NDA 19-950 (001)

6. Peter Rickman Date 5/21/04
Director, DLPS Initials for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable ES dated 6/18/03 (verified 5/21/04) No O.A.I. Alerts noted. Refer to the administrative sign off form completed at the time of the tentative approval granted on 12/24/03. Since then, Sicor submitted a minor amendment dated 1/5/04 requesting final approval based upon the anticipated expiration of the '216 patent on 1/29/04. CMC remains acceptable 5/5/04. Methods validation will not be request - does not conform to current M.V. criteria.

6. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes ☐ No ☐ Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: At the time of filing, Sicor made a paragraph III certification to Pfizer's '216 patent that was scheduled to expire on 1/29/04. However, Pfizer was subsequently granted pediatric exclusivity for Diflucan, which effected extended Pfizer's '216 patent by a period of pediatric exclusivity until 7/29/04.

This ANDA is recommended for a second tentative approval - Sicor has addressed Pfizer's period of exclusivity.

7. Gary Buehler Date 5/24/04
Director, OGD Initials for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

8. Project Manager, Team Ted Pelat Date 5/24/04
Review Support Branch Initials _____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
3:33 Time notified of approval by phone 3:35 Time approval letter faxed
FDA Notification:
_____ Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/24/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-653 Applicant SICOR Pharmaceuticals
Drug Fluconazole Injection, 10mL and 200mL vials Strength(s) 2mg/mL

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

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

1. Martin Shimer
Chief, Reg. Support Branch
Date 7 July 2004 Initials MMS | Date _____ Initials _____

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# _____
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter: PIL to '216; ACK Fed Exclusivity exp of 7/29/2004
Comments: ∴ eligible for Full Approval on 7/29/2004

2. Project Manager, Feldlot Team 9
Review Support Branch
Date 6/30/04 Initials CP | Date 7 Initials _____

Original Rec'd date 1-31-03
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 2-3-03
Date of EER Status 6-16-03
Patent Certification (type) II
Date of Office Bio Review 9-5-03
Date Patent/Exclus.expires 7-29-04
Date of Labeling Approv. Sum 10-8-03
Citizens' Petition/Legal Case Yes ☐ No ☑
Date of Sterility Assur. App. 9-4-03
(If YES, attach email from PM to CP coord)
Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☐
Acceptable Bio reviews tabbed Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☒ Date 5-24-03
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

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

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Date 7/20/04 Initials RCA
Comments: No comments. Rep

REVIEWER:

FINAL ACTION

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

Date_____
Initials_____

6. Vacant
Deputy Dir., DLPS

RLD-Diflucan Injection, 2mg/mL, 100mL
Pfizer Central Research
NDA 19-950 (001) 400mg/200mL
Lot 0.9% Sodium Chloride Injection

Date_____
Initials_____

7. Peter Rickman
Director, DLPS

Date 7/21/04
Initials [signature] for

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition Filed? Yes ☐ No ☐
Comments: Acceptable EES dated 6/18/03 verified 7/21/04). No O.A.I. alerts noted
Refer to the administrative sign off forms completed at the time of the
tentative approvals issued on 12/24/03 and 5/24/04. On 5/24/04 Sicor
OR submitted a minor amendment to request final approval of this ANDA.
Sicor stated that no CMC changes had been made to the ANDA since the TA.
FBZ found acceptable for final approval 7/19/04. CMC found acceptable for
approval 7/16/04. Methods validation was not requested - does not meet
current I.V. criteria.

8. Robert L. West
Deputy Director, OGD

Date 7/21/2004
Initials [signature]

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition Filed? Yes ☐ No ☐
Comments: Sicor made a paragraph III certification to the '216 patent
that expired on January 29, 2004. The '216 patent was effectively extended
until 7/29/04 upon the grant of pediatric exclusivity to Pfizer. Sicor
has revised its paragraph III certification to a paragraph II certification,
and has addressed Pfizer's exclusivity. This ANDA is recommended for final
approval upon the expiration of Pfizer's pediatric 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 Review Support Branch
N/A Date PETS checked for first generic drug (just prior to notification to firm)

Ted Pabst

Date 7/29/04
Initials [signature]

Applicant notification:
11:02 am Time notified of approval by phone 11:02 Time approval letter faxed
FDA Notification:
7/29 10 am Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/29 10 a.m. Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-653

CORRESPONDENCE

GensiaSicor™
PHARMACEUTICALS
A sicor inc. Company

January 31, 2003

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

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

Dear Mr. Buehler:

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

Strength	Total Drug Content	How Supplied
2 mg/mL	200 mg per 100 mL vial	100 mL Single Dose Vials Packaged 6 per Shelf Pack
	400 mg per 200 mL vial	200 mL Single Dose Vials Packaged 6 per Shelf Pack

Gensia Sicor's proposed drug product is the generic version of Pfizer's Diflucan® in Sodium Chloride 0.9%, pursuant to NDA No. 19-950 (001). Pfizer's drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 22nd Edition*. The approved drug product marketed by Pfizer is available as a 100 mL and 200 mL single dose glass bottle.

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

RECEIVED
FEB 03 2003
OGD / CDER

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

Fluconazole Injection will be packaged in glass vials. The vials will be sealed with stoppers from [redacted] composed of [redacted] Gray.

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

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

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

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

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

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

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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

ANDA 76-653

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalia A. Lowe
19 Hughes
Irvine, CA 92618-1902

MAR 10 2003

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.

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

DATE OF APPLICATION: January 31, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 3, 2003

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:

Ted Palat
Project Manager
(301) 827-5849

Sincerely yours,

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

ANDA 76-653
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 10-MAR-2003 date
HFD-615/SMiddleton, CSO date
Word File
V:\FIRMSAM\GENSIA\LTRS&REV\76653.ACK
F/T EEH 03/10/03
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

GensiaSicor™
PHARMACEUTICALS
A sicor Company

76-653

July 2, 2003

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

NEW CORRESP
NC

RE: Change of Corporate Company Name

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

In accordance with the provisions of Section 314.97 of the *Code of Federal Regulations, Title 21*, we hereby notify FDA that effective July 15, 2003, Gensia Sicor Pharmaceuticals, Inc. intends to change its corporate company name to SICOR Pharmaceuticals, Inc. Please note there is no transfer of corporate assets or ownership due to the name change of the company. This notification represents a change in company name only.

Included with this letter is a listing of all approved, tentatively approved, and pending ANDAs that will convert under the name of SICOR Pharmaceuticals, Inc. For the convenience of the Agency, we are providing 122 copies of this letter such that there are two letters available per ANDA for filing purposes.

We trust that the information provided in this correspondence is satisfactory to effect the change of company name. Should you have any questions regarding this matter, please feel free to contact me at (949) 457-2808 or Ms. Elvia Gustavson, Director, Regulatory Affairs at (949) 455-4724.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

Attachment

cc: Ms. Gladys Lee Holley, Technical Information Specialist
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Rockville, MD 20855

Mr. Alonza Cruse, District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED
JUL 07 2003
OGD / CDER

S:\Name Change\2003 Company Name Change FDA ltr.doc

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

NOR AMENDMENT

DA 76-653

ICE OF GENERIC DRUGS, CDER, FDA
ument Control Room, Metro Park North II
) Standish Place, Room 150
kville, MD 20855-2773 (301-594-0320)

JUL 9 2003

LICANT: Gensia Sicor Pharmaceuticals, Inc. TEL: 949-457-2808

ATTN: Rosalie A. Lowe FAX: 949-583-7351

M: Ted Palat PROJECT MANAGER: 301-827-5849

Madam:

acsimile is in reference to your abbreviated new drug application dated January 31, 2003, submitted pursuant tion 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluconazole for Injection, 2 mg/mL, in 100 mL 0 mL vials.

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

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

AL INSTRUCTIONS:

Chemistry comments attached. 7-9-03

OCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND ONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM SURE UNDER APPLICABLE LAW.

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

JUL 9 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-653 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Fluconazole Injection, 2 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF [redacted] is deficient and the holder has been informed of the deficiencies.

2. [redacted]

3.

4.

5.

6.

7.

8.

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

1. Please note that using the same Lot Number for the "Compounded Lot" and for "100 mL Fill/100 mL Vial" is confusing. We recommend using different identification number for all future production/validation batches.

2. A method validation request will be sent to an FDA laboratory. Once samples have been requested, any modification to the method in response to any of the deficiencies listed above should also be communicated to the laboratory.

Sincerely yours,

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

1.1

********** -COMM. JOURNAL- ********** DATE JUL-16-2003 ***** TIME 15:46 ********

MODE = MEMORY TRANSMISSION START=JUL-16 15:45 END=JUL-16 15:46

FILE NO.=005

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK		919495837351	004/004	00:00:46

-FDA CDER OGD LPS -

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

********** -

76-653

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: July 16, 03

To: Rosalie Lowe

Phone: **Fax:** 949-583-7351

From: Chan Park, R.Ph., Ph.D.

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

Number of Pages:___
(Including Cover Sheet)

Comments: RE: 76-653 (Fluconazole Inj.)
Labels deficiencies per the phone
Call to Barbara. Thanks,
Chan

Signed Application Form

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

ANDA Number: 76-653 Date of Submission: January 31, 2003

Applicant's Name: GensiaSicor Pharmaceuticals, Inc.

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

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

   a. Relocate the text "Sterile... Injection" to appear immediately below the established name of your drug product.

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

   c. Revise to read "Single-dose Vial".

   d. You may revise "**NOTE**: Any..." statement to read "**NOTE**: Discard unused portion.".

   e. 200 mg/100 mL

      We ask you to increase the readability of the name and place of the manufacturer by increasing the background contrast and/or any other means. The ___ print on the ___ background does not render a sufficient contrast.

2. CARTON

   See comments under CONTAINER, where applicable.

3. INSERT

   a. General

      i. Although the print size may meet the minimum requirement, we encourage you to increase this to enhance the readability of your labeling.

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

      iii. It appears that the efficacy and safety profile of the oral and injection form of fluconazole are similar to each other as the pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. Therefore, we ask that you include information related to the oral form although your drug product is injection. See comments below.

      iv. We acknowledge that you carved out all information associated with vaginal candidiasis as this is the indication specific to the 150 mg tablet only. We find this acceptable.

   b. DESCRIPTION - Second paragraph:

      "chemical formula" rather than "_____formula"

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics in Children

Relocate "(36%)", (33%), and (37%)" in the first column to the last one.

ii. Drug Interaction Studies

A) Antacid:

Please include a disclaimer for Maalox®.

B) Phenytoin - First sentence:

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

iii. Microbiology

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

d. INDICATIONS AND USAGE

Revise to read "Fluconazole injection is ...

e. PRECAUTIONS

1. Delete the subsection heading "———— ".

ii. Drug Interactions - Tacrolimus:

Retain the second paragraph "Fluconazole tablets... is presently unknown." appearing in the innovator's labeling.

iii. Carcinogenesis, Mutagenesis and Impairment of Fertility

A) Retain the first paragraph "Fluconazole showed no... hepatocellular adenomas." appearing in the innovator's labeling.

B) Include the following as the second sentence to the first paragraph you proposed:

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.

C) Second paragraph, first sentence:

...rates treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral...

f. DOSAGE AND ADMINISTRATION

i. Dosage and Administration in Adults:

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

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

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

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

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

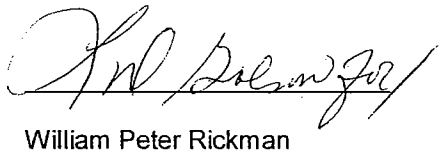
ii. Administration - First paragraph:
Fluconazole injection may be administered... [add "injection"]

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

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

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

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



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

sicor
PHARMACEUTICALS, INC.

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

July 31, 2003

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

RE: Fluconazole for Injection
2 mg/mL
ANDA: 76-653
ORIG AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-653, for Fluconazole for Injection, 2 mg/mL, submitted on January 31, 2003. Reference is also made to the deficiency letter dated July 9, 2003.

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

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

Sincerely,

Rosalie A. Lowe

RECEIVED
AUG 0 1 2003
OGD/CDER

Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fluconazole\Amends\Amend1.doc
cc: Mr. Alonza Cruse
District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

sicor
PHARMACEUTICALS, INC.

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

July 31, 2003

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

ORIG AMENDMENT
N/A

RE: Fluconazole for Injection
2 mg/mL
ANDA: 76-653

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-653, for Fluconazole for Injection, 2 mg/mL, submitted on January 31, 2003. Reference is also made to the deficiency letter dated July 16, 2003.

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

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

Sincerely,

Rosalie A. Lowe

RECEIVED
AUG 0 1 2003
OGD/CDER

Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fluconazole\Amends\Amend2.doc
cc: Mr. Alonza Cruse
District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

sicor
PHARMACEUTICALS, INC.

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

August 22, 2003

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

ORIG AMENDMENT

N/A.S

RE: Fluconazole for Injection, 2 mg/mL
ANDA: 76-653

TELEPHONE AMENDMENT – Microbiology

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-653, for Fluconazole for Injection, 2 mg/mL, submitted on January 31, 2003. Reference is also made to the telephone call of August 15, 2003, between myself and Nrapendra Nath, Ph.D., Microbiology Reviewer, Office of Generic Drugs, FDA. Dr. Nath brought to our attention a discrepancy with regard to the vial sizes reported on page 2088 of our sterility assurance package in the ANDA.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to revise the **microbiology** information to reflect validation data to support the ——————— of a 200 mL vial size.

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

RECEIVED
AUG 25 2003
OGD/CDER

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

NAF
1/21/04
GR

sicor
PHARMACEUTICALS, INC.

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

January 5, 2004

ORIG AMENDMENT
N/HAM

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

RE: Fluconazole Injection, 2 mg/mL
ANDA: 76-653

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-653, for Fluconazole Injection, 2 mg/mL, submitted on January 31, 2003. Reference is also made to the Agency's letter of tentative approval dated December 24, 2003.

In accordance with the tentative approval granted for this application, we are amending the application to advise that no changes have been made to labeling, chemistry, manufacturing, or controls. SICOR plans to initiate commercial distribution of this product following the expiration of U.S. Patent No. 4,404,216, held by Pfizer, NDA No. 19-950 (001), which expires on January 29, 2004, as listed in our Paragraph III Patent Certification. Therefore, we request final approval for this ANDA be granted upon expiration of the aforementioned patent.

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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

RECEIVED
JAN 08 2004
OGD/CDER

ORIGINAL

sicor
PHARMACEUTICALS, INC.

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

May 24, 2004

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

ORIG AMENDMENT
N/am

RE: Fluconazole Injection, 2 mg/mL
ANDA: 76-653

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-653, for Fluconazole Injection, 2 mg/mL, submitted on January 31, 2003. Reference is also made to the Agency's letter of tentative approval dated May 24, 2004.

In accordance with the tentative approval granted for this application, we are amending the application to advise that no changes have been made to labeling, chemistry, manufacturing, or controls. SICOR plans to initiate commercial distribution of this product following the expiration of U.S. Patent No. 4,404,216 on July 29, 2004. Therefore, we request final approval for this ANDA be granted upon expiration of the aforementioned patent.

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

RECEIVED
MAY 26 2004
OGD/CDER

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