021506_Original_Approval_Package.PDF

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Approval Package for:

APPLICATION NUMBER:

21-506

Trade Name:	Mycamine
Generic Name:	Micafungin sodium for Injection
Sponsor:	Fujisawa Healthcare, Inc.
Approval Date:	June 15, 2005
Indications:	Provides for the use of Mycamine (micafungin sodium) for Injection for prophylaxis of Candida infections in patients undergoing hamatopoietic stem cell transplantation.

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APPLICATION NUMBER:

21-506

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Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:

21-506

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506
NDA 21-754

Fujisawa Healthcare, Inc.
Attention: Mr. Robert M. Reed
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Reed:

Please refer to your new drug application (NDA) dated April 29, 2002, received April 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-506. The August 24, 2004 submission, received August 25, 2004, constituted a complete response to our January 29, 2003 approvable letter.

We acknowledge receipt of your submissions to NDA 21-506 dated:

October 1, 2004	December 23, 2004	February 9, 2005
October 15, 2004	January 6, 2005	February 11, 2005
October 20, 2004	January 10, 2005 (2)	February 15, 2005
October 25, 2004	January 26, 2005	February 28, 2005
October 29, 2004	January 27, 2005	March 8, 2005
November 12, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)
December 22, 2004	February 4, 2005 (2)	

We also refer to your new drug application dated April 23, 2004, received April 26, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-754.

We acknowledge receipt of your submissions to NDA 21-754 dated:

May 11, 2004	December 22, 2004	February 4, 2005 (2)
August 24, 2004	December 23, 2004	February 11, 2005
September 22, 2004	January 6, 2005	February 18, 2005
October 1, 2004	January 10, 2005 (3)	February 22, 2005
October 20, 2004	January 26, 2005	February 28, 2005
November 12, 2004	January 27, 2005	March 8, 2005
November 18, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)

These new drug applications provide for the use of Mycamine™ (micafungin sodium) for Injection, for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506) and for the treatment of esophageal candidiasis (NDA 21-754).

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDAs 21-506 and 21-754.**" Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring the pediatric study requirement for ages 0 to 16 years for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation and for the treatment of esophageal candidiasis.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the prophylaxis of *Candida* infections in patients ages 0 to 16 years old undergoing hematopoietic stem cell transplantation,

2. Deferred pediatric study under PREA for the treatment of esophageal candidiasis in patients ages 0 to 16 years old.

Final Report Submissions: March 30, 2010

Submit final study reports to NDA 21-506 only. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-506 for this drug product, not to NDA 21-754. In the future, do not make submissions to NDA 21-754 except for the final printed labeling requested above.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

1. text for the package insert,
2. immediate container
3. carton labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
3/16/05 12:54:49 PM
for Mark J. Goldberger, MD MPH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-506

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506

Fujisawa Healthcare, Inc.
ATTN: Robert Reed, Associate Director, Regulatory Affairs
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548

Dear Mr. Reed:

Please refer to your new drug applications (NDA) dated April 29, 2002, received April 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine (micafungin sodium) for injection, — 50 mg.

We acknowledge receipt of your submissions dated:

June 4, 2002	August 28, 2002 (2)	September 10, 2002	October 29, 2002
June 10, 2002	August 29, 2002	September 13, 2002	November 4, 2002
June 21, 2002	September 3, 2002	September 18, 2002	November 19, 2002
August 6, 2002	September 4, 2002	September 26, 2002 (2)	January 10, 2003 (2)
August 9, 2002	September 5, 2002	September 27, 2002	
August 26, 2002 (2)	September 6, 2002 (2)	October 10, 2002	

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

The one study submitted in support of prophylaxis of — in patients undergoing hematopoietic stem cell transplantation, Study 98-0-050, alone did not provide sufficiently robust statistical evidence of superiority of micafungin over fluconazole, a comparator not approved for this indication. Specifically, the results of this analysis were largely determined by patients with "possible" as opposed to probable or proven fungal infection. In addition, prior to approval for prophylaxis of — in patients undergoing hematopoietic stem cell transplantation, it is expected that micafungin sodium should demonstrate activity in the treatment of documented invasive *Candida* — infections. Studies — 98-0-047 failed to provide sufficient information to demonstrate such activity. Thus, the results from Study 98-0-050 alone do not provide substantial evidence of efficacy. In order for this indication to be approved, it will be necessary to provide data from additional controlled clinical trials.

In addition, it will be necessary for you to submit draft labeling revised to reflect additional safety or efficacy data submitted.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, we have the following concerns regarding your application. While it is not required that you address these issues prior to approval, we recommend that you do so when you respond to the above deficiencies.

1. The following investigations would provide valuable information regarding the safe and effective use of micafungin sodium. You may be able to conduct some of these studies in the course of further development of Mycamine prior to approval; otherwise, they may constitute requests for post-marketing commitments at the time of approval.

   - Adequately determine the basic parameter values, dose linearity, and time dependency in micafungin pharmacokinetics at the proposed clinical dosing regimen at steady-state.

   - Analyze the effects of age, gender, and race on micafungin pharmacokinetics.

   - Determine the complete steady-state pharmacokinetic profiles of the most abundant metabolite (M5) and active metabolites (M1 and M2) in a multiple-dosing regimen.

   - Adequately determine the extent of protein binding of parent compound *in vivo*.

2. Provide updated site-specific stability data.

3. Revise the drug product specification and, in particular, the acceptance criteria for
   — The available release and stability data indicate that lower acceptance criteria are appropriate. Please tighten the acceptance criteria accordingly or provide further justification for their retention. In addition, please add a second — test for the drug product, e.g.,
   — .

4. Since micafungin sodium is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the Act as provided by 21 CFR 299.4(e). They can be reached at the following address:

   Secretary
   United States Adopted Names (USAN) Council
   c/o American Medical Association
   P.O. Box 10790
   Chicago, Illinois 60610

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Goldberger
1/29/03 01:33:02 PM