

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-754

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



New Medicines for New Times

Fujisawa Healthcare, Inc.

Regulatory Affairs

Three Parkway North

Deerfield, Illinois 60015-2548

Tel. (847) 317-8985 Telefax (847) 317-7286

www.fujisawa.com

April 23, 2004

Renata Albrecht, MD
Director, Division of Special Pathogen and Immunologic Drug Products
FDA, CDER, HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

Re: **NDA #21-754**
MYCAMINE (micafungin sodium) FOR INJECTION
— 50 mg

SUBMISSION OF ORIGINAL NEW DRUG APPLICATION

Dear Dr. Albrecht:

Fujisawa Healthcare, Inc. (FHI) is hereby submitting an original New Drug Application (NDA) pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for MYCAMINE® (micafungin sodium) FOR INJECTION, — 50 mg for the treatment of esophageal candidiasis.

The NDA archival copy is being submitted in an electronic format pursuant to the general requirements provided in FDA Guidance Document, IT3. The electronic archive copy consists of one DLT II tape (approximately 4.6 gigabytes) and has been confirmed to be virus-free by Norton Antivirus software (Version 7.0).

This NDA has been prepared in the Common Technical Document (CTD) format; however the electronic archive copy complies with the file and folder conventions specified in Guidance Document IT3. A detailed roadmap of the CTD submission (with cross reference to the corresponding section of the Form 356h) is provided in **Attachment 1**.

As agreed with the Division during our July 25, 2003 Pre-NDA Meetings and at the March 28, 2003 and March 8, 2004 Type A Meetings for NDA #21-506, Fujisawa has extensively cross referenced NDA #21-506 for this NDA. The introduction to each CTD module/section (with the exception of CTD Module 2, Section 2.3) includes a brief statement as to which information is included in NDA #21-754 and that which is cross-referenced to NDA#21-506. Per agreement with the Division, CTD Module 2, Section 2.3 will be cross-referenced in its entirety to CTD Module 3 in NDAs #21-506 and #NDA 21-754 and is not included in this NDA.

Included as **Attachments 2** and **3** of this cover letter are the relevant Patent Information (Section 13) and Patent Certification (Section 14) for micafungin sodium drug substance.

Provided as **Attachments 4** and **5** of this cover letter are the Debarment Certification (Section 16) and the Field Copy Certification (Section 17).

The User Fee Cover Sheet and supporting information (Section 18) is provided as **Attachment 6** and the Financial Disclosure Information (Section 19) is included as **Attachment 7**.

Renata Albrecht, MD
NDA #21-754
MYCAMINE (micafungin sodium) FOR INJECTION
Page 2 of 2

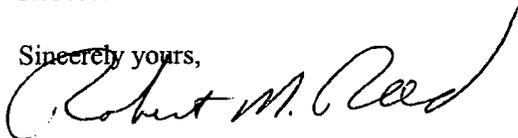
Chemistry, Manufacturing and Controls administrative information is located in **Attachment 8** of the cover letter. The following information has been included:

- DMF Authorization Letter for Drug Substance (DMF #12,856)
- DMF Authorization Letter for ~~DMF #12,856~~ (DMF # ~~12,856~~)
- Certificate of Translation for CMC Documents in NDA
- cGMP Certification for ~~Manufacturing Facility~~ Manufacturing Facility
- Environmental Assessment – Request for Categorical Exclusion
- Stability Commitment for Drug Product
- USAN Adoption Statement

Micafungin sodium is a member of a new class of cyclic lipopeptides, 1,3-beta-D-glucan synthesis inhibitors, that act by inhibiting 1,3-beta-D-glucan synthase, an enzyme essential for the synthesis of fungal cell walls. This mechanism of action is unique to the class. Micafungin sodium has broad-spectrum activity against *Candida* and *Aspergillus* species, clinically important pathogens that cause systemic fungal infections. Based on the data presented in this submission, FHI believes MYCAMINE (micafungin sodium) FOR INJECTION is safe and effective for the treatment of patients with esophageal candidiasis.

We look forward to a collaborative review of the data presented in this NDA. Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **847/317-8985** or Rebecca Iksuz at **847/317-8907**.

Sincerely yours,



Robert M. Reed
Associate Director, Regulatory Affairs

cc: Susan Peacock

**PATENT SUBMISSION/CERTIFICATION
FOR
MICAFUNGIN SODIUM**

Time Sensitive Patent Information
Pursuant to 21 C. F. R. 314.53
For
NDA # 21-754

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: MYCAMINE
- Active Ingredient(s): micafungin sodium (FK463)
- Strength(s): 50 mg
- Dosage Form: Lyophilized powder
- Approval Date:

A. Patent Information – granted patents

- 1) U.S. Patent Number: 5,376,634 covers the generic scope of micafungin sodium.
Expiration Date: December 27, 2011 ✓
- 2) U.S. Patent Number: 6,107,458 covers the specific scope of micafungin sodium.
Expiration date: September 29, 2015
- 3) U.S. Patent Number: 6,265,536 covers the broader scope of micafungin sodium.
Expiration date: September 29, 2015 ✓
- 4) U.S. Patent Number: 5,502,033 covers the starting compound for preparing micafungin sodium.
Expiration date: December 27, 2011 ✓
- 5) U.S. Patent Number: 6,207,434 covers the acylase produced from actinomycetes, that deacylates the starting compound of micafungin sodium.
Expiration date: March 6, 2017 ✓
- 6) U.S. Patent Number: 6,146,872 covers the acylase produced from fungus (*Oidiodendron*), that deacylates the starting compound of micafungin sodium.
Expiration date: June 11, 2017 ✓

- 7) U. S. Patent Number: 6,372,474 covers the acylase produced from fungus (*Verticillium*), that deacylates the starting compound of micafungin sodium.
Expiration date: September 12, 2017^v
- B. Patent Information – patents under examination
- 1) Application Number: 09/308,237 covers the metabolites of micafungin sodium.
Filing date: May 21, 1999
- 2) Application Number: 09/786,125 covers the composition of micafungin sodium.
Filing date: March 1, 2001
- 3) Application Number: 10/050,150 covers the broader scope of acylase produced from fungus (*Oidiodendron*), that deacylates the starting compound of micafungin.
Filing date: January 18, 2002

Name of Patent Owner: Fujisawa Pharmaceutical Company, Ltd.

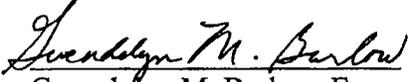
U.S. Agent: Fujisawa Healthcare, Inc., the applicant for this
NDA #21-754, is a wholly owned subsidiary of Fujisawa
Pharmaceutical Company, Ltd.

C. The undersigned declares that the above stated United States Patent Numbers (6,107,458, 5,376,634, and 6,265,536) covers the composition, formulation, and/or method of use of micafungin sodium. This product is the subject of this application for which approval is being sought.

The undersigned claims, upon approval, 5 years marketing exclusivity based on §314.108 (b)(2) of the Code of Federal Regulations.

The expiration date for the formulation patents (U.S. Patent Number 6,107,458 and U.S. Patent Number 6,265,536) is September 29, 2015. In addition, the sponsor requests an additional 6 months of exclusivity based on section 505A of the Federal Food, Drug, and Cosmetic Act.

To the best of the sponsors knowledge or belief, micafungin sodium has not been previously approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act containing any active moiety in micafungin sodium for which approval is sought.


Gwendolyn M. Barlow, Esq.
Assistant Director
Fujisawa Healthcare Inc.

4/12/04
Date



New Medicines for New Times

Fujisawa Healthcare, Inc.

Three Parkway North

Deerfield, Illinois 60015-2548

Tel. (847) 317-8985 Telefax (847) 317-7286

www.fujisawa.com

robert_reed@fujisawa.com

May 11, 2004

Renata Albrecht, M.D.
Director, Division of Special Pathogens and
Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

**RE: NDA 21-754
FK463 for Injection**

SUBMISSION OF REVISED PATENT INFORMATION/CERTIFICATION

Dear Dr. Albrecht:

Please find attached revised patent information/certifications (FDA Form Number 3542a for Patent Numbers **5,376,634**, **6,107,458**, and **6,265,536**) for FK463 for Injection. The aforementioned patents do not include patents that pertain solely to intermediates. Patent information pertaining to intermediates is available upon request. An electronic archive copy of this information is also included in this submission.

Please feel free to contact me at **847/317-8985** or Rebecca Ikusz at **847/317-8907** if you have any questions or concerns.

Sincerely yours,

A handwritten signature in black ink that reads 'Robert M. Reed'. The signature is fluid and cursive, with the first name 'Robert' being particularly prominent.

Robert M. Reed
Associate Director, Regulatory Affairs

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 21-754	
		NAME OF APPLICANT / NDA HOLDER Fujisawa Healthcare, Inc.	
<p align="center"><i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i></p>			
TRADE NAME (OR PROPOSED TRADE NAME) Mycamine			
ACTIVE INGREDIENT(S) micafungin sodium (FK463)		STRENGTH(S) 50 mg	
DOSAGE FORM Lyophilized powder			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p>For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p>FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</p>			
<p>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</p>			
1. GENERAL			
a. United States Patent Number 5,376,634		b. Issue Date of Patent 12/27/1994	c. Expiration Date of Patent 12/27/2011
d. Name of Patent Owner Fujisawa Pharmaceutical Co., Ltd.		Address (of Patent Owner) 4-7 Doshomachi 3-chome	
		City/State Chuo-ku, Osaka	
		ZIP Code Japan	FAX Number (if available) 81-6-6206-7926
		Telephone Number 81-6-6202-1141	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Fujisawa Healthcare, Inc.		Address (of agent or representative named in 1.e.) 3 Parkway North	
		City/State Deerfield, Illinois	
		ZIP Code 60015	FAX Number (if available)
		Telephone Number (847) 317-8800	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Swendolyn M. Barton

5/11/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Fujisawa Healthcare, Inc.

Address

3 Parkway North

City/State

Deerfield, Illinois

ZIP Code

60015

Telephone Number

(847) 317-8800

FAX Number (if available)

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

d) Did the applicant request exclusivity?

YES /X/ NDA 21-506: submission dated 4/29/02 NO /___/
NDA 21-754: submission dated 4/23/04

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years _____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally

know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the

its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! !
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! !
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !
! _____ ! _____
! _____ ! _____
!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !
! _____ ! _____
! _____ ! _____
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature:

(Christina H. Chi, Ph.D.)

Date: 3/9/2005

Title: Regulatory Health Project Manager

Signature of Division Director:

(Renata Albrecht, M.D.) Date:

cc:

Archival NDA

HFD-590/Division File

HFD-590/RPM/Christina Chi

HFD-610/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

Form OGD-011347 Revised 05/10/2004

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

/s/

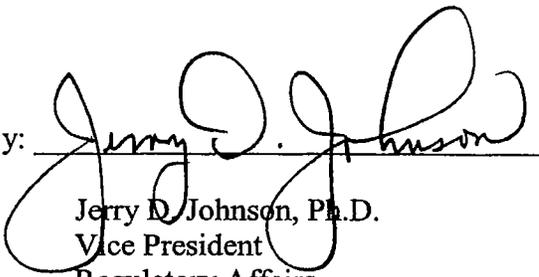
Renata Albrecht
3/9/05 02:32:51 PM

Submission dated
April 23, 2004.

Micafungin (FK463)
Esophageal Candidiasis
Original NDA 21-754

DEBARMENT CERTIFICATION

Fujisawa Healthcare, Inc., certifies that in support of this New Drug Application, the company did not and will not use in any capacity the services of any person or firm debarred under sections 306 (a) or (b).

By: 
Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

Date: 15 April 2004

PEDIATRIC PAGE

NDA # : 21-754 (original) Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: April 26, 2004 PDUFA Goal Date: May 26, 2005 Action Date: March 16, 2005

HFD: 590 Trade and generic names/dosage form: Mycamine (micafungin sodium) for IV injection, 50 mg

Applicant: Fujisawa Healthcare, Inc. Therapeutic Class: 4030410

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes**; all the above. (Please proceed to the next section).
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): None

(Each indication covered by this application must have pediatric studies: Completed, Deferred, and/or Waived.)

Number of indications for this application(s): One

Indication: for the treatment of esophageal candidiasis.

Is this an orphan indication?

- Yes**. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes**: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver X Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies: N/A

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

Section B: Partially Waived Studies: N/A

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. 0 yr. 16 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
 - Disease/condition does not exist in children
 - Too few children with disease to study
 - There are safety concerns
 - Adult studies ready for approval
 - Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): March 30, 2010

Section D: Completed Studies: N/A

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

This page was completed by:

{See appended electronic signature page}

Christina H. Chi, Ph.D.
Regulatory Project Manager

Authority signature:

{See appended electronic signature page}

Diana Willard
Chief, Regulatory Project Manager Staff

cc: NDA 21-754
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 2-28-2005)

**This is a representation of an electronic record that was signed electronically and
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/s/

Diana Willard
3/16/05 07:29:38 PM
NDA 21-754/Pediatric Page

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-754: for the treatment of esophageal candidiasis	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: Mycamine™ (micafungin sodium) for Injection (Intravenous Infusion, not for IV bolus injection), 50 mg/vial (single use vial)		Applicant: Fujisawa Healthcare, Inc. (as of 4/1/2005 will be renamed: Astellas Pharma US, Inc.)
RPM: Christina H. Chi, Ph.D.		HFD- 590 Phone # 301-827-2127
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 		
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		
❖ User Fee Goal Dates (Extension letter of 2/18/05 under "Outgoing Correspondence").		
		May 26, 2005
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	<input checked="" type="checkbox"/> Paid UF ID number 4756	
<ul style="list-style-type: none"> • User Fee waiver 	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A	
<ul style="list-style-type: none"> • User Fee exception 	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) N/A	
➤ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • This application is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	3/09/05 N/A
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	NDA Regulatory Filing Review 6/8/04
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	none
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(X) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None (X) (Sponsor's) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	With the Agency's input: Package insert dated 3/10/05
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	DMETS reviews: 8/5/04, 11/19/04 DDMAC review: 8/25/05 Labeling Meetings: see reviews
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	Ambisome, Diflucan, Cancidas
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	With the Agency's input: Carton & immediate container of 3/10/05
<ul style="list-style-type: none"> Reviews 	See discipline reviews
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	None
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Letters: Filing: 6/9/04; Acknow.: 6/28/04, Extension letter: 2/18/05 Faxes: 9/10, 10/27, 11/04 (2),

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay

	11/15, 12/14, and 12/20/2004. 1/3, 1/6, 1/14, and 3/15/2005.	
❖ Memoranda and Telecons Minutes of Meetings		
• EOP2 meeting (indicate date)		
• Pre-NDA meeting (indicate date)		
• Pre-Approval Safety Conference (indicate date; approvals only)	2/4/2005	
• Other		
❖ Advisory Committee Meeting		
• Date of Meeting		N/A
• 48-hour alert		
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A	
Summary Application Review		
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Deputy Office Director 3/16/2005 Medical Team Leader & Division Director Review of 3/16/2005	
Clinical Information		
❖ Clinical review(s) (indicate date for each review)	3/14/2005	
❖ Microbiology (efficacy) review(s) (indicate date for each review)	2/18/2005	
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	a. see Clinical review : p. 351 b. ODS Hepatic Safety: 1/31/2005 c. ODS Post-Marketing: 2/22/2005	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	See Clinical Review pp. 13 & 357.	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	3/16/2005	
❖ Demographic Worksheet (NME approvals only)	N/A	
❖ Statistical review(s) (indicate date for each review)	3/4/2005	
❖ Biopharmaceutical review(s) (indicate date for each review)	3/3/2005	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A	
❖ Clinical Inspection Review Summary (DSI)	N/A	
• Clinical studies		
• Bioequivalence studies		
CMC Information		
❖ CMC review(s) (indicate date for each review)	3/7/2005	
❖ Environmental Assessment	Please see Chemistry Review p. 40	
• Categorical Exclusion (indicate review date)	See Chemistry review p. 40 dated 3/7/2005	
• Review & FONSI (indicate date of review)		
• Review & Environmental Impact Statement (indicate date of each review)	See Chemistry review p. 10 dated 3/7/2005	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	2/24/2005	
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable (See Chemistry review p. 38 dated 3/7/2005) () Withhold recommendation	

❖ Methods validation	(X) Completed (See Chemistry review p. 38 dated 3/7/2005) () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	3/14/2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

MEMORANDUM

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

DATE: March 15, 2005

TO: The NDAs 21-506 and 21-754 file

FROM: Christina H. Chi, Ph.D.

SUBJECT: **FDA Requests to Fujisawa for more Information on (pending) NDAs 21-506 and 21-754, Mycamine (micafungin sodium) for (IV) injection, 50 mg/vial, from December 21, 2004, until March 4, 2005**

The following requests were sent to Fujisawa per electronic mail:

- 1) **Date:** Tues 12/21/2004, 03:35 PM
Subject: NDAs 21-506 and 21-754 for Micafungin
Message: Request for Information from Fujisawa (directly from M.Singer, M.D.)
 1. Autopsy reports for the following pediatric patients:
 - 262773 (98-0-046)
 - 084782 (98-0-046)
 - 059773 (98-0-046)
 2. Table summarizing all serious renal adverse events in pediatric patients (< 16 years old), regardless of relationship to study drug.
 3. Narrative summaries for each pediatric patient (< 16 years old) with the following serious adverse events:

Respiratory System:
respiratory failure
dyspnea
hypoxia
respiratory distress syndrome
lung hemorrhage
lung edema

Body as a Whole:

allergic reaction

ascites

facial edema

Cardiovascular System:

arrhythmia

bradycardia

shock

hypotension

hypertension

deep thrombophlebitis

heart failure

heart arrest

vasodilatation

ventricular tachycardia

Nervous System:

intracranial hemorrhage

convulsion

brain edema

cerebral hemorrhage

cerebrovascular accident

coma

encephalopathy

subdural hematoma (listed under cardiovascular)

hemiplegia

stupor

Hemic and Lymphatic System:

thrombocytopenia

leukopenia

leukocytosis

cyanosis

coagulation disorder

Metabolic and Nutritional Disorders:

hypokalemia

hypophosphatemia

Urogenital System:

oliguria

Skin and Appendages:

skin necrosis

Special Senses:

Papilledema

Digestive System:

gastrointestinal hemorrhage

hematemesis

stomach ulcer hemorrhage

intestinal perforation

Include patient number, study protocol, other adverse events, start and stop dates micafugin, concomitant medications, and underlying conditions. Additionally, a separate dataset is requested for these patients for all laboratory tests over time, with unique identifier (patient number) for each row.

3. Please provide narrative summaries for all pediatric patients (< 16 years old) who discontinued micafungin due to adverse events.

4. Case report forms for the following pediatric patients:

203605 (98-0-050)

084782 (98-0-046)

002772 (98-0-046)

5. Further information regarding micafungin-treated pediatric patient who died due to renal failure. Was this patient number 509773 in study 98-0-046 or a different patient? If a different patient, we will need narrative summary and dataset with BUN and creatinine over time.

6. For micafungin-treated pediatric patients who experienced serious laboratory abnormalities, please provide a short narrative summary for each patient and a dataset for each patient (by patient number and study protocol) with laboratory data over time. Please include micafungin dose, start and stop dates.

7. Case report forms for the following patients:

063788 (98-0-046)

1141003 (98-0-050)

10705001 (03-7-005)

203605 (98-0-050)

1143501 (98-0-050)

8. Table of subjects/patients in safety database who discontinued micafungin due to a renal adverse event- please list patient/subject number, adverse event, date of onset, study protocol, micafungin dose and duration, day of discontinuation, severity, seriousness and outcome of event.

9. Table of patients in safety database who died due to a renal adverse event listed by patient number and study protocol, dose and duration of micafungin, onset of adverse event, and short narrative summary.

2) **Date: Wed 12/22/2004 11:25 AM**

Subject: Request for information (direct from M. Singer, M.D.)

Message:

Mr. Reed,

Please copy me your responses by fax (301)827-2475 or e-mail. We have an additional request regarding NDA 21-506:

1. Please provide a table of hepatic adverse events including hepatic laboratory abnormalities (AST, ALT, Alkaline phosphatase, direct, indirect, and total bilirubin), by duration of therapy for the 50 mg dose of micafungin (1 mg/kg in pediatric patients). Please combine data from studies 98-0-050 and 98-0-047 and include a separate table for the hepatic adverse events for fluconazole from study 98-0-050.

We also have some additional requests regarding NDA 21-754:

1. Please provide a Table by patient and study protocol, all patients with serious hematologic adverse events; and (in a separate table) all patients who died due to serious hematological adverse events; and in another table, all patients who discontinued micafungin due to a hematologic adverse event.

2. Please provide narrative summaries for all patients with the serious hematologic adverse events (regardless of relatedness to micafungin):

Leukopenia

Thrombocytopenia

Anemia

Cyanosis

Coagulation disorder

Pancytopenia

Hemolysis

Erythrocytes abnormal

Thrombotic thrombocytopenic pupura

For the above patients, please provide a dataset by patient number and study, with micafungin dose, duration, start and stop dates, onset date of adverse event, outcome, and hematologic laboratories over time(including WBC, platelets, hemoglobin, hematocrit, absolute neutrophil count, and prothrombin time).

3.For patients who died of a hematologic adverse event, please provide narrative summary and laboratories as in item 2 above.

4. Please provide narrative summary and dataset (as in item 2)for all patients who discontinued (or required interruption or dose-reduction) of micafungin for a hematologic adverse event.

5. For healthy volunteers who had any hematologic adverse event, please provide short descriptive summary for subject, and dataset as in item 2.

6. Narrative summary and dataset (as in item 2) for all patients who experienced hemolysis, hemolytic anemia or abnormal erythrocytes as adverse events (regardless of relationship to micafungin or to seriousness of event).

Thank you for your prompt attention to our requests,

Mary Singer, M.D.

3) Date: Wed 01/05/2005 5:57 PM
Subject: RE: FK463 - Follow-up to January 5th Fax Message:
Message:
Dear Robert:

Sorry, I forgot to include the response to items 3a and 6 of our Dec. 21 request: Yes, the proposed data structure is acceptable.

Christina

4) Date: Mon 01/24/2005 5:50 PM
Subject: NDAs 21-506 and 21-754: Urgent Request
Message:

We have an urgent request and because the due date of these NDAs is very near, I am going to e-mail (instead of the more formal fax) it to you.

Please send us ASAP the following MedWatches for the 3 cases of TEN:

PSUR-1: Unknown MCN

PSUR-2: 2003JP006304

PSUR-3: 2003JP007123

5) Date: Tue 01/25/2005 3:18 PM
Subject: NDA 21-754: interaction study 03-0-176
Message:

Please provide a graphic representation of data for ALT (y-axis) vs. time (x-axis) for each patient in the interaction study 03-0-176 (micafungin plus mycophenolate mofetil).

6) Date: Wed 01/26/2005 8:14 AM
Subject: micafungin
Message: (direct from Mary Singer, M.D. to Fujisawa):

I have some additional requests for information:

1. For the interaction study with mycophenolate mofetil, (03-0-176) please also provide a listing of adverse events by subject in addition to the graphic representation for ALT data by subject, requested on 1/25/05. Please also provide graphic data for AST by subject.
2. For the above study, please propose a rationale for the increases in ALT seen in healthy volunteers.
3. Please provide the same data (graphic representation of ALT and AST over time; and listing of adverse events by subject) for the drug interaction studies with cyclosporine, tacrolimus, and sirolimus.
4. For all healthy volunteers in any study who received at least 150 mg/day micafungin (alone), please provide individual subject graphic profiles for AST and ALT over time, as well as listing of adverse events

7) Date: Tue 02/01/2005 9:33 AM

Subject: NDA 21-754: INFORMATION REQUEST

Message:

The Clinical discipline needs the following information:

1. A listing by patient number and protocol of all patients in the safety database who received mycophenolate mofetil and micafungin concomitantly. Please provide profiles for each of these patients, including baseline conditions, micafungin dose and duration, adverse events, and hepatic laboratories, AST, ALT, bilirubin, alkaline phosphatase over time, and graphic representation of AST and ALT over time. Additionally, please provide narrative summaries, if available.
2. A listing of generic names for those drugs in the drug compatibility study listed as incompatible with micafungin, or caused reduced potency of micafungin. Additionally, please note which of these drugs are not approved for use in the U.S.
3. Tables of common adverse events ($\geq 1\%$) in the safety database (2402 subjects, and 1980 patient) by MedDRA Body System and Term.

8) Date: Wed 02/02/2005 11:41 AM

Subject: NDA 21-754: Mycafungin information request

Message:

Please provide a listing by patient number and protocol of all patients in the safety database who received either tacrolimus, sirolimus, ritonavir, cyclosporine, and nifedipine with micafungin concomitantly. Please provide profiles for each of these patients, including baseline conditions, micafungin dose and duration, adverse events, and hepatic laboratories, AST, ALT, bilirubin, alkaline phosphatase over time, and graphic representation of AST and ALT over time. Additionally, please provide narrative summaries, if available.

9) Date: Thu 02/03/2005 11:58 AM
Subject: URGENT REQUEST
Message:

Please provide us with the following information as soon as possible:

1. In Study 98-0-050 suspected systemic fungal infection was established if all of the following criteria were met for at least 96 hours:
 - neutropenia (ANC <500 cells/mm³);
 - persistent or recurrent fever ($\geq 100.4^{\circ}\text{F}$, $\geq 38.0^{\circ}\text{C}$) for which there was no known etiology; AND
 - failure to respond to at least 96 hours of broad spectrum antibacterial therapy.

In the study report, 64/425 micafungin and 98/257 fluconazole patients received empirical therapy for a suspected fungal infection. Please provide a listing of patients who met all three criteria above, regardless of whether or not empirical therapy was actually initiated. For patients who did not receive empirical therapy, despite their qualification, please indicate whether any were treated empirically at a later time or whether they developed a proven/probable infection during the study. Please indicate the timeline of empirical therapy or treatment of proven/probable infection in relation to study drug and the period of neutropenia/fever.

2. For patients who developed a proven or probable infection, please indicate if any were treated empirically with antifungal therapy at any point prior to the diagnosis of proven/probable infection. Please indicate the drug, dose, and timeline of the empiric therapy in relation to diagnosis of proven/probable infection.

3. Please clarify whether or not doses higher than 50 mg/day of micafungin and 400 mg/day of fluconazole were administered to any patient during the study, as empirical therapy, treatment of a proven/probable infection, maintenance therapy, or new prophylaxis. If higher doses were used, please provide information on the patients receiving the higher dose, including duration of therapy and relationship to development of a proven/probable infection.

Please send this information in the form of SAS (.xpt) data transport files as well as summary listings and clinical narratives in a .pdf file.

4. In Study GLR000510, please summarize the mean (range) QT prolongation in the beagle dogs that received 10 and 32 mg/kg . Further, please summarize the mean (range) QT prolongation in all of the normal volunteer studies, including all drug-interaction studies

10) Date: Mon 02/07/2005 1:56 PM

Subject: NDA 21-754 - February 3 Response

Message:

Your email on Friday 2/4/2005 7:04 contains a partial response to our request for further information on patients in the prophylaxis study 050 who met criteria for suspected fungal infection but who did not receive empirical therapy. However, it does not contain the SAS transport file as requested.

We are resending the following request to clarify the information we are seeking:

Please provide the agency with the following patient listings for Study 050:

- 1) a list of patients in the micafungin and fluconazole groups who received systemic antifungal therapy anytime from end of prophylactic therapy to 4 weeks post end of prophylactic therapy
- 2) a listing of the above patients in either treatment group who developed probable and proven fungal infection
- 3) a listing of patients in the mycamine and fluconazole treatment groups with persistent fever and neutropenia despite 72 hours of antibacterial therapy at any time during prophylactic therapy to the end of prophylactic therapy and from the end of prophylactic therapy to 4 weeks after the end of prophylactic therapy

Please send this information in the form of SAS data transport files as well as summary listings in a .pdf file as soon as possible.

11) Date: Mon 02/07/2005 6:28 PM

Subject: Urgent Information Request for Mycamine, micafungin for Injection

Message:

These are the additional information we need:

1. Please characterize the hepatic events and clinical hepatic safety in patients who received MYCAMINE with fluconazole, nifedipine, and ritonavir, including information on dose adjustment, drug discontinuation and clinical adverse events in relation to concomitant drug exposure and the magnitude of transaminase elevations noted.

2. Please provide autopsy reports for the following patients:

063785 (study 046)

3423101 (study 050)

585271 (study 047)

3. As outlined in the fax accompanying the proposed label, which was sent 2/4/05, we would like to identify patients in a systemic order who meet the criteria for treatment failure. Starting with the full analysis set:

- a. Please identify patients who died through the end of the study. Any patient who was diagnosed (by the independent investigator) as having a proven or probable infection should be listed. Remove these patients from the patient population. Then, please then identify:
- b. Patients who were diagnosed (by the independent investigator) as having a proven or probable infection. Remove these patients from the patient population. Then, please identify:
- c. Patients who met the criteria of persistent fever and neutropenia despite 96 hours of antibacterials prior to the end of prophylactic therapy. Only those patients who met the protocol specified criteria should be listed, regardless of whether or not they received systemic antibacterials. Remove these patients from the patient population. Then, please identify:
- d. Patients who received systemic antifungal therapy anytime during the study, regardless of the reason indicated by the investigator. Please indicate which patients were treated prior to the end of prophylactic therapy and those who were treated between the end of prophylactic therapy and end of study. Remove these patients from the patient population. Then, the remaining patients may be used to calculate treatment success.

Please send all the information in the form of SAS data transport files as well as summary listings in a .pdf file as soon as possible.

12) Date: Thu 02/10/2005 2:18 PM

Subject: Clarification to our 2/4/05 Micafungin Information request

Message:

We are sending this message regarding our 2/4/05 request:

In order to both clarify and to narrow down our request for information sent with our labeling revisions on 2/4/05 (#2g), please see the following:

1. For patients in study 98-0-050, please provide a table showing the proportions of patients with serious hepatic adverse events in those who received:

- micafungin (without nifedipine)
- micafungin + nifedipine
- fluconazole (without nifedipine)
- and fluconazole + nifedipine,

with links to the data provided previously (patient listing and patient profile of all patients with serious hepatic events and graphic representation of ALT and ALT in all patients).

2. For patients in study 98-0-050, please provide listing of patients who received micafungin plus nifedipine who had AST and/or ALT elevation ≥ 5 times upper limit of normal (any time during study), with links to previous data for micafungin-treated patients. Additionally, please provide a table comparing rates of AST/ALT elevation ≥ 5 x ULN for patients who received:

- micafungin (without nifedipine)

- micafungin plus nifedipine
- fluconazole (without nifedipine)
- fluconazole plus nifedipine.

3. Please send the same analysis as requested in # 1 and 2, above, for patients in study 98-0-050 who received mycophenolate mofetil, cyclosporine or tacrolimus with either micafungin or fluconazole.

4. For patients in study FG463-21-09, please provide same information as requested in # 1 and 2 above, for those who received ritonavir with either micafungin or fluconazole.

5. If any of the individual studies included patients with concomitant micafungin plus fluconazole, similar information comparing serious hepatic adverse events, and AST/ALT elevations $\geq 5 \times$ ULN, to patients who received micafungin alone or fluconazole alone in those studies would be useful.

13) Date: Mon 02/14/2005 2:10 PM

Subject: Request re: NDAs 21-506 & 21-754 Mycamine

Message:

We have the following clarification request:

The 'susp50.pdf' document containing a listing of patients with suspected fungal infection in study 050 submitted last week on a diskette labeled N21506\050209 has the following footnote: " (*) met criteria for suspected fungal infection, but did not receive empiric therapy". We are unable to identify which patients this footnote is referring to. Please specify which patients met criteria for suspected fungal infection but did not receive empiric therapy.

14) Date: Thu 02/17/2005 12:14 PM

Subject: Question regarding NDA 21-754 Mycamine

Message:

We have a question regarding the data we received in response to our question 2g as amended on 2/10/05:

Did all the hepatic SAEs and AST/ALT elevations to $> 5 \times$ ULN occur during or after concurrent administration of micafungin with the second drug (cyclosporine, mycophenolate...)? Or did some of these events or laboratory abnormalities occur during the study, but prior to the concurrent use of micafungin and the second drug? If the latter is true, then please exclude those patients and re-analyze the data as per our previous request.

15) Date: Fri 03/04/2005 04:31 PM

Subject: FDA Request for MYCAMINE NDA 21,506 Analysis Clarification

Message:

We have the following request pertaining to study 98-0-050.

We noticed in Table 13.4.4.1 in the original study report for 98-0-050 that there were 16 patients (7 micafungin, 9 fluconazole) who were classified as 'N/A'. These patients were also classified among the full analysis set population within the 'OUTCOME' dataset as '9' for 'SUCCSSCD' variable. We are providing these 16 patient numbers below.

Please provide the outcome of these 8 patients who did not die during study nor were found to have proven, probable or suspected fungal infection, based on your analysis of outcome by the protocol specific criteria (submission entitled 'Revision of Prophylaxis Efficacy Table-Table 2k', letter date 2/15/05). We believe that these 8 patients should remain as failures in efficacy analysis and should be reported as such in the label. Overall efficacy results should not be affected.

<u>Patient Numbers</u>	<u>Treatment Group</u>
0511015	Micafungin
0571001	Micafungin
0701002	Fluconazole
3421016	Micafungin
4881004	Micafungin
0081009	Fluconazole
0703002	Fluconazole
4881001	Micafungin

0202602-death already treated as failure
0511019-death already treated as failure
0622501-death already treated as failure
0791007-death already treated as failure
1413002-death already treated as failure
3423101-death already treated as failure
4053104-death already treated as failure
4213602 -death already treated as failure

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/s/

Christina Chi
4/7/05 11:44:48 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 4, 2005
TIME: 3:00 - 5:00 PM
LOCATION: 9201 Corporate Blvd, Rockville, MD.
APPLICATION: NDAs 21-506 and 21-754
DRUG NAME: Mycamine™, micafungin sodium, 50 mg/vial, for IV Injection
TYPE OF MEETING: Pre-Approval Safety Meeting

MEETING CHAIR: Mary Singer, M.D.
MEETING RECORDER: Christina H. Chi, Ph.D.

FDA ATTENDEES: (Title and Office/Division)

Renata Albrecht, M.D., Division Director
Shukal Bala, Ph.D., Microbiology Team Leader
Christina H. Chi, Ph.D., Regulatory Project Manager
Phillip Colangelo, Ph.D., Clinical Pharmacology and BioPharmaceutics Team Leader
Cheryl Dixon, Ph.D., Acting Biostatistics Team Leader
Evelyn Farinas, R.Ph., Safety Evaluator, DDRE (HFD-430)
Steve Hundley, Ph.D., Pharm.Toxicology Acting Team Leader
Jang Ik Lee, Ph.D., Clinical Pharmacology and BioPharmaceutics Reviewer
Owen McMaster, Ph.D., Pharm.Toxicology Reviewer
Joette Meyer, Pharm.D., Medical Reviewer
Eileen A. Navarro, M.D., Medical Team Leader
Quynh Nguyen, Pharm.D., Project Manager, DDRE (HFD-430)
John Powers, M.D., Lead Medical Reviewer
David Roeder, M.Sc., ADRA, ODE IV
Adrienne Rothstein, Pharm.D., Safety Evaluator, DDRE (HFD-430)
Mark Seggel, Ph.D., Chemistry Acting Team Leader
Mary Singer, M.D., Medical Reviewer
LaRee Tracy, Ph.D., Biostatistics Reviewer
Via telephone: Min Chen, R.Ph., Associate Director, DDRE (HFD-430)

EXTERNAL CONSTITUENT ATTENDEES: None

BACKGROUND:

Mycamine™ (micafungin sodium) is a new molecular entity submitted for approval 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). Micafungin sodium product has been approved and marketed in Japan as Funguard® since October 2002.

MEETING OBJECTIVES:

To review the clinical safety experience in both NDA applications and the Japanese post-marketing experience with an emphasis on serious hepatic, renal, hematologic, hypersensitivity, and cardiac events to obtain insight for the labeling and development of risk management plan.

DISCUSSION POINTS AND DECISIONS (AGREEMENTS) REACHED:

The details of the adverse events can be found in both the medical officer's reviews and the Office of Drug Safety (ODS) consults reviews.

Following is a listing of the safety issues identified and the Divisions' risk management plan for the identified risks in consultation with the ODS (agreed upon at the meeting):

Safety Issues

Risk Management Plan

Anaphylaxis/anaphylactoid reactions:

Warning in label
Postmarketing surveillance by ODS

Hypersensitivity:

Rash, erythema multiforme, TEN

Postmarketing surveillance by ODS for serious rash, erythema multiforme, toxic epidermal necrolysis, Steven's Johnson syndrome

Hepatic safety:

Hepatic laboratory abnormalities
Hepatic failure or dysfunction

Precaution in label
Postmarketing surveillance by ODS for serious hepatic failure or impairment, liver damage

Drug interactions:

Increased ALT in mycophenolate-micafungin interaction study

Hepatic precaution in label

Renal safety:

Renal failure, renal impairment, renal laboratory abnormalities,

hemolytic uremic syndrome

Precaution in label
Postmarketing surveillance by ODS for serious renal failure, hemolytic uremic syndrome

Hematologic safety:

Hemolysis, hemolytic anemia
Leukopenia, anemia, thrombocytopenia, pancytopenia, thrombotic thrombocytopenic purpura (TTP)

Precaution in label for hemolysis
Postmarketing surveillance by ODS for serious hemolysis, hemolytic anemia, TTP, ITP, and pancytopenia

Vascular Reactions:

Phlebitis, thrombophlebitis

Postmarketing surveillance by ODS for serious deep venous thrombosis, arterial thrombosis, pulmonary embolism, myocardial infarct or ischemia, stroke

Cardiovascular Safety:

Shock, cardiac arrest, arrhythmia

Postmarketing surveillance by ODS for serious events of shock, cardiac arrest, arrhythmia, QTc prolongation

Infusion-related Reactions:

Hypertension, hypotension,
Vasodilatation, tachycardia, dyspnea,
cyanosis, chills/rigors

Postmarketing surveillance by ODS for serious events of hypertension, hypotension, cyanosis.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There were no unresolved issues and no additional studies proposed.

ACTION ITEMS:

ODS will monitor post-marketing adverse events.

ATTACHMENTS/HANDOUTS:

3 handouts were distributed during the meeting:

- a listing of the safety issues identified and the Divisions' risk management plan for the identified risks by Dr. Mary Singer as listed under "DISCUSSION POINTS AND DECISIONS (AGREEMENTS) REACHED" of this document and also can be found in her review.
- A drug safety review by John Senior, M.D., Medical Safety Reviewer of ODS, HFD-030 (please see under ODS post-marketing safety review, appended to review of NDAs 21-506 and 21-754)
- A post-marketing safety review by Adrienne Rothstein, Pharm.D., Safety Evaluator of DDRE, HFD-430 (please see under ODS post-marketing safety review, appended to review of NDAs 21-506 and 21-754).

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/s/

Renata Albrecht
3/14/05 06:04:13 PM



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 April 23, 2004 new drug application (NDA) 21-754 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg. We also refer to your August 24, 2004 resubmission of NDA 21-506 for Mycamine™ (micafungin sodium) for Injection, 50 mg.

On January 28, 2005, we received your January 27, 2005 major amendment to these applications. The receipt dates are within 3 months of the user fee goal dates. Therefore, we are extending the goal dates by three months to provide time for a full review of these submissions. The extended user fee goal dates are May 26, 2005 for NDA 21-754 and May 25, 2005 for NDA 21-506.

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}

Diana Willard
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Diana Willard

2/18/05 09:44:42 AM

NDA 21-506 and NDA 21-754/Extension of User Fee Goal Date



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: January 14, 2005

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 2

Comments: Please review this request and respond at your earliest convenience.

Document to be mailed: YES NO

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

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Memorandum

TELEPHONE FACSIMILE

Date: January 14, 2005

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA clarification and request for additional clinical information on NDAs
21-754 and 21-506 for Mycamine (micafungin sodium).

Clinical:

We have a question regarding the Japanese label, in the section, "Precautions during Use" section 3 "Incompatibility"- Table 1 (Drugs which cause immediate precipitation); and Table 2 (Drugs which may reduce potency):

There is no information about micafungin precipitation or reduced potency with other drugs provided in the proposed U.S. label.

Please provide all relevant information regarding incompatibility and proposed changes in label.

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/s/

Christina Chi
1/14/05 03:53:04 PM
CSO

Mary Singer
1/14/05 04:11:55 PM
MEDICAL OFFICER
01-14-05 Request for info



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: January 6, 2005

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 2

Comments: Please review the following document and respond at your earliest convenience
(per e-mail to C.Chi and LaRee Tracy, and a formal submission to the NDA)

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: January 6, 2005

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA's request for additional information to NDA 21-754 for Mycamine
(micafungin sodium)

Biostatistics:

1. Please submit an additional dataset containing information on all patients in the full analysis set in Study 03-7-005 who met the primary endpoint of endoscopic cure at EOT. In this dataset please include the following:
 - Patient ID
 - Listing of all concomitant antifungal therapies received post-randomization along with date therapy was initiated, date stopped (if applicable) duration and reason for therapy
 - Patient status at the 2 and 4 week follow-up visit (i.e. relapse, no relapse, death, or LTF) along with 2 and 4 week visit dates
 - Randomized study treatment along with start and stop dates
 - Clinical outcome at EOT

2. Please submit an additional dataset containing information on all patients in the full analysis set in Study FG463-21-09 who met the primary endpoint of endoscopic cure at EOT. In this dataset please include the following:
 - Patient ID
 - Listing of all concomitant antifungal therapies received post-randomization along with date therapy was initiated, date stopped (if applicable) duration and reason for therapy
 - Patient status at the 2 follow-up (i.e. relapse, no relapse, death, or LTF) along with 2 week visit date
 - Randomized study treatment along with start and stop dates
 - Clinical outcome at EOT

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Christina Chi
1/6/05 04:00:05 PM
CSO

Mary Singer
1/6/05 04:41:08 PM
MEDICAL OFFICER
Request for information 1-06-05



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: January 3, 2005

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 3

Comments: Please review this request and respond at your earliest convenience.

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: January 3, 2005

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA request for additional clinical information on NDAs 21-754 and 21-506 for Mycamine (micafungin sodium).

Clinical:

Please provide the following additional information:

1. Listing (by patient number and study) and narrative summaries for **all** patients (regardless of drug relatedness) with serious adverse events and for patients in whom micafungin was discontinued due to adverse events in the following COSTART Systems:

Respiratory System
Cardiovascular System
Body as a Whole
Digestive System
Nervous System:
Metabolic and Nutritional disorders
Urogenital System
Skin and Appendages
Musculoskeletal system
Special Senses
Hemic and Lymphatic system

For patients with serious adverse events in the cardiovascular system including (but not limited to) the following COSTART terms: arrhythmia, ventricular tachycardia, myocardial infarct, heart arrest, bradycardia, tachycardia, atrial flutter, atrial fibrillation, please also provide EKG and vital sign data.

2. Listing (by subject number and study), and short descriptive summaries for all healthy volunteers with any cardiovascular adverse event, including EKG and vital sign data.
3. Listing (by subject number and study), and short descriptive summaries for all healthy volunteers with any allergic or histamine-type reaction (including, but not limited to rash, maculopapular rash, pruritis, vesiculobullous rash, facial edema, skin erythema, and vasodilation, and dyspnea).
4. Final narrative summary and outside hematology consultation report for subject number 24 in study FG463-21-06 (hemolysis in healthy volunteer).
5. Short descriptive summary for healthy volunteers who developed anorexia, esophagitis, mouth ulceration, and stomatitis.
6. Definition of the COSTART term "hyperlipemia". Does this refer to hypercholesterolemia, hypertriglyceridemia, both, or neither?
7. Summary tables of pertinent laboratory data from subjects and volunteers (listed by patient/subject number and study) with hyperlipemia and hypercholesteremia listed as adverse events.
8. Short descriptive summary for healthy volunteers and laboratory data for subjects with hypokalemia reported as an adverse event.
9. Listing (by patient number and study), and narrative summaries for all micafungin-treated patients with a serious-adverse event that resulted in death.
10. Listing (by patient number and study) of all serious adverse events, and narrative summaries for all micafungin-treated patients who died.
11. In the Tables showing primary cause of death by COSTART Term, are these same events also listed in the Tables showing serious adverse events, or are these additional serious adverse events which resulted in death? Similarly, in the tables showing incidence of adverse events resulting in study drug discontinuation, are these events also included in the Tables of all adverse events or serious adverse events?
12. Please define the following terms used in the global periodic safety update:
"ADRs and AEs"
"Unlisted and Listed ADRs and AEs"

13. Measures of central tendency and shift tables for WBC and platelets for all patients and subjects.
14. Autopsy report for patient number 2506 in study FG463-21-09 (site BR006).
15. Regarding item #1 sent in an email by Dr. Mary Singer to Fujisawa on December 22nd (hepatic adverse events for the 50 mg micafungin dose), please provide incidence rates using the number of patients as the denominator and not number of events.
16. Please provide narratives for the two patients in Study 98-0-050 who discontinued micafungin due to hepatic-related adverse events considered to be related to study drug. If these narratives have already been provided as part of another request, please provide the date on which they were submitted.
17. Regarding Item 6 of your submission dated October 25, 2004, for all tables submitted please provide incidence rates by number of patients, instead of number of events. For example, Table R6 2 should be recreated to provide incidence rates for events considered to be the primary cause of death for patients receiving the 50 mg (1 mg/kg) dose of micafungin. The denominator for these incidence rates should be number of deaths.
18. Please also provide a table of the incidence of treatment-related adverse events by COSTART term for the 50 mg (1 mg/kg) dose of micafungin and fluconazole, by dose, for Studies 98-0-050, FG-463-21-09, and 98-0-047. The denominator should be number of patients.
19. Please resend File: 14.1-14.3.pdf that contains the protocol and SAP for study FG09FG09 CSR in a pdf format as soon as possible. (The link to this document is: \\Cdsesub1\n21754\N_000\2004-04-23\CLINSTAT\FG09\APP , and only this particular file is corrupted.

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/s/

Christina Chi
1/4/05 10:21:49 AM
CSO

Joette Meyer
1/4/05 12:50:34 PM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: December 20, 2004

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 2

Comments: Please review the following document and respond at your earliest convenience
(per e-mail to C.Chi and LaRee Tracy, and a formal submission to the NDA)

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: December 20, 2004

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA's comment to NDA 21-754 for Mycamine (micafungin sodium),
submission dated September 29, 2004, pertaining to the use of the
proposed closed testing procedure in the primary efficacy analysis of study
03-0-192.

Biostatistics:

We have the following comment pertaining to your submission dated September 29, 2004 that provides discussion regarding use of the proposed closed testing procedure in the primary efficacy analysis of study 03-0-192:

The Division has reviewed your detailed discussion pertaining to the use of the closed testing procedure as proposed in the primary efficacy analysis for Study 03-0-192 and find it acceptable. Please note that failure to reject the null hypothesis in the first step, i.e. the lower bound of 95% confidence interval calculated around the difference between pooled micafungin groups (150 mg/day and 100 mg/day) and caspofungin is less than -0.15, will prevent further comparisons (i.e. pair-wise comparisons) resulting in a failure to demonstrate non-inferiority of either micafungin treatment groups to comparator.

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/s/

Christina Chi
2/10/05 06:05:19 PM
CSO



Memorandum

TELEPHONE FACSIMILE

Date: December 14, 2004

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA request for additional clinical information on NDAs 21-754 and 21-506 for Mycamine (micafungin sodium).

Clinical:

We are requesting the following clinical information at your earliest convenience:

1. Case report forms for the following patients:
 - 10705001 (study 03-7-005)
 - 0122004 (study 98-0-050)
 - 0133501 (study 98-0-050)
 - 057502 (study 98-0-050)
 - 0702002 (study 98-0-050)
 - 1141003 (study 98-0-050)
 - 1413001 (study 98-0-050)
 - 3103 (study FG-21-09)
 - 5501, 5904, 6202, and 6902 (study FJ0003)
2. Tables by patient number showing all subjects in micafungin safety database who had AST and/or ALT elevation to > 10X upper limit of normal, alone or with conjoint elevation of bilirubin. Please show protocol, micafungin dose and duration, time

course of hepatic (AST, ALT, bilirubin, alkaline phosphatase) laboratory values, and all serious and non-serious adverse events for each patient.

3. Tables by subject number of healthy volunteers who had AST and/or ALT elevation to > 2 X upper limit of normal, alone or with conjoint bilirubin elevation. Please show protocol, time course of hepatic laboratory values, micafungin dose and duration, any adverse events.
4. Narratives (and case report forms) for all patients with hepatic failure in 01-0-124 study for micafungin and fluconazole-treated patients.
5. Narratives (and case report forms) for all 10 hepatic failures and 4 "liver damage" in pooled safety database (narratives received for serious, but not for non-serious hepatic failure and liver damage).
6. The denominator data for tables showing conjoint elevation of transaminases and bilirubin for patients with normal or elevated transaminases at baseline for the following Appendices in the safety update:
 - 13.1.1, 13.1.2.1, 13.1.2.2, 13.1.3, 13.1.4.1, 13.1.4.2, 13.1.5.1, 13.1.5.2
 - 13.2.1, 13.2.2.1, 13.2.2.2, 13.2.3, 13.2.4.1, 13.2.4.2, 13.2.5.1, 13.2.5.2
 - 13.3.1, 13.3.2.1, 13.3.2.2, 13.3.3, 13.3.4.1, 13.3.4.2, 13.3.5.1, 13.3.5.2
 - 13.4.1, 13.4.2.1, 13.4.2.2, 13.4.3, 13.4.4.1, 13.4.4.2, 13.4.5.1, 13.4.5.2
7. Autopsy report and pathology data for patient 585271 (study 047), and any other autopsy or pathology data on patients who had serious hepatobiliary adverse events or died due to hepatic failure.
8. For each micafungin-treated patient in safety database with a serious hepatobiliary adverse event, death due to hepatic failure, or a hepatobiliary adverse event resulting in micafungin discontinuation we have received a narrative summary, but are requesting the following additional information:
 - a. Dataset for each of these patients including AST, ALT, bilirubin, alkaline phosphatase (PT, if available) by date of test, start and stop date of micafungin. Please include all hepatic laboratory tests performed including baseline, during therapy, after treatment. Also specify upper limits of normal for each laboratory test in dataset (for the lab used to obtain the data). For example:

Patient Number ##### Protocol ###

Micafungin	Micafungin dose	Date of laboratory test	AST (U/L) ULN=	ALT (U/L) ULN=	Bilirubin (mg/dL) ULN=	Alkaline phosphatase (U/L) ULN=
		date				
Start date	100 mg	date				
		Date				
		date				
		date				
		date				
Stop date	150 mg	date				
		date				

ULN=upper limit of normal

- b. Graphic plot of these laboratory values over time for each patient including the information above.
9. For each healthy volunteers and patients who had combined AST/ALT elevation to > 3 x ULN and bilirubin elevation to > 2x ULN at any time during micafungin treatment, we are requesting the following information:
 - a. Short narrative summary including age, gender, micafungin dose and duration, concomitant medications, other adverse events, and any other pertinent information.
 - b. Dataset and graphic data as described above.
10. All information given to the expert panel in regard to the patients with serious hepatic adverse events, particularly any information which is not found in the narrative summary or dataset (for example, the hospital discharge summary, autopsy results and pathology results from autopsy or biopsy). It is important that we receive the same package of information (and in the same format) which the panel received, including the background document outlining the process and timing of the review and detailed information on each patient.
11. Summary data for patients who received at least 150 mg/day micafungin for at least 14 days:
 - c. Hepatic adverse events (all; serious; discontinuations)
 - d. Deaths due to hepatic adverse events
 - e. Hepatic laboratory abnormalities (summarized in mean and shift tables for each laboratory test, and conjoint elevation of bilirubin >2x ULN and transaminases > 3X ULN).
 - f. These patients should also be summarized as in item 1 above.

12. Summary data for all healthy volunteers who received who received at least 150 mg/day micafungin for at least 14 days, (or at least 10 days if 14 days not available), as in number 4 above. Those with serious hepatobiliary events or AST >3 x ULN and bilirubin > 2X ULN should be summarized as in item 2 above.
13. Please send us a sample of the requested data within 10 days, before sending all the information requested, so that we can review and request changes, as needed.
14. Further information on the two pediatric patients (under 16 years old) who had hepatic failure listed as an adverse event in Appendix 4.1.1, ISS, e NDA 21-754. Include patient number, study protocol, and whether the event was considered serious. For both of these patients, please provide a narrative summary and other pertinent information, including micafungin dose, duration, other adverse events, and concomitant medications. Hepatic laboratory data should be provided as a dataset and graphic plots, as requested in item 1 above.
15. Autopsy and pathology data on patient numbers 262779 (study 98-0-046), and 059533 (study 98-0-043).
16. Tables showing all serious hepatic adverse events (regardless of relationship to micafungin) in pediatric patients in the safety database (and in fluconazole-controlled studies), including patient number and study protocol.
17. Please confirm that there were no deaths in micafungin-treated pediatric patients due to hepatic failure or other hepatobiliary adverse events.
18. Patient numbers and the information requested in item 2 above for pediatric patients who had elevations of AST/ALT and bilirubin to ≥ 2 x ULN at any time during micafungin treatment (including all patients listed in Table 14, pediatric use summary, section 5.3.5.3.2).
19. For the tables on conjoint frequency of transaminase and bilirubin elevation in pediatric patients (Appendix 13.2.3, and 13.4.3 in section 5.3.5.3.2, eNDA 21-754), please provide denominator data, and in which study these patients were enrolled (i.e. why aren't all 244 pediatric patients shown in these tables?). Additionally for these tables, what is considered upper limit of normal (ULN)?
20. Summaries for all serious hematologic and cardiovascular postmarketing adverse events (similar to previous request for hepatic and renal postmarketing data).

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/s/

Christina Chi
12/14/04 04:41:16 PM
CSO

Mary Singer
12/17/04 07:49:46 AM
MEDICAL OFFICER
Request for information

Memo

To: Renata Albrect, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products; HFD-590

From: Felicia Duffy, RN, BSN
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Through: Alina Mahmud, R.Ph., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

CC: Anne Marie Homonnay-Weikel
Project Manager, Division of Special Pathogen and Immunologic Drug Products; HFD-590

Date: November 16, 2004

Re: ODS Consult 02-0128-3; Mycamine (Micafungin Sodium for Injection); NDA 21-506;
August 24, 2004 submission

This memorandum is in response to an October 25, 2004 request from your Division for a re-review of the proprietary name, Mycamine. The proposed proprietary name, Mycamine, was found acceptable by DMETS in reviews dated September 17, 2002 (ODS Consult #02-0128-1) and July 7, 2004 (ODS Consult #02-0128-2). Labels and labeling have not been re-submitted for re-review and comment at this time. Please refer to ODS Consult #02-0128-2, Section III, for DMETS' most recent comments on the carton label, container labeling, and package insert.

Since the July 7, 2004 review, DMETS identified the established name of Proamatine (Midodrine HCl), a prescription medication indicated for the treatment of symptomatic orthostatic hypertension, as a potential sound-alike drug to Mycamine. Both names contain 3 syllables, share the same first syllable (My vs. Mi), and have endings that rhyme (-amine vs. -odrine). However, the middle of each name is phonetically distinct (myCAMine vs. miDOdrine). Although both names share some phonetic similarities, they differ in indication for use (candidiasis vs. orthostatic hypertension), strength (50 mg/vial vs. 2.5 mg, 5 mg and 10 mg), dosage form (injectable vs. tablets), usual adult dosage (50 mg – 150 mg vs. 10 mg), frequency of administration (daily vs. TID), and route of administration (intravenous vs. oral). Based on the aforementioned differences between Mycamine and Midodrine, the potential for name confusion is minimal. Additionally, DDMAC finds the proprietary name Mycamine acceptable from a promotional perspective.

In summary, we have no objections to the use of the proprietary name, Mycamine. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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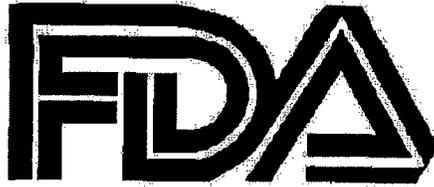
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/s/

Felicia Duffy
11/19/04 09:50:07 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/19/04 09:52:25 AM
DRUG SAFETY OFFICE REVIEWER



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: November 15, 2004

To: Robert M. Reed Associate Director, Regulatory Affairs	From: Anne Marie Homonnay-Weikel Regulatory Project Manager
Company: Fujisawa Healthcare, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (847) 317-7286	Fax Number: 301-827-2475
Phone Number:	Phone Number: 301-827-2183

Subject: FDA Information Request for NDA 21-754

Total no. of pages including cover: 2

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To facilitate completion of our review of your NDA submission, please provide the following additional information:

1. Summary tables indicating the reasons for treatment discontinuation for the following:
 - a summary table including all studies (combined) in the safety database
 - summary tables for the individual studies in the safety database
 - all fluconazole-controlled studies
 - by micafungin dose
2. In addition to all serious adverse events in the fluconazole-controlled studies, as requested previously, please provide summary tables for serious drug-related adverse events in these studies combined.

3. For common adverse events in fluconazole-controlled studies, the following terms were combined into a category/syndrome of "gastrointestinal bleeding/peptic ulcer disease": melena, gastritis, hematemesis, rectal hemorrhage, stomach ulcer, hemorrhagic gastritis, duodenitis, esophageal hemorrhage, peptic ulcer, stomach ulcer hemorrhage, and duodenal ulcer. There were more adverse events in the micafungin group than the fluconazole group for this category, however, the number of patients in each treatment group having one or more of those adverse events is needed to determine incidence.

Similarly, when the terms tuberculosis, aggravated tuberculosis, reactivated tuberculosis, and reactivated pulmonary tuberculosis are combined into the category "tuberculosis", there were more events in the micafungin group. Likewise for "pneumonia", including the terms pneumonia and interstitial pneumonia.

Please provide the number of patients who had one or more of the adverse events in these categories/syndromes ("gastrointestinal bleeding/peptic ulcer disease", "tuberculosis", and "pneumonia").

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/s/

Anna-Marie Homonnay
11/15/04 09:38:23 AM
CSO

Anna-Marie Homonnay
11/15/04 09:40:42 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: December 14, 2004

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 4

Comments: Please review this request and respond at your earliest convenience.

Document to be mailed: YES NO

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2004

To: Robert M. Reed Associate Director, Regulatory Affairs	From: Anne Marie Homonnay-Weikel Regulatory Project Manager
Company: Fujisawa Healthcare, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (847) 317-7286	Fax Number: 301-827-2475
Phone Number:	Phone Number: 301-827-2183

Subject: FDA Information Request

Total no. of pages including cover: 2

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We are consulting with the FDA Office of Drug Safety on the NDA review so we need extra paper copies of the submission and the safety data reformatted.

These should be sent directly as a desk copy to the reviewing safety consultant in the FDA Office of Drug Safety:

John Senior, M.D.
HFD-030
Parklawn Room 15B-33
5600 Fishers Lane
Rockville, MD 20857

1. Hard copies of entire submission- including 120 day safety update, and any additional data received (i.e. patient narratives...)

2. Tabulated test results for all liver function tests (AST, ALT, Alk Phos, bilirubin, and INR and GGT, if available) by date, as well as reference ranges in an EXCEL database. (these should be for entire safety database, by protocol, treatment, dose, and duration). We have this database in SAS.

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/s/

Anna-Marie Homonnay
11/8/04 09:57:27 AM
CSO

Anna-Marie Homonnay
11/8/04 10:01:36 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2004

To: Robert M. Reed Associate Director, Regulatory Affairs	From: Anne Marie Homonnay-Weikel Regulatory Project Manager
Company: Fujisawa Healthcare, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (847) 317-7286	Fax Number: 301-827-2475
Phone Number:	Phone Number: 301-827-2183

Subject: FDA Labeling Recommendations

Total no. of pages including cover: 1

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Please find below the comments we have received from the Office of Drug Safety regarding the safe labeling of the product:

A. CONTAINER LABEL (50 mg/vial)

1. The 50 mg/vial label uses a color to designate the strengths. This color blends into the background color of the container label and decreases the prominence and legibility of the strength. Please revise.
2. Currently the phrase " " appears in all upper case letters, whereas the established name appears in lower case letters. Please revise so that the established name and the phrase " " have the same prominence and case.
3. Please add the statement " "

B. CARTON LABELING (50 mg/vial - 10 vials per carton)

1. Please add the statement "
2. Increase the prominence of the statement "

C. PACKAGE INSERT LABELING

1. Dosage and Administration

- Please remove the _____
- Please _____ phrase "without a bacteriostatic agent" which appears as a descriptor to 0.9% sodium chloride for injection, USP, diluent used for reconstitution and dilution.

- 

2. Storage of Mycamine

Under "Storage of Reconstituted Product Concentrate", it currently states that the product should be protected from light, and could be stored for up to 24 hours at room temperature. This statement implies the product can be used for multiple doses. However, the product does not contain a preservative, and should be discarded after each use. Please revise the statement to _____

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/s/

Anna-Marie Homonnay
11/4/04 04:04:23 PM
CSO

Anna-Marie Homonnay
11/4/04 04:06:19 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 2004

To: Robert M. Reed Associate Director, Regulatory Affairs	From: Anne Marie Homonnay-Weikel Regulatory Project Manager
Company: Fujisawa Healthcare, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (847) 317-7286	Fax Number: 301-827-2475
Phone Number:	Phone Number: 301-827-2183

Subject: FDA Information Request for NDA 21-754 and 21-506

Total no. of pages including cover: 1

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Please provide the following:

1. In the 120-day safety update (summary of clinical safety), 2 deaths in the micafungin group were attributed to hepatic failure. In which study (or studies) were these 2 patients? Please provide case report forms and narrative summaries for these patients, including underlying disease, baseline conditions, prior and concomitant medications, dose and duration of micafungin, adverse events, timing and duration of adverse events, severity, outcome of adverse events, laboratory data, cause of death, contributing factors in death, assessment of relatedness to micafungin, and autopsy or liver biopsy reports (if any).
2. We are requesting that Fujisawa have an expert panel of hepatologists (external panel) review all deaths due to hepatic failure and serious adverse events of hepatic failure in the safety database (blinded as to whether patient was on micafungin or fluconazole) to further assess drug-relatedness.
3. Additionally, please provide us with any autopsy or other histopathological data (eg. liver biopsy) for all patients in the safety database who had hepatic failure listed as a serious adverse event.

4. Please provide narrative summaries for any fluconazole-treated patients in the safety database who died due to hepatic failure, or who had hepatic failure as a serious adverse event (include same information as requested above).
5. For patient 10705024 (study 005) please provide generic drug names for "Brufen", "Cozole", and "Domicum".
6. For patient 10745031 (study 005), please provide generic drug name for "Ciprobay".
7. For patient 10665037 (study 005), please provide generic drug name for "Cifran".
8. Please summarize in table form the incidence of primary cause of death for patients who received micafungin or fluconazole for each of the fluconazole-controlled studies. Please provide these data for individual studies, and for all fluconazole-controlled studies combined.
9. Please summarize in table form the incidence of all serious adverse events regardless of relationship to study drug, for patients who received either micafungin or fluconazole for each of the fluconazole-controlled studies (individually and combined).
10. Please summarize in table form the incidence of all adverse events resulting in drug discontinuation regardless of relationship to study drug for patients who received either micafungin or fluconazole in all fluconazole-controlled studies (individually and combined).
11. In review of study 005, we noticed that pneumonia and tuberculosis were reported as adverse events more frequently in the micafungin group than in the fluconazole group. For each of the fluconazole-controlled studies, both individually and combined, please provide a listing by patient, of those who developed any type of pneumonia or tuberculosis as an adverse event, a serious adverse event or as the cause of death. Include patient identification and study, the event, onset of event in relationship to study drug (eg. pneumonia started on day 3 of 14 days micafungin treatment), and outcome of adverse event for patients treated with either micafungin or fluconazole. If pneumonia and/or tuberculosis did, in fact, occur more frequently in micafungin-treated patients, either in the individual studies or in the aggregate data, please provide reason(s) or a mechanism whereby this may have occurred.
12. Please provide the narrative summary for patient 466171 (study 98-0-046) whose death was previously reported in NDA 21-506 as possibly related to micafungin.
13. Please provide a clinical narrative for Patient 123-3502 in Study 98-0-050.

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/s/

Anna-Marie Homonnay
10/28/04 02:32:40 PM
CSO

Anna-Marie Homonnay
10/28/04 02:36:06 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

Date: September 10, 2004

To: Robert Reed	From: Christina H. Chi
Company: Fujisawa Healthcare, Inc	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	Fax number: (301) 827-2326
Phone number: (847) 317-8985	Phone number: (301) 827-2127

Subject: Request for Additional Clinical Information.

Total no. of pages including cover: 4

Comments: Please review this request and respond at your earliest convenience.

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: September 10, 2004

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

To: Robert Reed
Associate Director, Regulatory Affairs
Fujisawa Healthcare, Inc

NDA: 21-754

Drug: Mycamine (micafungin sodium) for Injection

Subject: FDA request for additional information on NDA 21-754 for Mycamine (micafungin sodium) for treating esophageal candidiasis (EC), Protocol 03-7-005, in the 120-day safety update of August 24, 2004.

Clinical:

We are requesting the following clinical information at your earliest convenience:

1. The case report forms from study 03-7-005 (random 10% sample from each arm):

03145014	10665032	03145006	10615001
03235007	10665034	03235009	10655004
03235016	10695024	03235013	10665033
03235017	10705016	03245011	10665038
03235022	10705044	10305003	10665049
10365005	10705058	10365007	10695007
10445001	10745015	10445004	10755007
10575001	10745019	10475001	10755011
10575023	10745027	10495002	10765004
10575024	10745046	10575007	11635001
10595002	10745056	10575026	11645004
10595010	11635005	10575042	11645008
10605003	02545003	10605001	

2. The case report form and narrative summary for patient 1018P (center code ZA001) from study FG463-21-09.
3. Narrative summaries for all micafungin-treated patients who experienced the following adverse events regardless of any relationship to micafungin:
 - Hepatic failure or fulminant hepatitis
 - Any serious hepatic adverse event (clinical or laboratory)
 - Any serious renal adverse event (clinical or laboratory)

Include all subjects who meet the above criteria found in the safety database (2402 subjects) as well as in the database which includes postmarketing safety data. The narrative summaries should include medical history, allergies, concomitant medications, micafungin dose, timing of micafungin dosing (start and stop dates) and date of adverse event (AE), severity of AE, resolution of AE, and any other pertinent information regarding the AE.

4. Please provide the clinical dataset for study 005 using the following variables as columns, with a unique row for each patient:

Patient number
Treatment assignment
Dose
Start date medication
Stop date medication
Treatment duration
Age
Sex
Race
Baseline CD4 count
Full analysis set
Modified full analysis set
Per protocol set
Organism(s) isolated at baseline
Endoscopic grade at baseline
Endoscopic grade at EOT
Endoscopic grade 2 weeks post-treatment
Endoscopic grade 4 weeks post-treatment
Endoscopic response at EOT
Endoscopic response at 2 weeks post-treatment
Endoscopic response at 4 weeks post-treatment
Esophageal candidiasis (EC) clinical symptom grade at baseline
EC clinical symptom grade EOT
EC clinical symptom grade 2 weeks post-treatment
EC clinical symptom grade 4 weeks post-treatment
Clinical response at EOT

Clinical response at 2 weeks post-treatment
 Clinical response at 4 weeks post-treatment
 Overall response at EOT
 Overall response at 2 weeks post-treatment
 Overall response at 4 weeks post-treatment
 Oropharyngeal candidiasis (OPC) symptom grade at baseline
 OPC clinical symptom grade at EOT
 OPC clinical symptom grade at 2 weeks post-treatment
 OPC clinical symptom grade at 4 weeks post-treatment
 OPC clinical response at EOT
 OPC clinical response at 2 weeks post-treatment
 OPC clinical response at 4 weeks post-treatment
 Mycological response at EOT
 Mycological response at 2 weeks post-treatment
 Mycological response at 4 weeks post-treatment
 Relapse at 2 weeks post-treatment
 Relapse at 4 weeks post-treatment

5. With reference to the datasets contained in the Safety Update (8/24/04):
- a. We were unable to locate the file “isd\labs.xpt” under “crt\isd\” folder. The “define.pdf” file indicated that the laboratory values could be obtained in the dataset “labs.xpt”. However, when that file (“labs.xpt”) is opened from the “define.pdf” file, it does not contain the relevant chemistry data.
 - b. Please explain the contents of the files, “chem1.xpt”, “chem2.xpt”, “chem3.xpt”, and “chem4.xpt”.
 - c. Please provide a dataset with the following laboratory values as columns (one column for each scheduled and unscheduled laboratory value obtained) and a unique row for each patient: SGOT, SGPT, total bilirubin, and alkaline phosphatase. Please refer to the Table below, which is an example of the requested dataset.

Protocol	Patient	SGOT baseline	SGOT Day 7	SGOT Day 14	SGOT EOT	SGOT Other visit	SGOT Other visit
001	001	xx			xx		
001	002	xx			xx		
002	001	xx			xx		
002	002	xx			xx		
002	003	xx			xx		

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/s/

Christina Chi
9/10/04 04:55:00 PM
CSO

Eileen Navarro
9/13/04 08:37:15 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 10, 2004	DESIRED COMPLETION DATE: August 10, 2004 PDUFA DATE: Feb. 25, 2005	ODS CONSULT #: 02-0128-2
-------------------------------------	--	---------------------------------

TO: Renata Albrect, M.D.
Director, Division of Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Susan Peacock
Project Manager
HFD-590

PRODUCT NAME:
MycamineTM
(Micafungin Sodium for Injection)
50 mg

SPONSOR: Fujisawa

NDA #: 21-754

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, MycamineTM. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name MycamineTM acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 7, 2004

NDA NUMBER: 21-754

NAME OF DRUG: **Mycamine™**
(Micafungin Sodium for Injection)
50 mg _____

NDA SPONSOR: Fujisawa

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products for an assessment of the proprietary name "Mycamine™" regarding potential name confusion with other proprietary or established drug names. The container label, carton and package insert labeling were provided for review and comment.

The proposed name, Mycamine™ (NDA 21-506) was previously reviewed and found acceptable by DMETS on September 17, 2002 (ODS Consult # 02-0128-1). NDA 21-506 received an approvable action in January, 2002 for _____. The Division indicated that before NDA 21-506 could receive an approval with an indication for _____, the drug must first be approved for _____. Therefore, the sponsor submitted NDA 21-754, seeking an approval for _____. The sponsor will resubmit NDA 21-506 (with an indication of prophylaxis of _____ pending the approval of NDA 21-754 (with an indication of _____).

PRODUCT INFORMATION

Mycamine™ contains mycafungin, which inhibits the synthesis of 1,3-beta-D-glucan, an essential component of the cell wall of susceptible fungi. Mycamine is indicated for the treatment of patients with esophageal candidiasis. The recommended dose for the treatment of esophageal candidiasis is _____ 150 mg per day, administered by intravenous infusion. The diluent to be used for reconstitution and dilution is 0.9% sodium chloride for injection, USP (without a bacteriostatic agent). In addition, 5% dextrose injection, USP, may also be used. Mycamine™ will be available in _____ 50 mg _____ in packs of ten individual vial cartons.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databasesⁱⁱⁱ for existing drug names which sound-alike or look-alike to “Mycamine” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database^{iv} and the data provided by Thomson & Thomson’s SAEGIS Online Service^v were also conducted. An expert panel discussion was conducted to review all findings from the searches. Prescription studies were conducted in the previous review (ODS Consult # 02-0128-1), and not repeated during this analysis.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Mycamine. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name acceptable from a promotional perspective.
2. In our initial review, DMETS identified the names Hycomine, Micrainin, Mylaramine, Mysoline, and thiamine has having potential for confusion with Mycamine. Since the completion of our initial consult, the Expert Panel identified 2 proprietary names that were thought to have potential for confusion with Mycamine. An additional name, Miacalcin, was identified through independent review. These products are listed in Table 1 (page 4), along with the dosage forms available and usual dosage.

ⁱ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.

^{iv} WWW location <http://www.uspto.gov>.

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Mycamine (Rx)	Mycafungin Sodium for Injection 25 mg and 50 mg	50 mg to 100 mg by IV infusion daily.	
Myoview (Rx)	Technitium Tc99 for Injection	Range: 5 to 33 mCi For stress and rest imaging, 2 separate doses are used. When injections are administered on the same day, the first should be 5-12 mCi followed by a second dose of 15-33 mCi given 1 to 4 hours later.	**L/A
Mycodone (Rx)	Hydrocodone Tablets 5 mg	Take one tablet every 4 to 6 hours.	**L/A
Miacalcin (Rx)	Calcitonin-Salmon Injection: 200 IU/mL Nasal Spray: 200 IU/actuation	<u>Injection:</u> 100 IU/day subcutaneously or intramuscularly. <u>Nasal Spray:</u> 200 IU intranasally every day, alternating nostrils daily.	**S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Mycamine were discussed by the Expert Panel.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name “Mycamine”, the products considered to have potential for name confusion with Mycamine include: Myoview, Mycodone, and Miacalcin.

1. Myoview was identified to look similar to the proposed name, Mycamine (see page 5). Myoview contains technetium Tc99m, a diagnostic radiopharmaceutical indicated for scintigraphic imaging of the myocardium. It is also useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium. The recommend dose ranges from 5 millicuries to 33 millicuries, with imaging beginning fifteen minutes following administration of the agent. The look-alike similarity of the names is attributed to the beginning letter combinations “My”. The third letters of each name (“o” vs. “c”), as well as the ending letter combinations (“view” vs. “mine”) also look similar, depending on how they are scripted. Myoview and Mycamine share an overlapping dosage form (injection), route of administration (intravenously), and have overlapping numerals in their dosing strengths (5 millicuries vs. 50 mg). Both products differ in dosing regimen (two separate doses which given one to four hours apart vs. daily). Although Myoview and Mycamine are both packaged in vials, Myoview consists of a kit containing five vials of a sterile, non-pyrogen freeze dried mixture, along with the appropriate number of radiation labels, whereas Mycamine is available as 50 mg vials and in packs of ten individual vial cartons. Because Myoview is a radiopharmaceutical, special precautions are taken during the preparation of the drug,

which requires the preparer to wear water proof gloves, and use appropriate shielding at all times when handling the reconstituted vial or syringe containing the radioactive agent. Lastly, Myoview and Mycamine will not be stored together; Myoview requires refrigeration, unlike Mycamine. Given the differences in dosing, administration, and storage, DMETS believes that the risk of confusion between the products is minimal.

Myoview

Mycamine

Myoview

Mycamine

2. Mycodone was identified to have look-alike similarities to the proposed name, Mycamine (see below). Mycodone contains hydrocodone, a semi-synthetic opiate agonist, indicated for the relief of pain. The recommended dose of Mycodone is one tablet every four to six hours. Both names consist of eight letters, begin with the letter combination “Myc”, and end with the letters “ne”. The fourth letter of each name (“o” vs. “a”), as well as the sixth letter of each name (“o” vs. “i”), look similar when scripted. However, if the upstroke of the letter “d” is prominent in Mycodone, this helps to distinguish the names when written. Mycodone and Mycamine have overlapping numerals in their strength (5 mg vs. 50 mg). They differ in route of administration (oral vs. intravenous), dosage form (tablet vs. injection), and dosing regimen (every 4 to 6 hours vs. daily). Lastly, Mycodone is a schedule II controlled narcotic medication, which has more stringent storage requirements, and therefore, will not be stored near Mycamine on pharmacy shelves. Despite some look-alike similarities between the products, DMETS believes that the aforementioned product differences minimize the risk of confusion and error between Mycodone and Mycamine.

Mycodone

Mycamine

Mycodone

Mycamine

3. Miacalcin was identified as having sound-alike similarities to the proposed name Mycamine. Miacalcin contains calcitonin-salmon. It is indicated for the treatment of postmenopausal osteoporosis, Paget’s disease of the bone, and Hypercalcemia. Miacalcin is available as an injection in a strength of 200 IU/mL, and as a nasal spray in a strength of 200 IU/actuation. The beginning of each name is phonetically similar (“Mia” vs. “Myca”), particularly if the “i” in Miacalcin is pronounced with a long vowel sound (i.e., Mī a). Both names also contain the strong sound of the letter “c”, although at different places in each name. However the number of syllables (four vs. three), in addition to the fact that the endings of the names are distinguishable from each other when pronounced (“calcin” vs. “mine”) help to distinguish the names from one another. Miacalcin and Mycamine share an overlapping dosage form (injection), route of administration (intravenous), dosing strength (100 IU/day vs. — mg/day), and dosing regimen (daily). Despite these product similarities, DMETS believes that the lack of convincing sound-alike similarities between the names reduces the risk of confusion between Miacalcin and Mycamine.

IV. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Mycamine™. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this

Review in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name Mycamine acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
8/5/04 09:11:00 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/5/04 01:34:42 PM
DRUG SAFETY OFFICE REVIEWER
for Carol Holquist



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-754

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

Dear Mr. Reed:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mycamine (micafungin sodium) For Injection, 50 mg

Review Priority Classification: Standard (S)

Date of Application: April 23, 2004

Date of Receipt: April 26, 2004

Our Reference Number: NDA 21-754

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 25, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 25, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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 note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

NDA 21-754

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

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

Sincerely,

{See appended electronic signature page}

Ellen F. Molinaro
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
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/

Ellen Molinaro
6/28/04 03:40:59 PM
NDA 21-754

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES NO

• Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
The entire NDA.

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES NO

• Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:

• Patent information submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES, _____ years NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“*[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*” Applicant may not use wording such as “To the best of my knowledge”

• Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

• Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 55,322
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES NO

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- **Did the applicant:**
 - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO
 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO
 - EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO
 - OR
 A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 8, 2004

BACKGROUND:

On April 29, 2002, Fujisawa submitted NDA 21-506 for the indication of prophylaxis of _____ in patients undergoing hematopoietic stem cell transplantation. The Division took an approvable action on this NDA on January 29, 2003. Fujisawa proposed an action plan to respond to the issues raised in the action letter in February 2003. The February response letter included a request to meet with the Division in order to discuss the proposed action plan. Following a March 2003 meeting with the Division, Fujisawa received a letter from the Division, dated May 23, 2003, with comments and recommendations. On November 24, 2003, the Division sent a facsimile to Fujisawa in response to their pre-NDA briefing package submitted to the IND 55,322 on October 24, 2003, containing questions regarding the submission of a New Drug Application (NDA) for Esophageal Candidiasis (EC). On January 28, 2004, Fujisawa requested another meeting with the Division to discuss the next steps for the approval of NDA 21-506. In the briefing document for this meeting, Fujisawa addressed the comments and recommendations listed under Item 1, Prophylaxis of _____ of the May 23, 2003 letter. Fujisawa proposed to submit a new NDA seeking approval of micafungin for the treatment of esophageal candidiasis. They also proposed that the approval of the EC indication, and the already submitted, approvable NDA 21-506, would be adequate for approval of micafungin for the Prophylaxis of *Candida* infections in Patients Undergoing Hematopoietic Stem Cell Transplantation.

ATTENDEES: Ekopimo Ibia, Marc Cavaillé-Coll, LaRee Tracy, Karen Higgins, Jang-Ik Lee, Philip Colangelo, Lynn Steele-Moore, Shukal Bala, Owen McMaster, Mark Seggel, Renata Albrecht, Steven Gitterman, and Mary Singer.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Mary Singer
Statistical:	LaRee Tracy
Pharmacology:	Owen McMaster
Chemistry:	Mark Seggel
Environmental Assessment (if needed):	
Biopharmaceutical:	Jang Ik-Lee
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Lynn Steele-Moore
DSI:	
Regulatory Project Management:	Susan Peacock
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY NA _____ FILE X REFUSE TO FILE _____

STATISTICS FILE X REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE X REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE X REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Follow-up with the Division of Pediatrics on whether to waive or defer this product for pediatric studies.

Susan Peacock
 Regulatory Project Manager, HFD-590

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

/s/

Susan Peacock
6/8/04 02:56:35 PM
CSO

Susan Peacock
6/8/04 02:57:51 PM
CSO

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Fujisawa Healthcare, Inc. 3 Parkway North Deerfield, IL 60015-2548	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021754
2. TELEPHONE NUMBER (Include Area Code) (847) 317-8872	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Mycamine (micafungin sodium) for Injection	6. USER FEE I.D. NUMBER 4756

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Senior Director, Regulatory Affairs	DATE 4/19/04
---	--	-----------------



New Medicines for New Times

Fujisawa Healthcare, Inc.

Donald E. Baker, J.D.

Senior Director, Regulatory Affairs

Three Parkway North

Deerfield, Illinois 60015-2548

Tel. (847) 317-8872 Telefax (847) 317-7286

www.fujisawa.com

E-Mail: don_baker@fujisawa.com

April 19, 2004

Food and Drug Administration
Mellon Client Service Center (36090)
Room 670 – 500 Ross St.
Pittsburgh, PA 15262-0001

**Re: NDA 21-754
Application Fee for:
Mycamine (micafungin sodium)
For Injection
User Fee Identification Number 4756**

Dear Madam/Sir:

Fujisawa Healthcare, Inc. (FHI) intends to submit to the FDA's Division of Special Pathogens and Immunologic Drug Products on or about April 26, 2004 an original New Drug Application (NDA 21-754) with clinical data, for Mycamine (micafungin sodium) for the treatment of esophageal candidiasis.

Enclosed please find check number 867690 in the amount of Five Hundred Seventy Three Thousand, Five Hundred Dollars (\$573,500.00), as payment in full for the assessed FY 2004 application fee.

Should you have any questions regarding this payment, please do not hesitate to contact me at (847) 317-8872.

Sincerely,

Donald E. Baker, JD

Sr. Director, Regulatory Affairs