CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-506

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Fujisawa
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

February 3, 2005

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

Re: NDA 21-506 and 21-754
FK463 (micafungin) for Injection

SUBMISSION OF PATENT CERTIFICATION/CMC UPDATE
(Form 3542a for Patent Number 6774104 – Update on [redacted], Drug Product Formulation)

Dear Dr. Albrecht:

Please find attached (**Attachment 1**) the FDA Form 3542a for Patent Number 6774104 for Micafungin for injection. A copy of the patent is also included (**Attachment 2**).

Please note that Fujisawa Healthcare, Inc. has elected not to pursue the commercialization of the [redacted] drug product formulation at this time.

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

Sincerely yours,

Robert M. Reed
Associate Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	February 3, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(847) 317-8985	(847) 317-7286
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Three Parkway North Deerfield, IL 60015-2548	N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-754

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
micafungin sodium	MYCAMINE

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Please Refer to Package Insert		FK463, FK 463, FK-463, FR179463
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Powder for concentration for infusion	50 mg	Intravenous

(PROPOSED) INDICATION(S) FOR USE:
Treatment of esophageal candidiasis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Patent Certification Information / CMC Update (regarding product formulation)

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF — DMF — IND 55,322 NDA 21-506

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Robert M. Reed	Robert M. Reed Associate Director, Regulatory Affairs	2/3/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Three Parkway North Deerfield, IL 60015-2548	(847) 317-8985

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
ood and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
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.

Submission dated 9/29/20[illegible]

PATENT SUBMISSION/CERTIFICATION
FOR
MICAFUNGIN SODIUM

Time Sensitive Patent Information
Pursuant to 21 C. F. R. 314.53
For
NDA # 21-506

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

- Trade Name: —
- 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

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 #21-506, 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

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

June 4, 2002
Date

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8985 / Telefax (847) 317-7286

Fujisawa

June 4, 2002

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

Re: NDA #21-506
(micafungin sodium) FOR INJECTION
50 mg

SUBMISSION OF REVISED PATENT CERTIFICATION INFORMATION

Dear Dr. Albrecht:

On April 29, 2002, Fujisawa Healthcare, Inc. (FHI) submitted an original New Drug Application (NDA) pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for (micafungin sodium) FOR INJECTION, 50 mg.

At the request of the Division, Fujisawa is hereby submitting a revised patent certification for **(Attachment 1)** of this cover letter.

The sponsor believes that is entitled to 5 years of exclusivity based on 21CFR§314.108(b)(2). The expiration date for the formulation patents (U.S. Patent Numbers 6,107,458 and 6,265,536) is September 29, 2015.

Fujisawa also requests that the exclusivity period be extended in accordance with Section 505A of the Food Drug and Cosmetic Act. Fujisawa believes that the studies submitted in NDA #21-506 are adequate to assess the safety and efficacy of the drug product in the proposed indications in all relevant pediatric populations in accordance with 21CFR§314.55. A detailed summary of the investigations in the pediatric population in accordance with 21CFR§314.50 can be found in the Pediatric Use Report in NDA Section 8.

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 Jerry D. Johnson, Ph.D. at **847/317-8898**.

Sincerely yours,

Robert M. Reed

Robert M. Reed
Associate Director, Regulatory Affairs

cc: Yoon Kong

PATENT SUBMISSION/CERTIFICATION
FOR
MICAFUNGIN SODIUM

Time Sensitive Patent Information
Pursuant to 21 C. F. R. 314.53
For
NDA # 21-506

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Expiration date: June 11, 2017

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Gwendolyn M. Barlow

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

June 4, 2002
Date

PATENT SUBMISSION/CERTIFICATION
FOR
MICAFUNGIN SODIUM

Time Sensitive Patent Information
Pursuant to 21 C. F. R. 314.53
For
NDA # 21-506

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Name of Patent Owner: Fujisawa Pharmaceutical Company, Ltd.

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EXCLUSIVITY SUMMARY FOR: Original NDAs # 21-506 & 21-754

SUPPL #: __N/A__

Trade Name: Mycamine Generic Name: micafungin sodium

Applicant Name: Fujisawa Healthcare, Inc. HFD #: 590

Approval Date If Known: March 11, 2005.

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

____505(b)(1)____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

____N/A_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____ N/A _____

_____

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 Writen 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

approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or

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

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-506 (original) **Supplement Type (e.g. SE5): N/A** **Supplement Number: N/A**

Stamp Date: April 29, 2002 **PDUFA Goal Date: May 25, 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 prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

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**
- ☐ [X] **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 21-506**
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 this page is the manifestation of the electronic signature.

/s/

Diana Willard
3/16/05 07:32:09 PM
NDA 21-506/Pediatric Page

Submitted in the origin
NDA dated April 29, 200

Micafungin (FK463)
Original NDA 21-506

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

Date: 19 April 2002

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

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-506: for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation This action package contains information of the 2nd review cycle as well as the 1st review cycle (with the issuance of an approvable letter on 1/29/03)	Efficacy Supplement Type SE- **N/A**	Supplement Number: **N/A**
Drug: Mycamine™ (micafungin sodium) for Injection (Intravenous Infusion, not for 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: **(X) 505(b)(1)** ( ) 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.**) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X) Standard** ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates (Extension letter under "Outgoing Correspondence")	May 25, 2005
❖ Special programs (indicate all that apply)	**(X) None** Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X) Paid** UF ID number **4327**
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) **N/A**
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) **N/A**

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X) Verified** 1. Orig. subm. dated 4/29/2002: a. Granted patents: US 5,376,634 Exp. 12/27/2011; US 5,502,033 Exp. 12/27/2011; US 6,107,458 Exp. 9/29/2015; US 6,146,872 Exp. 6/11/2017; US 6,207,434 B1 Exp. 3/6/2017; US 6,265,536 B1 Exp. 9/29/2015; US 6,372,474 B1 Exp. 9/12/2011. b. Patent under examination: 09/308,237 filed on 5/21/1999; 09/786,125 filed on 3/1/2001; 10/050,150 filed on 1/18/2002 2. Revised subm. dated 6/4/2002: a. Granted patents: US 5,376,634 Exp. 12/27/2011; US 5,502,033 Exp. 12/27/2011; US 6,107,458 Exp. 9/29/2015; US 6,146,872 Exp. 6/11/2017; US 6,207,434 B1 Exp. 3/6/2017; US 6,265,536 B1 Exp. 9/29/2015; US 6,372,474 B1 Exp. 9/12/2011. b. Patent under examination: 09/308,237 filed on 5/21/1999; 09/786,125 filed on 3/1/2001; 10/050,150 filed on 1/18/2002 3. Revised subm. dated 2/3/05: US 6,774,104 Exp. 1/8/2021; US 6,265,536 B1 Exp. 9/29/2015; US 6,107,458 Exp. 9/29/2015; US 5,376,634 Exp. 12/27/2011.
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified **N/A** 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) **N/A**
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A**
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) **N/A** (no paragraph IV certification) ( ) Verified

• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	**N/A**
Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	( ) Yes ( ) No
*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? (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))).	( ) Yes ( ) No
*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 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)	
• 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.)	3/9/2005 **N/A**
• 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: 7/15/02
General Information	
❖ Actions	
• Proposed action	**(X) AP** ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE for NDA 21-506 on 1/2920/03
• Status of advertising (approvals only)	**(X)**Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• 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))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	**With the Agency's input**:Package insert dated 3/10/2005
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS reviews: (see also under 1st cycle:8/9/02, 9/20/02); 2nd cycle: 11/19/2004. DDMAC review: 8/25/2005 Labeling Meetings: see reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**Ambisome, Diflucan, Cancidas**

❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	**With the Agency's input**:Carton & immediate container of 3/10/05
• Reviews	See discipline reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Extension letters:10/18/02, 2/18/05 Meeting:3/10/03 Faxes: 9/24, 12/3, 12/9, and 12/17/02; 1/21/03; 3/4/, 9/10, 10/22, 10/27, and 11/04/04 (2); 1/14 and 3/15/2005.
❖ Memoranda, Telecons and Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	2/4/2005
• Other	12/4, 12/6 and 12/19/2002; 1/13 and 3/28/2003.
❖ 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 3/16/05 Medical Team Leader & Division Director Review of 3/16/2005
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	1st cycle:3/14/2005; 2nd:3/14/2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	1st cycle:12/21/2002; 2nd:2/18/2005
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	a. See clinical review b. ODS Hepatic Safety: 1/31/2005 c. ODS: 2/22/2005 of Japanese post-marketing experience
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	1st cycle:12/13/02, 2nd: See Clinical review pp.8, 135, and 193-196.
❖ 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)*	1st cycle:1/31/03; 2nd: 3/8/2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1st cycle: 1/23/03; 2nd:3/3/2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/19, 10/22 and 12/31/2002 (3); 3/5/2003.

• Bioequivalence studies	**N/A**
[redacted]	
❖ CMC review(s) *(indicate date for each review)*	1st cycle: 7/22/2003; 2nd:3/7/2005
❖ Environmental Assessment	[redacted]
• Categorical Exclusion *(indicate review date)*	See Chemistry Rev., 2nd cycle p.40 dated 3/7/2005
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	See Chemistry Rev., 2nd cycle p.10 3/7/2005
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	1st cycle:1/29/03 and 2nd: 2/23/2005
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed (See Chemistry Rev., 2nd cycle p.38 dated 3/7/2005 ( ) Requested ( ) Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	1st cycle: undated; 2nd 3/14/2005
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**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).

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

FACSIMILE TRANSMISSION COVER SHEET

Date: March 16, 2005 **Number of pages (incl. cover sheet):** 4+1=5

TO: Mr. Robert Reed

COMPANY: Fujisawa Healthcare, Inc.

FAX NUMBER: 847-317-7286

MESSAGE: Congratulations!

NDAs 21-506 and 21-754 are approved.

The approval letter is attached.

The labelings are going (Christina H. Chi, Ph.D
to be done by mail)

Note: We are providing the attached information via telefascimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Christina H. Chi, Ph.D. **TITLE:** Regulatory Health Manager

TELEPHONE: 301-827-2127 **FAX NUMBER:** 301-827-2326/2325

Deputy Office Director Review Memo

Applicant: Fujisawa Healthcare, Inc.

NDA #s: NDA 21-506 & NDA 21-754

Drug: Micafungin sodium for injection

Trade Name: Mycamine™

Indications: (1) Treatment of patients with esophageal candidiasis
(2) Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation

NDA 21-506
Date of submission: April 29, 2002
Date of resubmission: August 24, 2004

NDA 21-754
Date of submission: April 23, 2004 -- NDA 21-754

Date of Major Amendment: January 31, 2005
(to NDAs 21-506 and 21-754)

PDUFA goal date: May 24, 2005

RECOMMENDATIONS:

Approval for NDA 21-754 and NDA 21-506 for the following indications:

- Treatment of patients with esophageal candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506)

Background
Fujisawa Healthcare, Inc. originally submitted an NDA (NDA 21-506) for Mycamine (micafungin sodium) for injection on April 29, 2002. The actions on this original submission were as follows: Approvable for the indication of prophylaxis of —— in patients undergoing hematopoietic stem cell transplant, ——

). Following the issuance of an Approvable letter for the indication prophylaxis of n patients undergoing hematopoietic stem cell transplant, there were discussions with the company about approaches to satisfy the clinical deficiencies in the Approvable letter. NDA 21-754, Mycamine for the treatment of esophageal candidiasis, was submitted on April 23, 2004. NDA 21-506 was re-submitted on August 24, 2004 seeking the modified indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. (The resubmission of NDA 21-506

Other agents approved for the indications being sought in these NDAs include the following:

- Treatment of patients with esophageal candidiasis
  - Cancidas® (caspofungin acetate) (IV)
  - Diflucan® (fluconazole) (oral and IV)
  - Sporanox® (itraconazole) (oral solution)
  - Vfend® (voriconazole) (oral and IV)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
  - Diflucan® (fluconazole) (oral and IV)

NDA 21-506 and NDA 21-754

The Chemistry for Mycamine™ is discussed in Dr. Seggel's review and he has recommended approval for NDAs 21-506 and 21-754 with regards to Chemistry. Mycamine (micafungin sodium) for injection is a sterile lyophilized powder for reconstitution and intravenous infusion. Micafungin sodium is light sensitive and therefore the drug product vials are wrapped in a UV protective material and the diluted infusion solution should also be protected from light, as stated in the Mycamine product label. Dr. Riley's Product Quality Microbiology Review also recommends approval for NDAs 21-506 and 21-754.

The Pharmacology/Toxicology studies for Mycamine are summarized in Dr. McMaster's review. His review notes that in animal studies the target organs are primarily the liver and testes. The Animal Toxicology section of the label describes the liver changes noted in animal studies. The testicular findings from the animal studies are described in the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection within the Precautions section of the label. Mycamine is labeled as Pregnancy Category C.

The Clinical Pharmacology of Mycamine is described in Dr. Jang-Ik Lee's Clinical Pharmacology and Biopharmaceutics Review. Micafungin is highly protein bound (>99%). It is metabolized to M-1 by arylsulfatase, followed by further metabolism to M-2 by catechol-O-methyltransferase and subsequent hydroxylation. Based upon preclinical studies, the enzymatic activities responsible for metabolism to M-1 and M-2 are found in liver, kidney, adrenals, and other organs. Micafungin is a substrate for and a weak inhibitor of CYP3A, but CYP3A is not a major mechanism of metabolism in vitro. Mass

balance studies show that more than 70% of micafungin is eliminated in the feces. Dose adjustment in patients with renal impairment is not required. In patients with moderate hepatic impairment, no dosage adjustment is required; patients with severe hepatic patients have not been evaluated. As noted in the Dr. Jang-Ik Lee's review, with regards to the pediatric pharmacokinetic data, there were unexplainable outliers and a number of samples were not collected at critical timepoints. Based upon these apparent methodologic problems with the study, the pharmacokinetics have not been adequately characterized in pediatric patients 2 to 16 years of age.

The microbiology of micafungin is described in Dr. Shukal Bala's microbiology Team Leader's review, Dr. Fred Marsik's microbiologist's review for NDA 21-506 and Dr. Bala and Dr. Kalavati Suvarna's microbiologist's review for the related NDAs, —— —— Micafungin is a semisynthetic lipopeptide of the echinocandin class of antifungal agents. Its mechanism of action is inhibition of synthesis of 1,3-β-D-glucan; 1,3-β-D-glucan is an essential component of fungal cell walls and is not present in mammalian cells. As noted in the microbiologist's review, micafungin's metabolite M-2 has activity *in vitro* similar to the parent compound, the metabolite M-1 has 4 to 16-fold less activity than the parent compound, and M-5 has only a small fraction of the activity of the parent compound. The metabolites M-1 and M-2 are present in plasma only at very low levels, while M-5 is the predominate metabolite found in plasma.

The results of the clinical trials providing safety and efficacy data for micafungin have been thoroughly discussed in the Medical Officer reviews by Drs. Singer, Ibia, and Meyer; the statistical reviews by Dr. Tracy; and the Division Director and Team Leader Review by Drs. Albrecht and Navarro. For a detailed review of the findings of the clinical studies, the reader is referred to their reviews.

Treatment of patients with esophageal candidiasis - Efficacy
For the indication of esophageal candidiasis the applicant provided data from three studies of micafungin in the treatment of esophageal candidiasis and data from a non-comparative study of micafungin for the treatment of candidemia or invasive candidiasis. The three studies available at the time of submission of NDA 21-754 and that formed the basis for filing the NDA for the esophageal candidiasis indication were two phase 2 dose ranging studies examining the effectiveness of micafungin in the treatment of patients with esophageal candidiasis and a non-comparative study of micafungin for candidemia or invasive candidiasis. At the time of the 120-day safety update, the applicant submitted the study report and data from a randomized, double-blind comparative phase 3 study examining the effectiveness of micafungin 150 mg/day intravenously compared to fluconazole 200 mg/day. These four studies are briefly summarized in the paragraphs that follow.

Study 97-7-003 was a phase 2 dose de-escalation study examining the effectiveness of micafungin at doses of 12.5, 25, 50, 75, 100 mg/day intravenously for 14 days that enrolled a total of 120 HIV-positive patients with esophageal candidiasis by clinical signs and symptoms with endoscopic confirmation. The number of patients enrolled by dosage regimen was distributed approximately equally between the five study groups.

The primary efficacy endpoint, clinical response at the end of therapy found the following clinical response rates for patients in the clinical response category of "cleared" by dose group for the per protocol population: 12.5 mg/day 33% (6/18); 25 mg/day 54% (7/13); 50 mg/day 87% (13/15); 75 mg/day 84% (16/19); 100 mg/day 95% (18/19). The findings for the secondary endpoints, endoscopic response, mycological response, and overall treatment response, supported the findings for the primary efficacy endpoint of clinical response at end of therapy. The study showed a dose response for micafungin.

Study FG463-21-09 was a phase 2 randomized, double-blind, dose ranging study with an active control arm (fluconazole 200 mg/day). Patients were randomized 1:1:1:1 to one of the four treatment groups; micafungin at 50 mg/day, 100 mg/day, or 150 mg/day or fluconazole 200 mg/day. The primary endpoint was endoscopic response (proportion of patients with endoscopic grade 0) at end of therapy. Included among the secondary endpoints were clinical response, mycologic response, overall therapeutic success, and relapse at 2-weeks post-therapy. The study enrolled HIV-positive patients $\geq$ 18 years of age with clinical signs and symptoms of esophageal candidiasis and endoscopic and microbiological/histological confirmation. A total of 251 patients were randomized to one of the four treatment groups as follows: 65 patients to micafungin 50 mg/day; 65 patients to micafungin 100 mg/day; 60 patients to micafungin 150 mg/day; and 62 patients to fluconazole 200 mg/day. The duration of therapy as specified in the protocol was 14 days with an option to extend to 21 days. The endoscopic cure rates at end of therapy by treatment group were 67% (44/64) for micafungin 50 mg/day; 77% (48/62) for micafungin 100 mg/day; 90% (53/59) for micafungin 150 mg/day; and 87% (52/60) for fluconazole 200 mg/day. The findings for the primary endpoint were supported by the findings from the secondary endpoints. The study found a dose-response for micafungin and similar response rates for micafungin 150 mg/day compared to fluconazole 200 mg/day. Rates for Total Relapse by treatment group at the 2-week follow-up visit were as follows 33% (13/39) micafungin 50 mg/day; 27% (13/48) for micafungin 100 mg/day; 20% (10/50) for micafungin 150 mg/day; and 16% (8/51) for fluconazole 200 mg/day. The category of Total Relapse included patients with relapse, missing data, or patients receiving systemic antifungal treatment after study therapy was completed.

Study 03-7-005 was a pivotal phase 3 randomized (1:1), double-blind, active controlled trial comparing the efficacy and safety of micafungin 150 mg intravenously daily or fluconazole 200 mg intravenously daily for a minimum of 14 days and a maximum of 42 days. The primary efficacy endpoint was endoscopic response at end-of-therapy. Included among the secondary endpoints were clinical response, relapse at 2-weeks and 4-weeks post-therapy, and changes in clinical symptoms. The protocol also included criteria for assessing mycological response. The entry criteria required confirmed esophageal candidiasis based upon endoscopy with microbiological/ histological criteria. The study enrolled 523 patients within the age range of 17 to 87 years of age; 260 were randomized to micafungin 150 mg/day and 258 were randomized to fluconazole 200 mg/day. Most patients were HIV-positive with CD_4 cell counts < 100 cells/mm^3. Approximately 90% had a positive culture at baseline and

almost all had *C. albicans*. Non-albicans isolates occurred very infrequently and were often co-isolates along with *C. albicans*. The outcomes for the study in the modified full analysis set [or modified intent-to-treat population (mITT) - patients who received at least one dose of study drug and had positive histology or cytology at baseline] are summarized in table 1.

Table 1. Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of Treatment - Study 03-7-005

Treatment Outcome*	Micafungin 150 mg/day	Fluconazole 200 mg/day	% Difference† (95% CI)
	N=260	N=258	
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8)
Overall Therapeutic Cure	223 (85.8%)	220 (85.3%)	0.5% (-5.6, +6.6)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0% (-11.6, +5.6)

*Endoscopic and clinical outcome were measured in the modified intent-to-treat population, including all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was determined in the per protocol (evaluable) population, including patients with confirmed esophageal candidiasis who received at least 10 doses of study drug, and had no major protocol violations.
†calculated as micafungin – fluconazole

Micafungin 150 mg/day was found to be non-inferior to fluconazole 200 mg/day. Additional analyses in the other analysis populations (e.g., ITT and per protocol populations) supported the results of the analyses in the mITT population.

Relapse at 2- and 4-weeks post-therapy was assessed in patients who achieved overall therapeutic success at end of therapy. Relapse was defined as a recurrence of clinical symptoms or endoscopic lesions (endoscopic grade > 0). The relapse rates by treatment group are summarized in table 2.

Table 2. Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients with Overall Therapeutic Cure at the End of Treatment - Study 03-7-005

Relapse	Micafungin 150 mg/day N=223	Fluconazole 200 mg/day N=220	% Difference* (95% CI)
Relapse† at Week 2	40 (17.9%)	30 (13.6%)	4.3% (-2.5, 11.1)
Relapse† Through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6% (-4.0, 13.1)

*calculated as micafungin – fluconazole;
N=number of patients with overall therapeutic cure (both clinical and endoscopic cure at end-of-treatment);
†Relapse included patients who died or were lost to follow-up, and those who received systemic anti-fungal therapy in the post-treatment period

Most patients (89%) in Study 03-7-005 had concurrent oropharyngeal candidiasis (OPC) along with their esophageal candidiasis (EC). In the subgroup of patients with concurrent OPC along with their EC the response rate for resolution of signs and symptoms of OPC at the end of therapy was 192/230 (84%) in micafungin-treated

patients and 188/229 (82%) of fluconazole-treated patients. In the subgroup of patients with resolution of their EC and OPC at end of therapy, 32% of the micafungin-treated patients and 18% of the fluconazole-treated patients had Relapse of OPC at 2-weeks post-treatment. [The category of Relapse included relapse (OPC grade>0), patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period]. The cumulative Relapse by treatment group at 4-weeks post-treatment was 52% in the micafungin group and 39% in the fluconazole group.

Study 98-0-047 was an open-label, non-comparative study that enrolled patients with candidemia and invasive candidiasis. This study included 288 evaluable patients of whom 99 had esophageal candidiasis. Most patients received micafungin therapy alone at doses between 50 to 100 mg/day. The response rate for success based upon the investigator's global assessment was 92% (91/99) [92% success = 65% complete response and 27% partial response].

The Applicant has provided two adequate and well-controlled studies, the phase 3 study (Study 03-7-005) that examines micafungin at a dose of 150 mg/day and the phase 2 dose ranging active controlled study (Study FG463-21-09) for the indication of treatment of esophageal candidiasis. Additional supportive data from Study 97-7-003 and Study 98-0-047 have also been provided. The evidence from these studies supports the efficacy of micafungin 150 mg/day intravenously for the indication of treatment of esophageal candidiasis.

Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation - Efficacy

For the indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation data is provided from Study 98-0-050, a phase 3 prophylaxis study in hematopoietic stem cell transplant recipients, data supporting the efficacy of micafungin in the treatment of established infections due to *Candida* spp. derived from the pivotal and supportive studies for the indication of treatment of esophageal candidiasis, and the data in support of

Study 98-0-050 was a phase 3, randomized (1:1), double-blind study of micafungin compared to fluconazole for prophylaxis of fungal infections in patients undergoing hematopoietic stem cell transplant (HSCT). Patients received micafungin 50 mg/day or fluconazole 400 mg/day. Prophylaxis with study drug was to continue until one of following occurred: the patient experienced neutrophil recovery to a post-nadir ANC of ≥ 500 cells/mm3 (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity; the investigator decided that it was in the best interest of the patient to discontinue; the patient declined further study participation; death occurred; or the patient received prophylactic

treatment to a maximum of 42 days after transplant (day +42 after transplant). The study enrolled 882 patients undergoing an autologous or syngeneic (46%) or allogeneic (54%) stem cell transplant. The average duration of drug administration was 18 days (range 1 to 51 days). Successful prophylaxis was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period. The results for Study 98-0-050 are summarized in Table 3. The rate of Treatment success by treatment groups were micafungin 80.9% (344/425) compared to 74.2% (339/457) for fluconazole; treatment difference (micafungin – fluconazole): +6.8% [95% CI=1.3%, 12.2%].

Table 3. Results from Clinical Study of Prophylaxis of *Candida* Infections in Stem Cell Transplant Recipients – Study 98-0-050

Outcome	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Treatment Success*	344 (80.9%)	339 (74.2%)
Treatment Failure	81 (19.1%)	118 (25.8%)
All Deaths[1]	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)[1]	6 (1.4%)	8 (1.8%)
Suspected fungal infection[2]	53 (12.5%)	83 (18.2%)
Lost to follow-up	4 (0.9%)	1 (0.2%)

* Treatment difference (micafungin - fluconazole): +6.8% [95% CI=1.3%, 12.2%]
[1] Through end-of-study (4 weeks post-therapy)
[2] Through end-of-therapy

Although not a protocol endpoint, examination of the rates of proven or probable *Candida* infections show similar rates between the micafungin and fluconazole arms of the study. There were 4/425 (0.9%) proven or probable *Candida* infections in the micafungin arm and 2/457 (0.4%) in the fluconazole arm. In addition, although not counted in the endpoint, the use of systemic antifungal products was examined. In the post-treatment period (end of treatment through the 4-week end of study time point), antifungal therapy was used in 42% of the patients in each of the treatment arms.

A discussion of the dose for prophylaxis is provided in the Drs. Albrecht's and Navarro's review.

The Applicant has provided evidence that is sufficient to support that micafungin 50 mg/day intravenously is effective in the prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients. The efficacy data that support this conclusion are derived from the following:

- the findings from the phase 3 prophylaxis study, Study 98-0-050
- the demonstration of the efficacy of micafungin in the treatment of esophageal candidiasis (an established infection due to *Candida* spp.)

- the clinical data supporting the activity of the 50 mg/day dose in EC
- the data derived from the studies of *Candida* indications previously submitted to

These data collectively support the conclusion that micafungin 50 mg/day intravenously is effective in prophylaxis of *Candida* infections.

Safety

The Medical Officer review of the original NDA 21-506 concluded a favorable risk profile for micafungin, based on the data available from the 1368 subjects in the original micafungin NDA submission, the majority of whom received the 50-mg dose of micafungin. The current total safety database is comprised of 2402 subjects (patients and volunteers) who received micafungin. The aggregate safety information evaluated in the current review incorporates updated safety data from the original NDA 21-506 (prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients), new safety data from the esophageal candidiasis in NDA 21-754 (esophageal candidiasis), new clinical data contained in the 120-day safety update, and postmarketing data from Japan. A total of 726 (30%) subjects received $\geq$ 150 mg of micafungin, and of these, the majority (606/726 or 83.5%) received this dose for at least 10 days. The mean duration of treatment for all subjects was 20.1 days (range 1-681 days).

The review team analyzed data from all of these submissions. The safety of micafungin is reviewed in detail in Dr. Singer's Medical Officer Review and summarized in Dr. Albrecht's and Navarro's review. As part of the safety review, the division also consulted the Office of Drug Safety for review of the micafungin postmarketing data available from Japan and Dr. John Senior for a consult on the hepatic safety profile of micafungin. The consults from ODS and Dr. Senior provided an assessment on the safety issues that were the respective focus of the consultations along with suggestions for specific safety information for inclusion in product labeling.

Serious allergic reactions have been reported in the Japanese postmarketing experience including serious skin and vascular reactions with anaphylactic shock. A Warning in the Mycamine product label describes these reactions. Also of note, in the Adverse Reactions section of the label, information is provided describing adverse reactions involving histamine mediated symptoms.

The hepatic safety profile includes findings from preclinical studies that the liver was one of the target organs for toxicity. In the animal species tested, laboratory and histopathologic evidence of dose-related hepatotoxicity was noted, including single cell necrosis at 3-5X the human equivalent dose (HED). Transient increases in transaminases developed in normal volunteers most of which were mild (<3X ULN) and fully reversible. In comparative studies where the comparator was fluconazole, the incidence of hepatic adverse events was 19.0% (177/932) in the micafungin-treated group, compared to 21.0% (165/787) in the fluconazole-treated group. Serious adverse events were observed in 1.1% (10/932) of the micafungin and 1.4% (11/787) of the fluconazole treated group. The proportion of micafungin treated patients with significant

(>3X ULN) conjoint elevation of transaminases and bilirubin was similar to those observed in patients who received fluconazole. The Mycamine product label will include a statement in the Precautions section describing the hepatic effects of Mycamine.

Based upon the occurrence of serious postmarketing renal events including renal failure, the Japanese label for micafungin was revised to include renal failure as a clinically significant adverse event. In comparative studies where the comparator was fluconazole, serious renal adverse events including renal failure occurred in 12/932 (1.3%) micafungin-treated and 19/787 (2.4%) fluconazole-treated patients. The Mycamine product label will include a Precaution describing the renal effects of micafungin. A Precaution on hematologic effects is included to inform and describe the adverse hematologic effects that have been observed including hemolysis and hemolytic anemia.

Information regarding the drug interaction studies performed is included in the Precautions section of the label. The section informs the reader that patients receiving sirolimus or nifedipine in combination with micafungin should be monitored for toxicity and the dose of sirolimus or nifedipine should be reduced is necessary.

The Adverse Reactions section of the label Mycamine product label includes a description of injection site reactions ranging from pain to phlebitis and deep thrombophlebitis have been observed in patients receiving micafungin. Also described within this section are the data available from the postmarketing adverse event data from Japan[‡] along with a summary of the adverse reactions from the clinical trial in the NDA.

With regards to effect on cardiac repolarization, micafungin does not suppress the Ik_r channel current in hERG transfected cells nor does it prolong the duration of action potentials in a microelectrode study examining the effect on action potential. Preclinical studies reveal no increase in the QT interval in chronically dosed beagle dogs. No significant QTc prolongation was observed in normal volunteer studies, and no clinical cardiac events related to QT prolongation have been documented in patients who received micafungin.

The safety data on micafungin are derived from the database of 2402 subjects (patients and volunteers). Within the overall safety database a total of 726 (30%) subjects received $\geq$ 150 mg of micafungin (most for at least 10 days). We also have data from postmarketing experience from use of micafungin in Japan. This information provides sufficient data characterizing the safety profile to achieve a risk-benefit profile that supports the safety of micafungin in the proposed indications of (1) treatment of patients with esophageal candidiasis and (2) prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

[‡] Micafungin was approved in Japan in October 2002. The Japanese label describes doses of 50 to 150 mg and also includes a proviso for doses of up to 300 mg/day in selected circumstances.

Product Name and Clinical Inspections
The proprietary name, Mycamine, was reviewed by the Division of Medication Errors and Technical Support and found to be acceptable. The Division of Scientific Investigation inspections of selected clinical study sites were completed and the results of the site audits were that the data appear to be acceptable for review.

Phase IV
The pediatric studies required under PREA for the indications being approved in these NDAs are deferred. Other than the pediatric studies which are being deferred there are no phase 4 postmarketing commitments.

Recommendation
The applicant should be issued an **Approval** letter for the following indications:

- Treatment of patients with esophageal candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506)

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

/s/

Edward Cox
3/15/05 05:46:30 PM
MEDICAL OFFICER

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 grapic 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 (>= 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/mm^3);
- persistent or recurrent fever (≥100.4°F, ≥38.0°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 >= 5 x 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 x 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.

Patient Numbers	Treatment Group
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

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

/s/

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

DESK COPY

Fujisawa

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

March 10, 2005

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

Re: NDA 21-506 and 21-754
FK463 (micafungin) for Injection

SUBMISSION OF PROPOSED PRESS RELEASE

Dear Dr. Albrecht:

Please find attached for your review and comment, pdf versions of the draft package insert and the proposed press release for MYCAMINE which were submitted to the Division of Drug Marketing, Advertising and Communications (DDMAC) in electronic format for their review and comment.

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

Sincerely yours,

Robert M. Reed

Robert M. Reed
Director, Regulatory Affairs

3½ Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

__✓__ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

FACSIMILE TRANSMISSION COVER SHEET

Date: Febr. 22, 2005 **Number of pages (incl. cover sheet):** 3

TO: Mr. Robert Reed

COMPANY: Fujisawa Healthcare, Inc.

FAX NUMBER: 847-317-7286

MESSAGE: The following document is the extension letter regarding the User Fee Goal date (Review goal date).

Christina H. Chi, Ph.D.

Note: We are providing the attached information via telefascimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Christina H. Chi, Ph.D. **TITLE:** Regulatory Health Manager

TELEPHONE: 301-827-2127 **FAX NUMBER:** 301-827-2326/2325

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

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

/s/

Diana Willard
2/18/05 09:44:42 AM
NDA 21-506 and NDA 21-754/Extension of User Fee Goal Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	ODS POSTMARKETING SAFETY REVIEW	
TO: Mary Singer, M.D., M.P.H., Medical Officer Renata Albrecht, M.D., Director Division of Special Pathogens and Immunologic Drug Products (DSPIDP) HFD-590	**FROM:** Adrienne M. Rothstein, Pharm.D. Safety Evaluator Melissa M. Truffa, R.Ph. Safety Evaluator Team Leader DDRE (HFD-430)	**ODS PID #:** D040821 **DATE Completed:** February 18, 2005
DATE REQUESTED: Dec. 9, 2004	**REQUESTOR/Phone #:** Mary Singer, M.D., M.P.H., 301-827-2371	
DRUG (Generic): micafungin sodium	**NDA #** 021754, 021506	**SPONSOR:** Fujisawa Pharmaceutical Company, Ltd.
DRUG NAME (Trade): MYCAMINE™	**THERAPEUTIC CLASSIFICATION:** echinocandin antifungal agent	
EVENT: Review of Japanese postmarketing experience for serious hepatic, renal, hematologic, hypersensitivity and cardiac events.		

Executive Summary

DSPIDP is reviewing New Drug Applications for micafungin, which has been marketed in Japan since approval in October 2002. DDRE was asked to provide a safety review of postmarketing events from Japan to assist DSPIDP in their assessment of the MYCAMINE applications and the adequacy of the proposed labeling. DDRE reviewed the 2nd and 3rd PSUR prepared by Fujisawa, an English translation of the Funguard® label in Japan, and the draft Mycamine™ (micafungin sodium) package insert. In addition, the MedWatches for serious postmarketed hepatic, hematologic, and skin events received through August 31, 2004 were reviewed. The events of concern identified by DSPIDP were hepatic, renal, hematologic, hypersensitivity and cardiac events. As a result of this comprehensive review, DDRE has the following recommendations for your consideration:

Although most of the Japanese postmarketed cases were extremely complex with multiple concomitant medications and disease states that could predispose to hepatic events, the role of micafungin in the etiology of these events could not entirely be ruled out. Therefore, we recommend that hepatic events be listed as a **PRECAUTION** including the following: Laboratory abnormalities in liver function tests have been seen in . In some patients with serious underlying conditions who were receiving multiple concomitant medications along with micafungin, clinically significant hepatic abnormalities have occurred. Isolated cases of clinically significant hepatic dysfunction or worsening hepatic failure have been reported in patients; Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing MYCAMINE therapy.

Based on the review of the Japanese postmarketing data and the current Japanese labeling. we recommend that renal impairment be listed as a **PRECAUTION** including the following:

al

. Patients who develop abnormal renal function parameters during MYCAMINE therapy should be monitored for evidence of worsening renal function

The sponsor should consider adding a **WARNING** or **PRECAUTION** about the possibility of anaphylactoid reactions during micafungin infusions with recommendations to discontinue MYCAMINE and administer appropriate treatments if this reaction occurs.

Under **ADVERSE REACTIONS**, consider creating a separate paragraph to list the following **Additional Adverse Events from Japanese Postmarketing Sources:**

- Hepatic: hyperbilirubinemia, hepatic function abnormal, hepatic disorder, and hepatocellular damage
- Renal: acute renal failure and renal impairment.
- Hematologic: decreased white blood cell count, hemolytic anemia.
- Vascular: shock

A causal relationship to micafungin cannot be excluded for the events listed above.

Under **ADVERSE REACTIONS**, the sponsor should remove the from adverse events to be consistent with the current version of MedDRA. The sponsor should consider providing the micafungin treatment duration in the **ADVERSE REACTIONS** section describing adverse events from Phase III clinical trials. Under **ADVERSE REACTIONS**, the sponsor should remove the from the description of events from clinical trials. Under **DOSAGE AND ADMINISTRATION,** the sponsor should list the

In addition to the above mentioned labeling recommendations, consider reviewing the clinical data for occurrences of QTc prolongation and hemolytic uremic syndrome. Following the approval of MYCAMINE in the U.S., close monitoring of the following adverse events should be performed: QTc prolongation, hyponatremia, hemolytic uremic syndrome, and serious skin reactions.

Materials Reviewed

These comments are based on a review of the micafungin 2nd PSUR prepared by Fujisawa (data lock period: 08 Apr 2003 – 08 Oct 2003), 3rd PSUR (data lock period: 09 Oct 2003 – 08 Apr 2004), an English translation of the Funguard® (micafungin sodium) Japanese label (7th version, dated July 2004), and the draft Mycamine™ (micafungin sodium) package insert from the 120-day safety update to the NDA submissions (submitted on 24 August 2004). At the request of DSPIDP, the sponsor provided MedWatches for hepatic events, hematologic events and toxic epidermal necrolysis received through August 31, 2004, which were also reviewed for this summary.

U.S. and Japanese Drug Information for Micafungin Sodium

	United States	Japan
Drug Name	MYCAMINE	FUNGUARD
Approval Date	To be determined	08 October 2002
Indication	Treatment of patients with esophageal candidiasis and prophylaxis of *Candida* infections in patients	Infections caused by *Aspergillus* sp. and *Candida* sp., including fungemia, respiratory mycosis, and gastrointestinal mycosis

	undergoing hematopoietic stem cell transplantation (HSCT)	
Daily Dose	Treatment of Esophageal Candidiasis: Adults: 150 mg daily — Prophylaxis of *Candida* infections in patients undergoing HSCT: Adults: 50 mg daily —	Adults: 50-150 mg, up to 300 mg daily for severe or refractory infections For patients weighing </= 50 kg, dose NTE 6mg/kg/d
Patient Population	., Adults	Safety of micafungin in children not established (no clinical experience in Japan).
Maximum Daily Dose	Micafungin has been safely administered in repeated daily doses up to 896 mg (8 mg/kg) in adults and 4 mg/kg in pediatric patients.	Safety of daily doses up to 300 mg not fully established. No clinical experience in Japan with daily doses > 150 mg, limited clinical experience in foreign countries with daily doses of 300 mg.

Events of Concern:

I. HEPATIC (n=27)

Sponsor Proposed U.S. Labeling:

As noted in the **ADVERSE REACTIONS** section in the proposed U.S. label, increased alkaline phosphatase was reported in — of patients randomized to micafungin in a Phase 3 study comparing micafungin to fluconazole for the treatment of esophageal candidiasis. Less common hepatic events were increases in aspartate aminotransferase and alanine aminotransferase in 0.8% and 0.4% of patients randomized to micafungin, respectively. In a Phase 3 study comparing micafungin to fluconazole for the prophylaxis of *Candida* infections in patients undergoing HSCT commonly reported adverse events in patients randomized to micafungin were hyperbilirubinemia (2.8% of patients), abnormal liver function tests (0.7%), jaundice (0.5%), and increases in alanine aminotransferase (0.9%), aspartate aminotransferase (0.7%), and blood bilirubin (0.5%). There were Japanese post-marketing reports of hyperbilirubinemia, hepatic function abnormal, hepatic disorder, and hepatocellular damage listed in the **Overall MYCAMINE Safety Experience** section.

Japanese Labeling:

The Funguard labeling has a **PRECAUTION (CAREFUL ADMINISTRATION)** that use of Funguard in patients with hepatic impairment may aggravate hepatic impairment. There is also an **IMPORTANT PRECAUTION** noting that hepatic function disorder or jaundice may develop in patients receiving Funguard. Additionally, hepatic lesions were noted in the high dose treatment group in animal studies. Under **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**, hepatic function disorder with increased AST, ALT, GGT, or ALP, etc., or jaundice are listed with a recommendation that patients should be carefully monitored by periodic examination. Appropriate measures such as discontinuation of treatment should be taken if abnormalities are observed. Increased LDH was also listed as an adverse reaction from clinical trials in Japan at an incidence of 0.1% - <5%. In foreign clinical studies, increased AST (6.7% of patients), increased ALT (5.8%), increased ALP (5.6%), bilirubinemia (1% - <5%) were reported in patients treated with micafungin.

Due to the number of serious hepatic events for this product, a cumulative review was performed of all Japanese postmarketing serious hepatic events that the sponsor reported receiving through 31 August 2004. Serious hepatic events that were fatal or life-threatening in nature and any serious adverse event of hepatitis, fulminant hepatitis, hepatic failure, and liver damage were reviewed and the DDRE safety evaluator determined a causal relationship between the use of micafungin and the reported events (see Appendix 1). Almost all of the cases were extremely complex, with multiple concomitant medications and disease states that could predispose to hepatic events. The role of micafungin in the etiology of these events is therefore impossible to ascertain in most cases, but cannot be ruled out in a number of cases. Specifically, this review identified 6 serious events of hepatic failure, the causal role of micafungin was assessed as possibly related in 1 case and unlikely in 4; there was not enough information to make a causal assessment in the last case. There was 1 case of hepatitis, which was considered not related to micafungin. There were 3 serious events of hepatocellular damage; the causal relationship to micafungin was possible in 1 and unlikely in 2 cases. There were 2 serious events of liver disorder; both were considered possibly related to micafungin. There were 5 serious events of hyperbilirubinemia; the causal relationship to micafungin was possible in 2 and unlikely in 3 cases. For the 10 serious events of hepatic function abnormal, the causal relationship to micafungin was possible in 4 and unlikely in 5 cases; there was not enough information to assess the last case. See Appendix 1 for a concise description of these cases and a causal assessment of the hepatic events.

Summary of Hepatic Events:
Under **ADVERSE REACTIONS**, the proposed U.S. MYCAMINE label lists increased alkaline phosphatase as a common adverse event and increases in aspartate aminotransferase and alanine aminotransferase as less common hepatic events in patients randomized to micafungin in U.S. clinical trials for esophageal candidiasis. In a Phase 3 study for the prophylaxis of *Candida* infections in patients undergoing HSCT, commonly reported adverse events in patients randomized to micafungin were hyperbilirubinemia, abnormal liver function tests, jaundice, and increases in alanine aminotransferase, aspartate aminotransferase, and blood bilirubin. The —— also lists Japanese post-marketing reports of hyperbilirubinemia, hepatic function abnormal, hepatic disorder, and hepatocellular damage. Although the postmarketing cases reviewed were complex and the causal relationship was difficult to ascertain, the proposed U.S. labeling did not appear to adequately convey the hepatic risks for patients, especially those patients with existing hepatic impairment. Therefore we recommend that hepatic events be listed as a **PRECAUTION** including the following: Laboratory abnormalities in liver function tests have been seen in —— In some patients with serious underlying conditions who were receiving multiple concomitant medications along with micafungin, clinical hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction or worsening hepatic failure have been reported in patients —— Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing MYCAMINE therapy.

II. RENAL (n=25)

Sponsor Proposed U.S. Labeling:
The —— in the **ADVERSE REACTIONS** section of the proposed U.S. label lists Japanese post-marketing reports of acute renal failure and renal impairment.

Japanese Labeling:
The current Funguard labeling lists serious renal disorders, such as acute renal failure as

CLINICALLY SIGNIFICANT ADVERSE REACTIONS. The labeling states that patients should be carefully monitored by periodic exams with discontinuation of Funguard if abnormalities are observed. Increased BUN, increased creatinine and decreased creatinine clearance were also observed in clinical trials in Japan.

a. **Renal failure: (n=9)**

PSUR-2[1] includes **1 serious event of renal failure** that occurred in a 55 y/o male with pulmonary mycosis and history of traffic accident and loss of abdominal wall, diabetes mellitus, diabetes insipidus, and DIC. The patient was receiving 14 additional medications at event onset. On day 2 of micafungin, renal function parameters suddenly increased (max SCr=7.5, max BUN=126). A week later, micafungin, betamipron and panipenem were discontinued. Initially his renal function worsened, but the event resolved 6 weeks after onset. This event of renal failure was possibly related to micafungin. In PSUR-3[2] there were a total of **8 serious events of renal failure** (4 events of renal failure, 3 of acute renal failure, 1 of acute renal failure on chronic). One event of renal failure was considered unrelated to micafungin; the remaining cases did not have enough information for a causal assessment. Thus, there was 1 case of renal failure possibly related to micafungin.

b. **Renal impairment: (n=13)**

PSUR-2[1] includes **5 serious events of renal impairment**. Renal impairment was possibly related to micafungin in 3 cases and unlikely in 1 case; a causal assessment could not be made in the other case. In PSUR-3[2] there were **7 serious events of renal impairment**. Renal impairment was possibly related to micafungin in 2 cases; a causal assessment could not be made in the remaining 5 cases. In addition, there was **1 serious event of renal disorder** in PSUR-3. This case occurred in a 63 y/o male with diabetes mellitus and a severe renal disorder (exact disorder unspecified). One week after the initiation of micafungin, his serum creatinine increased and micafungin was discontinued. The concomitant medications were unknown. A causal assessment could not be made. Thus, there were 5 cases of renal impairment possibly related to micafungin.

c. **Hemolytic Uremic Syndrome: (n=3)**

There were no cases of hemolytic uremic syndrome (HUS) reported in PSUR-2[1]. In PSUR-3[2], there was 1 serious case of HUS possibly related to micafungin. The 120-day safety update was reviewed and 2 additional cases were identified, one of which was possibly related to micafungin. All **3 serious events of HUS** occurred in teenagers who were receiving imipenem/cilastatin concomitantly. Hemolytic anemia has been associated with imipenem/cilastatin, although hemolytic uremic syndrome is not specifically listed as an adverse reaction.[3] The first case of HUS occurred in a 15 y/o male with AML, sepsis and pneumonia. The patient developed an increased T.bili level, decreased hemoglobin, and decreased platelets about 2 days after micafungin (100 mg daily), 1 day after ceftazidime, and less than 1 day after imipenem/cilastatin (1 g daily) were initiated. Hematuria was observed the next day. About a week later, HUS was diagnosed. Micafungin and imipenem/cilastatin were discontinued and the event was improving.. In the second case, a 16 y/o female with AML received a peripheral blood stem cell transplant with TBI and tacrolimus. Ten days later, the patient developed febrile neutropenia and was treated with micafungin (50 mg daily) and antibiotics. A week later, imipenem/cilastatin (500 mg daily) was initiated. Nine days later, HUS was diagnosed based on hematuria and red cell

[1] Data lock period: 08 Apr 2003 - 08 Oct 2003
[2] Data lock period: 09 Oct 2003 - 08 Apr 2004
[3] PRIMAXIN® I.V. [package insert]. Whitehouse Station, N.J.: Merck & Co, Inc.; August, 2003.

fragmentation in her peripheral blood. Tacrolimus was discontinued of suspected thrombotic microcytic angiopathy. The patient expired 5 days later; the cause of death was renal failure, which may have been aggravated by HUS. The event was possibly related to micafungin. In the last case, a 12 y/o female with AML who was receiving micafungin and imipenem/cilastatin developed HUS. After an unknown period of time, the patient expired. A causal assessment could not be made based on information provided. Therefore, a causal role of micafungin in the development of HUS is possible in 2 serious cases.

Summary of Serious Renal Events:
For the 2nd and 3rd PSURs, there were a total of 9 events of renal failure, 13 events of renal impairment and 3 events of HUS. For the cases with enough information to make a causal assessment, only 1 event of renal failure, 5 events of renal impairment and 2 events of HUS were considered possibly related to micafungin. In addition, there were 3 serious reports of hyponatremia in PSUR-2, but there was inadequate information to evaluate these cases further — renal impairment and renal failure are described in the section in the proposed U.S. labeling for Mycamine. Based on the **CLINICALLY SIGNIFICANT ADVERSE REACTIONS** noted in the Japanese labeling, the sponsor should consider listing renal impairment as a **PRECAUTION** in the U.S. label, including the following —

Patients who develop abnormal renal function parameters during MYCAMINE therapy should be monitored for evidence of worsening renal function —

. Consideration should be made to review clinical trial data for events of hemolytic uremic syndrome. Events of hyponatremia and hemolytic uremic syndrome should be closely monitored after the approval of MYCAMINE in the U.S.

III. HEMATOLOGIC (n= 58)

Sponsor Proposed U.S. Labeling:
As noted in the **ADVERSE REACTIONS** section, anemia, leukopenia, neutropenia, and thrombocytopenia were commonly reported in patients randomized to micafungin in Phase 3 studies comparing micafungin to fluconazole for the treatment of esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing HSCT. In the **Overall MYCAMINE Safety Experience,** — anemia was listed as a — adverse event from the MYCAMINE clinical development program, —

Japanese Labeling:
The current Funguard labeling lists neutropenia (1.5%), thrombocytopenia or hemolytic anemia as **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**. Patients should be carefully monitored by periodic exams with discontinuation of Funguard if abnormalities are observed.

a. **Hemolysis: (n=10)**
There was 1 serious report of hemolytic anemia in PSUR-2, which occurred in a 70 y/o male with a fungal infection and PMH of aortic aneurysm, rectal cancer and interstitial pneumonia. The patient was receiving 11 concomitant medications at event onset. Based on the information provided, the causal relationship for the event of hemolytic anemia could not be assessed. In PSUR-3 there were 5 serious cases related to hemolysis, including hemolysis (1 event), hemolytic anemia (3), and intravascular hemolysis (1). These cases were not analyzed in the text of the PSUR, so the MedWatches submitted

by the sponsor for serious hematologic events were reviewed. In total, the sponsor reported **3 serious cases of hemolysis, 2 serious cases of intravascular hemolysis and 5 serious cases of hemolytic anemia through August 2004.** These 10 cases were examined closely to determine the causal relationship. In all 3 cases of hemolysis, the events were possibly related to micafungin. For intravascular hemolysis, one case was probably and the other was possibly related to micafungin. For hemolytic anemia, the causal relationship to micafungin was probable in 1 case, possible in 3, and unlikely in 1 case.

b. **Leukopenia: (n=7)**

In PSUR-2 there were 5 serious reports of decreased white blood cell count. Two events were probably, 1 was possibly and 2 were unlikely related to micafungin. In these cases the white blood cell count recovered within a week after the discontinuation of micafungin. In PSUR-3 there was 1 event of leukopenia (follow-up case), 1 of neutropenia, and 1 of agranulocytosis; no cases are described in the text of the PSUR. MedWatches for these events were obtained from the 120-day safety update. **In total there were 5 events of leukopenia, 1 event of neutropenia, and 1 of agranulocytosis received through August 2004.** Leukopenia and neutropenia were commonly reported in U.S. clinical trials and are not unexpected in this patient population requiring systemic antifungal medications.

c. **Anemia: (n=20)**

In PSUR-2 there were 2 serious events of anemia and follow-up to 1 serious case of aggravated anemia were reported in PSUR-2. Only 1 case was described in the PSUR and was determined to be unlikely related to micafungin. In PSUR-3 there were 8 serious cases of anemia and 1 serious case of aggravated anemia; no cases are described in the text of the PSUR. The 120-day safety update was consulted and **a total of 20 serious events of anemia were identified through August 2004.** Anemia was commonly reported in U.S. clinical trials and is not unexpected in this hospitalized patient population requiring systemic antifungal medications.

d. Thrombocytopenia: (n=14)

There were 3 serious reports of thrombocytopenia and 1 serious report of platelet count decreased in PSUR-2. In these 4 cases the platelet count was low prior to the initiation of micafungin, although a causal relationship was at least possible in 2 cases. In PSUR-3 a total of 2 cases related to thrombocytopenia were received, including 1 event each of idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura. The 120-day safety update was consulted and **a total of 14 serious events related to thrombocytopenia (including thrombocytopenic purpura) were identified through August 2004.** The sponsor reported that 11 serious cases of thrombocytopenia have been received through August 2004. The Japanese labeling was recently updated to list thrombocytopenia as an adverse event. There were 2 serious events of idiopathic thrombocytopenic purpura; there wasn't enough information about either case to make a causal assessment. There was 1 case of thrombotic thrombocytopenic purpura, which was possibly related to micafungin.

e. **Suppression of Multiple blood cell lineages: (n=7)**

There were no cases of serious adverse events related to suppression of multiple blood cell lineages received in PSUR-2. In PSUR-3, a total of 7 serious events related to suppression of multiple blood cell lineages were received, including 1 event of bone marrow depression and 6 events of pancytopenia. No cases were described in the text of the PSUR. The 120-day safety update was consulted to obtain MedWatches for these serious events. No additional cases were identified from the sponsor through

August 2004. Thus, there have been **7 serious events of this nature reported by the sponsor through August 2004**, including 1 event of bone marrow depression and 6 events of pancytopenia. The event of bone marrow depression had an unlikely causal relationship to micafungin. For pancytopenia, the causal relationship to micafungin was unlikely in 4 cases; in the remaining 2 cases, there was not enough information to make a causal assessment.

Summary of Hematologic Events:
The proposed U.S. labeling lists anemia, leukopenia, neutropenia, and thrombocytopenia as common adverse events under **ADVERSE REACTIONS**. Based on the serious events reviewed, leukopenia and thrombocytopenia appear to be reversible with micafungin discontinuation. Hemolytic anemia has rarely been reported from Japanese post-marketed experience. The proposed U.S. labeling appears to be adequate in regards to hematologic events, except to consider adding hemolytic anemia in the listing of adverse events from Japanese postmarketing sources. Unlabeled hematologic adverse events, such as ITP or TTP, should be closely monitored after the approval of MYCAMINE in the U.S.

IV. HYPERSENSITIVITY (n= 18)

Sponsor Proposed U.S. Labeling:
As noted in the **ADVERSE REACTIONS** section, rash and pruritus were reported in [redacted] of patients randomized to micafungin in Phase 3 studies comparing micafungin to fluconazole. [redacted] lists anaphylactoid reaction as [redacted] event from the MYCAMINE clinical development program and lists Japanese post-marketing reports of shock.

Japanese Labeling:
The current Funguard labeling lists shock and anaphylactoid reactions as **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**. Patients should be carefully monitored and if abnormalities such as decreased blood pressure, oral cavity discomfort, dyspnea, generalized flushing, angioedema, or urticaria, etc. are observed, Funguard should be discontinued. If necessary, appropriate measures such as maintenance of the airway or administration of adrenaline, steroids or antihistamines, etc. should be taken.

a. Allergic Reactions (n=7)

There were **3 serious anaphylactoid reactions** described in PSUR-2. The first case occurred in a 69 y/o female with cancer of the middle ear (s/p surgery and irradiation) with severe marrow depression, pneumonia, acute respiratory insufficiency, and DIC. The patient was receiving 17 drugs and platelets at the time of the event. Thirty minutes after the initiation of micafungin, the patient developed an anaphylactoid reaction, acute circulatory failure and generalized redness. Micafungin was discontinued and the event markedly improved with steroids. The event was probably related to micafungin. In the second case, a 60 y/o male patient with bronchopulmonary aspergillosis, asthma, and bronchitis developed symptoms immediately after the micafungin infusion began. The patient was receiving 10 medications at the time of the event. Micafungin was discontinued and event resolved that same day. The event was probably related to micafungin. In the third case, a 13 y/o female patient with deep mycosis, ALL (s/p BMT), renal failure, sepsis, DIC, and aggravated VOD developed symptoms "in the middle" of micafungin infusion. The patient was receiving 3 medications at the time of the event. Micafungin was discontinued and steroids administered. Her blood pressure normalized in 45 minutes, but the event outcome was unknown. The event was possibly related to micafungin.

In PSUR-3, there were **4 serious events related to allergic reactions, including 2 events of**

anaphylactic shock and 2 infusion related reactions. In the first case of anaphylactic shock, a 56 y/o female developed anaphylactic shock and intravascular hemolysis on the day that micafungin was initiated. Micafungin was discontinued and the patient was recovering at last report. The event was possibly related to micafungin. In the second case of anaphylactic shock, a 74 y/o male developed anaphylactic shock on the day that micafungin was initiated. Micafungin was discontinued and the event resolved. The event was possibly related to micafungin. In the first infusion related reaction, a 27 y/o female developed an unspecified infusion related reaction on the day that micafungin was initiated. Micafungin was discontinued and the event resolved. Event possibly related to micafungin. In the second case a 37 y/o female developed an infusion related reaction 4 days after the initiation of micafungin. Micafungin was discontinued 2 days later and the event resolved. Unable to make causal assessment based on line listing.

b. Serious Skin Events: (n= 6)

In PSUR-2 there were **2 serious skin events** reported, including toxic epidermal necrolysis and a serious case of dermatitis medicamentosa. The event of toxic epidermal necrolysis was reported in a 40 y/o female with candidal infection, SLE and UTI. One day after the initiation of micafungin, the patient developed SJS. Micafungin, immunoglobulin, imipenem/cilastatin, and amikacin were discontinued and steroids were administered. One week later, the patient improved. A causative drug cannot be specified, but micafungin cannot be excluded as a cause of the event. One serious event of dermatitis medicamentosa was listed in the report, but there was not enough information to make a causal assessment.

In PSUR-3, there were **3 serious skin events**, including toxic epidermal necrolysis, dermatitis medicamentosa and rash. Toxic epidermal necrolysis was reported in a 77 y/o male with candidal infection, lymphoma and operations for appendicitis and cholelithiasis. The patient was receiving ampicillin/sulbactam, cefozopran, and arbekacin at the time of the event. One week after initiation of micafungin, the patient developed redness on his upper body. Two days later, TEN was diagnosed. Micafungin and ampicillin/sulbactam were discontinued and steroids were administered. At last report, the patient was improving. Event possibly related to micafungin. A 70 y/o male developed dermatitis medicamentosa, increased eosinophil count, and pyrexia. The serious skin event occurred 22 days after initiation of micafungin. Micafungin discontinued and patient recovered. There was not enough information to make a causal assessment. In the third case, a 69 y/o male developed rash and increased bilirubin 26 days after the initiation of micafungin. Micafungin discontinued, but the events did not resolve. There was not enough information to make a causal assessment.

According to a cumulative listing, there was also **1 report of toxic epidermal necrolysis** discussed in PSUR-1 (08 October 2002 to 07 April 2003). The sponsor was contacted and the MedWatch was obtained for this case. This case is confounded by the fact that micafungin, impenem/cilastatin, erthyromycin, and clindamycin were all started and stopped around the same time. Twenty days later, the eruptions were almost resolved. One week later, the patient died of MOF. A causative drug could not be specified, but a contributory role of micafungin could not be excluded.

c. **Vascular Reactions: (n=5)**

There were no reports of vascular reaction in PSUR-2. In PSUR-3, there were **5 serious events of shock**; the verbatim terms for these cases include shock (1 event), acute circulatory failure (3), and circulatory failure (1). For these 5 events of shock, a causal role of micafungin was unlikely in 2 cases

and an assessment could not be made for the remaining 3 cases. The first case of acute circulatory failure occurred in a 54 y/o male with reported events of DIC, pneumonia, anemia, jaundice, increased GOT, GPT and BUN. Shock occurred 7 days after initiation of micafungin. The event had a fatal outcome. There was not enough information to make a causal assessment. The second case of acute circulatory failure occurred in a 63 y/o male with asthma. Shock occurred 2 days after initiation of micafungin. The event had a fatal outcome. There was not enough information to make a causal assessment. The third case of acute circulatory failure occurred in a 67 y/o male 83 days after initiation of micafungin. The event was fatal. The event of shock was unlikely related to micafungin. The only case of circulatory failure occurred in a 73 y/o female with reported events of respiratory failure, decreased hemoglobin, and increased ALP, GGT, BUN, creatinine and potassium. Shock occurred 765 days after initiation and 1 month after discontinuation of micafungin. Event had an unlikely causal relationship to micafungin. Finally, a case of shock occurred in a 59 y/o female after unknown duration of micafungin. The event outcome was unknown. There was not enough information to make a causal assessment.

Summary of Hypersensitivity Events:
Under the — in the proposed U.S. label, anaphylactoid reaction was identified as a — nt in the MYCAMINE clinical program. In the PSURs reviewed, there were 3 events of anaphylactoid reactions and 2 events of anaphylactic shock that were possibly or probably related to micafungin. The sponsor should consider adding a **WARNING** — about the possibility of anaphylactoid reactions during micafungin infusions with recommendations to discontinue MYCAMINE and administer appropriate treatments if anaphylaxis or anaphylactoid reactions occur. In addition, DDRE was able to identify three cases of TEN in which a causative drug could not be specified, but a contributory role of micafungin could not be excluded. Consideration should be made to review clinical trial data for serious skin events and events of this nature should be closely monitored following the approval of MYCAMINE in the U.S.

V. CARDIAC (n= 9)

Sponsor Proposed U.S. Labeling:
As noted in the **ADVERSE REACTIONS** section, tachycardia was commonly reported in patients randomized to micafungin in a Phase 3 study comparing micafungin to fluconazole for the prophylaxis of *Candida* infections in patients undergoing HSCT. In the **Overall MYCAMINE Safety Experience,** hypertension was considered a — adverse event from the MYCAMINE clinical development program. — were also listed; it is unclear if these cases are cardiac in nature.

Japanese Labeling:
The current Funguard labeling notes that hypertension and palpitation occurred in 0.1% to <5% of Japanese patients in clinical trials. Additionally, vasodilatation was noted in foreign clinical studies in patients treated with micafungin

a. Arrhythmias (n=4)
In PSUR-2 there was **1 serious report each of supraventricular tachycardia and ventricular tachycardia**, both were unlikely to be related to micafungin. In PSUR-3 there was **1 case each of atrial fibrillation and ventricular tachycardia**; neither could be assessed because they were not described in the text of the report. The event of supraventricular tachycardia occurred in a patient on TPN with no prior cardiac history. Three days after initiation of micafungin, patient developed PSVT with decreased

blood pressure and convulsions. The patient was cardioverted and disopyramide was initiated. It was unlikely that the event was related to micafungin. Ventricular tachycardia occurred in a patient receiving 8 other concomitant medications. The patient had a possible prior history of v. tach. Several weeks after an increase in the micafungin dose from 150 mg to 225 mg daily, the patient developed ventricular tachycardia on 12 sequential cycles on the ECG monitor. The heart rate returned to sinus rhythm spontaneously within several seconds without any treatment and the event did not recur (patient monitored by ECG). It was unlikely that the event was related to micafungin.

b. **Hypertension: (n=0)**

There were no serious reports listed in PSUR-2 or PSUR-3.

c. **Acute cardiac failure: (n=5)**

In PSUR-2, there was **1 case of acute cardiac failure** in a patient who developed prolonged QTc (QTc 500 msec). The patient was receiving amikacin, itraconazole, allopurinol, panipenem, betamipron, and trimethoprim/sulfamethoxazole at event onset. The cardiac event was possibly related to micafungin. In PSUR-3, there were **2 serious cases of cardiac failure, 1 case of aggravated cardiac failure, and 1 case of congestive cardiac failure**. There was not enough information provided to make a causal assessment of these 4 cases.

Summary of Cardiac Events:

Cardiac events appear to be adequately addressed by the proposed U.S. label. Prolongation of QTc should be evaluated by the sponsor, if not already done.

Overall Summary:

Refer to the summary table below for the distribution of reported adverse events in PSUR-2 and PSUR-3 from April 2003 to April 2004. As depicted below, serious events were commonly reported and comprised 61.3% of all reported adverse events, which is reasonable given the patient population being treated and need to administer micafungin intravenously. Serious adverse events were most commonly reported for the investigations, hepatobiliary, blood and lymphatic, infections and infestations, and respiratory SOCs. The majority of labeling recommendations from DDRE focus on these SOCs.

Summary Table of Adverse Events by System Organ Class from PSURs

System Organ Class	PSUR-2 Total	PSUR-2 Serious	PSUR-2 N/S	PSUR-3 Total	PSUR-3 Serious	PSUR-3 N/S	Percent Serious**
Hepatobiliary	38	20	18	74	43	31	9.6%
Investigations	27	11	16	204	96	108	16.3%
Skin & subcutaneous	16	2	14	16	4	12	0.9%
Blood & lymphatic	12	8	4	37	31	6	5.9%
Metabolism & Nutrition	10	6	4	24	7	17	2.0%
Gastrointestinal	9	7	2	14	10	4	2.6%
Renal & Urinary	7	6	1	20	18	2	3.7%
Cardiac	3	3	0	7	6	1	1.4%
Infections & Infestations	2	2	0	33	32	1	5.2%
Injury, poisoning & procedural complications	2	2	0	5	5	0	1.1%
Musculoskeletal & connective tissue	2	1	1*	1	0	1	0.2%

System Organ Class	PSUR-2 Total	PSUR-2 Serious	PSUR-2 N/S	PSUR-3 Total	PSUR-3 Serious	PSUR-3 N/S	Percent Serious**
Nervous system	2	1	1	13	11	2	1.8%
Respiratory	2	2	0	25	25	0	4.1%
Vascular	2*	1	1	7	5	2	0.9%
General	N/A	N/A	N/A	21	17	4	2.6%
Neoplasms	N/A	N/A	N/A	15	15	0	2.3%
Psychiatric	N/A	N/A	N/A	3	3	0	0.5%
Immune	N/A	N/A	N/A	2	2	0	0.3%
Ear & labyrinth	N/A	N/A	N/A	1	0	1	0%
Total	**134**	**72**	**62**	**522**	**330**	**192**	**61.3%**

* Error in report text ** Serious AEs as a percentage of total AEs for PSUR-2 & PSUR-3 combined.

Additional Concern: **Incompatibility/Decreased Potency**

The English translation of the Funguard label and a compatibility study provided by the sponsor notes that incompatibility (immediate precipitation) occurs with vancomycin, aminoglycosides and other drugs commonly used in this patient population. Also, there is decreased potency with ampicillin, trimethoprim/sulfamethoxazole, acyclovir, ganciclovir and acetalozamide. As these medications are likely to be used in this patient population, the proposed MYCAMINE labeling should reflect this incompatibility and the potential for decreased potency.

Discussion

The Japanese postmarketed safety data reviewed does provide some evidence that micafungin is associated with an increased risk for potentially clinically significant hepatic, renal, hematologic, hypersensitivity and cardiac events. However, the case numbers are limited, except for hepatic events, and almost all the cases are confounded by concomitant drugs and disease conditions which could themselves cause these events of concern. Also, it was difficult to reconcile the events received in the 2nd and 3rd PSUR and the sponsor's listing of serious events through August 2004. An attempt was made to characterize the safety profile of the micafungin based on the post-marketing data provided by the sponsor, although exact counts cannot be verified at this point in time. Regardless, recommendations can be made to expand the MYCAMINE label to provide a better representation of the micafungin safety profile and monitoring recommendations for this product. A recommendation was made to consider a **PRECAUTION** for hepatic events and continually assess the risk/benefit of MYCAMINE therapy in patients who develop worsening hepatic function. A recommendation was made to consider listing renal impairment as a **PRECAUTION**, with a recommendation to continually assess the risk/benefit of MYCAMINE therapy in patients who develop renal dysfunction. DDRE suggests that a **WARNING** [illegible] be considered for anaphylactoid reactions during micafungin infusions with recommendations to discontinue MYCAMINE and administer appropriate treatments. The sponsor should consider listing the concomitant drugs that are incompatible with or decrease the potency of MYCAMINE. In addition, consideration should be given to reviewing the clinical data for occurrences of QTc prolongation and hemolytic uremic syndrome, if not already conducted.

Reviewer's Signature / Date: /s/	
Division Director Signature / Date: /s/	

Appendix 1. Serious Hepatic Events of Concern*

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
HEPATIC FAILURE (n=6)					
2003JP007175	Hepatic failure, **renal impairment,** systemic mycosis, sepsis **Fatal**	15 y/o Male Aplastic anemia, appendicitis	150 mg daily Suspected candidemia 7 days	Pre-micafungin: AST 25, ALT 50. Maximum Levels: AST 4282, ALT 1387 (1 day after mica. d/c)	Amphotericin B, vancomycin, fluconazole, ceftazidime, imipenem/cilastatin, nartograstim, neurotropin, cysteine/aminoacetic acid/glycyrrhizic acid
Pt died of deep mycosis & sepsis. Hepatic dysfunction appeared and rapidly progressed to hepatic failure when ampho B added to existing micafungin therapy. Micafungin d/c and hepatic events resolved. Positive temporal relationship (7 days after initiation), positive dechallenge (3 days after discontinuation). Confounders: sepsis, amphotericin B, fluconazole. Possible causal relationship.					
2003JP007545	Hepatic failure, **sepsis,** renal insufficiency **Fatal**	56 y/o Male	100 mg Systemic Candidemia 2.5 weeks	Pre-micafungin: Alk Phos 329. Maximum Levels: AST 208, ALT 78, Alk Phos 485 (2 wks after mica. d/c)	imipenem/cilastatin, famotidine
Prior to micafungin, pt had sepsis with MOF. Pt died of sepsis, hepatic failure and renal failure 2.5 weeks after micafungin d/c. Confounding factors: famotidine. Unlikely causal relationship.					
2003JP007510	Hepatic failure, **renal insufficiency,** platelet count decreased, CPK decreased Not recovered	82 y/o Male aortic aneurysm rupture, atherosclerosis obliterans, interstitial pneumonia, gastric ulcer, paralytic ileus, renal failure	50 mg Respiratory monilisais 8 days	Pre-micafungin: T.bili 0.7 Maximum Levels: T.bili 4.9 (2 wks after mica. d/c)	Disopyramide, propofol, ranitidine, dinoprost, dopamine, furosemide,
"Hepatic failure" began 2 weeks after d/c of micafungin. Confounding factors: circulatory insufficiency. Unlikely causal relationship.					
2003JP000750	**Hepatic failure,** renal insufficiency, multi-organ failure **Fatal**	54 y/o Male Pneumonia, sepsis, hepatic failure, cirrhosis, esophageal varices, hemorrhagic shock	50 mg Systemic candida 2 days	Not provided.	Not provided.
Pt with hepatic failure, sepsis, cirrhosis and hemorrhagic shock prior to micafungin initiation. Pt died of his primary disease almost 3 weeks after micafungin discontinued. Unlikely causal relationship.					
2003JP000963	**Hepatic Failure Fatal**	79 y/o Male Hepatitis C, cirrhosis, hepatic cancer	150 mg Candidiasis 4 days	Pre-micafungin: T.bili 7.7 Maximum Levels: T.bili 20.3 (1 mo. after mica. d/c)	Not provided
Pt with hepatitis C, cirrhosis and hepatic cancer prior to micafungin initiation. Unlikely causal relationship.					
2003JP005939	**Hepatic failure Fatal**	60 y/o female Hepatitis B, AML	UNK UNK UNK	UNK	Not provided.
Sponsor classified as definitely not related to micafungin. Unable to assess causal relationship.					

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
HEPATITIS (n=1)					
2004JP000092	Hepatitis fulminant, **lactic acidosis,** febrile neutropenia, renal impairment **Fatal**	58 y/o female Malignant melanoma, sepsis	100 mg Bronchopulmonary aspergillosis 2 weeks	Pre-micafungin: N/A Maximum Levels: AST 18627, ALT 7,444, Alk Phos 163 (2 days after mica. d/c)	Trimethoprim/sulfamethoxazole
Pt with febrile neutropenia and sepsis fell into a shock state acutely before fulminant hepatitis occurred. Pt was also receiving trimethoprim/sulfamethoxazole. One day after micafungin discontinued, lactic acidosis and fulminant hepatitis were noted. Pt had no signs of hepatic dysfunction while receiving micafungin. Pt died of fulminant hepatitis. Unlikely causal relationship.					
HEPATOCELLULAR DAMAGE (n=3)					
2003JP006634	**Hepatocellular damage** **Fatal**	80 y/o male lung cancer, s/p excision of right upper lung 6 mos. prior, atherosclerosis obliterans	50 mg Fungal infection 8 days	Pre-micafungin: AST 10, ALT 5, Alk Phos 198 Maximum Levels: ALT 68, AST 79, Alk Phos 504, GGT 56 (while on mica) AST 271, ALT 556 (10 days after mica d/c; pt died next day)	vancomycin, prednisolone famotidine
Patient developed aspiration pneumonia and received with micafungin. A week later, pneumonia improved and pt weaned from mechanical ventilator. He then developed hepatic damage and micafungin was d/c. CT scan did not show dilation of bile duct. Hepatic damage continued to worsen and patient died of acute on chronic respiratory failure, 11 days after micafungin d/c. Event possibly related to micafungin based on the reported temporal relationship. Confounding factors: use of famotidine Possible causal relationship					
2003JP005832	**Hepatocellular damage** **Fatal**	72 y/o male therapy-resistant NHL, PMH of CMV-positive interstitial pneumonia 3 months earlier, which recurred	100 mg Pulmonary mycosis 2 weeks	Pre-micafungin: N/A Maximum Levels: T.bili 11 and up (while on mica) Echo showed hepatomegaly.	Cefepime, panipenem/betamipron, ganciclovir, zolpidem, omeprazole
Hepatic damage and jaundice appeared 11 days after initiation of micafungin. Hepatic damage was aggravated about 1 week later and micafungin was d/c. One week later MOF progressed. Two days later, pt died of malignant lymphoma and pneumonia. Confounding factors: intrahepatic infiltration of lymphoma or CMV infection, MOF, and use of cephalosporin. Unlikely causal relationship.					
2003JP006590	**Hepatocellular damage** **Fatal**	54 y/o female rheumatoid arthritis, amyloidosis, on a ventilator	150 mg Fungal pneumonia 11 days	Pre-micafungin: N/A Maximum Levels: ALT 267 (while on mica) AST 313, AST 147 three days later (while on mica)	Famotidine, midazolam, cefoperazone, prednisolone, furosemide
Six days after initiation of micafungin, moderate liver damage identified on biochemistry panel. Micafungin was continued and the event did not progress. Hepatic event unlikely related to micafungin, as LFTs were improving slightly until patient succumbed to multiple organ failure. Confounding factors: use of cephalosporin and famotidine. Unlikely causal relationship					
LIVER DISORDER (n=2)					
2003JP007054	**Liver Disorder** **Life-threatening**	70 y/o female Fungal pneumonia, esophageal	50-100 mg Fungemia	Pre-micafungin: AST 46, ALT 57, LDH 282, GGT	Meropenem, immunoglobulin

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
		carcinoma, bone marrow depression (s/p chemotx and radiation tx)	2 days	"slightly high" Maximum Levels: ALT 1654, AST 3900 (mica d/c that day)	
Ten days after micafungin d/c, LFTs decreased to approx 2x baseline levels. Confounding factors: use of meropenem, neoplastic disease. Possible causal relationship					
2003JP007474	**Liver Disorder** **Life-threatening**	87 y/o female atrial fibrillation, asthma, hypertension,	50-150 mg UNK UNK	Pre-micafungin: N/A Maximum Levels: AST 400 (w/ mica 150 mg/d)	Not provided
Liver disorder noted when micafungin dose increased from 50 to 150 mg daily. The dose of micafungin was reduced and she was recovering from the event. Possible causal relationship					
HYPERBILIRUBINEMIA (n=5)					
2004JP001016	**Hyperbilirubinemia** **Life-threatening**	63 y/o male small cell lung cancer, post-op pyothorax with multiple marsupialization procedures	50-75 mg Aspergillosis 6 weeks	Pre-micafungin: T.bili 0.4 Maximum Levels: T.bili 7.3 (mica d/c that day)	imipenem/cilastatin, famotidine
Massive bleeding due to pyothorax w/ administration of packed red blood cells. Hyperbilirubinemia noted for the first time. One week later, T.bili increased again in the absence of bleeding/transfusions and micafungin d/c. Seventeen days later, T.bili decreased to 1.1 and pt considered recovered. Confounding factor: use of famotidine, possible transfusion reaction, neoplastic disease. Possible causal relationship.					
2004JP000850	**Hyperbilirubinemia** **Fatal**	69 y/o female Parkinson's disease, aspiration pneumonia	300 mg Fungemia 3 days	Pre-micafungin: T.bili 1.42, D.bili 2.07 Maximum Levels: T.bili 31.32, D.bili 32.18 (1 week after mica d/c)	Diltiazem, ranitidine, isoxicam, piperacillin, amino acids and Hicaliq (glucose, potassium, magnesium, zinc, calcium)
Three days after initiation of micafungin, progressive hyperbilirubinemia noted. Pt had previously received isoxicam without developing hyperbilirubinemia. Plasma exchange conducted over 3 days, about 1 week after micafungin d/c. Pt also given transfusion of packed red blood cells at this time. Despite change of antibiotics, gamma globulin treatment and PRBC transfusion, pt died from event. Confounding factors: ranitidine, diltiazem. Possible causal relationship					
2003JP007337	**Hyperbilirubinemia** **Life-threatening**	75 y/o male Septic shock, paralytic ileus, colonic perforation, diffuse peritonitis	150 mg Candida pneumonia 6 days	Pre-micafungin: T.bili 4.3 (increasing at the time) Maximum Levels: T.bili 12.2 (mica d/c that day)	Panipenem/betamipron, clindamycin, fluconazole, vancomycin, ciprofloxacin
T.bili increased while on micafungin for 6 days. Micafungin d/c and the pt recovered from the event. However, patient experienced GI hemorrhage several days later, believed to be related to primary disease. Confounding factors: fluconazole, ciprofloxacin, clindamycin. Unlikely causal relationship					
2003JP006270	**Hyperbilirubinemia** **Fatal**	74 y/o male peritonitis due to perforation of duodenal ulcer, chronic renal failure	50 mg Systemic candida 7 days	Pre-micafungin: T.bili 4.8 Maximum Levels: T.bili 11 (mica d/c that day)	Omeprazole, vancomycin, gabexate, cefpirome, ranitidine, ampicillin/sulbactam
Pt was experiencing intraabdominal bile leak, endotoxemia, and MOF at the time of the event. T.bili peaked on day 7 of micafungin therapy. Micafungin d/c and T.bili decreased to 6.5 at the time of last report. One week later, pt died of hemorrhagic shock. Confounding factors: intraabdominal bile leak, endotoxemia, MOF, omeprazole, cephalosporin use, ranitidine, ampicillin/sulbactam. Unlikely causal relationship.					

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
2003JP006683	**Hyperbilirubinemia Fatal**	55 y/o female AML, s/p allogenic BSCT 3 weeks earlier	150 mg Pneumonia 12 days	Pre-micafungin: T.bili 1.0 Maximum Levels: T.bili 46.7 (6 days after mica d/c)	Cyclosporine, famotidine, vancomycin, imipenem/cilastatin, acyclovir, filgrastim, furosemide, fluconazole.
T.bili was normal prior to micafungin and began to increase 1 day after initiation of micafungin. Five days later, pt began to develop symptoms of GVHD including diarrhea, progressing to melena, skin eruption with decreased blood pressure and urine volume. Pt died of multi-organ failure 1 week after micafungin d/c. Confounding factors: GVHD, cyclosporine, famotidine, fluconazole, acyclovir, furosemide. Unlikely causal relationship.					
HEPATIC FUNCTION ABNORMAL (n=10)					
2003JP006719	**Hepatic function abnormal Fatal**	72 y/o male Sepsis, chronic cardiac failure,	100 mg Sepsis 1 day	Pre-micafungin: N/A Maximum Levels: AST 6703, ALT 3800, LDH 3760 (mica d/c that day)	Quinapril,
Post-transfusion hepatitis suspected and lamivudine initiated. However, test results did not indicate viral hepatitis. Pt died 2 days after initiation of micafungin; cause of death was MOF with aggravation of chronic heart failure due to fulminant hepatitis due to micafungin. Possible causal relationship.					
2004JP001237	Hepatic function abnormal, **multi-organ failure,** renal impairment, gastric mucosal lesion **Fatal**	84 y/o male angina, TIA, multiple cerebral infarction, pneumonia	300 mg Bronchopulmonary aspergillosis 6 days	Pre-micafungin: AST 20, ALT 23 Maximum Levels: AST 1004, ALT 755	Ozagrel, edaravone, aminophylline, clarithromycin
Pneumonia continually worsened. Pt developed hepatic dysfunction and renal impairment 6 days after initiation of micafungin. Micafungin was discontinued. Four days later, pt had tarry stools with anemia. Three days later, acute gastric mucosal lesion was diagnosed. The pt went on to develop disturbed consciousness with high levels of fibrinogen degradation products. Pt ultimately died of MOF 10 days after micafungin d/c. Confounding factors: clarithromycin, cerebral infarction. Possible causal relationship.					
2003JP007341	**Hepatic function abnormal Life-threatening**	41 y/o male Myelodysplastic syndrome, atrial fibrillation, acute on chronic heart failure, pneumonia, diabetes mellitus, hemochromatosis	300 mg Bronchopulmonary aspergillosis 5 days	Pre-micafungin: AST 25, ALT 24, LDH 1548, T.bili 0.88 Maximum Levels: AST 2292, ALT 1240, LDH 6886, T.bili 3.84 (mica d/c that day) Two weeks after mica d/c: AST 36, ALT 47, LDH 302	Itraconazole, meropenem, isoniazid, rifampin, menatetrenone (vit K 2), filgrastim, dobutamine, dopamine, morphine, furosemide, benproperine, ranitidine.
Four days after initiation of micafungin, rifampin and isoniazid initiated for tuberculosis and pt transiently fell into a shock state. Liver disorder was noted the next day and micafungin, itraconazole, rifampin, and isoniazid were discontinued that day. A week later, he was recovering from the hepatic disorder. Confounding factors: shock state, hemochromatosis, heart failure, itraconazole, ranitidine, furosemide, meropenem, isoniazid, rifampin. Possible causal relationship.					
2003JP005464	**Hepatic function abnormal Life-threatening**	75 y/o female Hepatic cirrhosis, emphysema, pulmonary hypertension, deep mycosis, h/o pulmonary tuberculosis	100 mg Fungal infection 7 days	Pre-micafungin: AST 17, ALT 9, Alk Phos 214, LDH 197, GGT 25, T.bili 0.7 Maximum Levels:	Isepamicin, teicoplanin, cefozopran, gabexate

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
				AST 429, ALT 398, LDH 986, Alk Phos 185, GGT 33, T.bili 1.5 (about 8 days after mica initiation) Two weeks after mica d/c: AST 36, ALT 47, LDH 302	
Hepatic function worsened after initiation of micafungin. General condition worsened at this time, with hypotension. Hepatic function began to improve with micafungin discontinuation, at this time blood pressure also began to improve. Confounding factors: hepatic cirrhosis, hypotension, use of cephalosporin, teicoplanin. Unlikely causal relationship.					
2003JP000021	**Hepatic function abnormal Life-threatening**	82 y/o male tuberculosis, pneumonia	150 mg Bronchopulmonary aspergillosis 2 days	Pre-micafungin: AST 47, ALT 23, T.bili 1.2 Maximum Levels: AST 1270, ALT 1253, T. bili 2.4	Cefozopran, itraconazole, roxatidine
LFTs rose about two days after initiation of micafungin. Micafungin and cefozopran were d/c that day and events resolved about 2 weeks later. Confounding factors: use of cephalosporin, itraconazole. Possible causal relationship.					
2003JP007507	Hepatic function abnormal, **pneumonia,** anemia **Fatal**	54 y/o female Diabetes mellitus, atypical pulmonary mycobacteriosis, chronic cardiac failure, mitral valve replacement	100 mg Pulmonary mycosis 8 days	Pre-micafungin: AST 36, ALT 22 Micafungin D/C: AST 21, ALT 16 Maximum Levels: AST 1709, ALT 603 (6 days after micafungin d/c)	Clarithromycin, aldactone, sivelestat, meropenem, aztreonam, famotidine, nitrazepam, amikacin, immunoglobulin
Micafungin discontinued before pt experienced increased LFTs. Six days after micafungin d/c, pt developed hepatic function disorder. Two weeks later (3 weeks after discontinuation of micafungin), the pt was recovering from hepatic dysfunction when she died of respiratory failure induced by pneumonia. Confounding factors: chronic cardiac failure, clarithromycin, famotidine, aztreonam, amikacin. Unlikely causal relationship					
2003JP006638	**Hepatic function abnormal Fatal**	20 y/o male ALL, s/p BMT 1 month prior	150-300 mg Fungal infection 1 month	Pre-micafungin: ALT 278, T.bili 2.99 Maximum Levels: AST 219 (10 days before death), ALT 278 (on same day mica initiated), T.bili 24.38 (day before pt died).	Meropenem, gabexate, hyoscine, prednisolone, filgrastim, lenograstim
After dose of micafungin increased from 150 to 300 mg daily, hepatic function parameters suddenly increased. On the same day, pt developed melena with massive hemorrhage and received multiple transfusions. Three days later, CMV antigen was positive and CMV colitis diagnosed. Pt continued to bleed from lower GIT. About 10 days later, pt died of hemorrhagic shock. Micafungin was ongoing at death. Confounding factors: CMV colitis, possible GVHD. Unlikely causal relationship.					
2003JP005221	**Hepatic function abnormal Fatal**	UNK y/o male Pulmonary tuberculosis, hepatitis C infection, hepatic failure, renal failure, cerebral infarction	50 mg UNK UNK	UNK	None reported.
Nine days after initiation of micafungin, pt developed hepatic function disorder due to hepatitis C and had increased SGOT, SGPT, and bilirubin. One week later, pt died of aggravation of primary disease. Confounding factors: hepatitis C infection, hepatic failure, renal failure, cerebral infarction. Unlikely causal relationship.					

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	ConMeds
2004JP000088	Hepatic function abnormal, **bronchopulmonary aspergillosis Fatal**	77 y/o female stomatitis, sepsis d/t pseudomonas aeruginosa, aplastic anemia, herpes simplex virus	150 mg bronchopulmonary aspergillosis 2 weeks	Pre-micafungin: AST 33, ALT 53 Maximum Levels: AST 148, ALT 223	Clindamycin, ceftazidime, fluconazole trimethoprim/sulfamethoxazole, filgrastim
Pt developed hepatic dysfunction 2 days after initiating micafungin. AST & ALT improved while receiving micafungin and the hepatic event was resolving. Pt died the next day of invasive bronchopulmonary aspergillosis. Confounding factors: sepsis, herpes simplex infection, cephalosporin use, trimethoprim/sulfamethoxazole, fluconazole. Unlikely causal relationship.					
2004JP001563	**Hepatic function abnormal Life-threatening**	77 y/o male MRSA infection, cardiac failure, vegetative state	100 mg Candidiasis 3 days	AST increased to 1000	Teicoplanin
Pt developed hepatic disorder with AST increased 3 days after initiation of micafungin. No other information available. Confounding factors: cardiac failure, teicoplanin. Not enough information for causal assessment.					

* Causal relationship between micafungin and the reported event(s) assessed by the author

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/s/

Adrienne Rothstein
2/18/05 02:01:36 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
2/22/05 03:16:53 PM
DRUG SAFETY OFFICE REVIEWER

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 thrombocyto-penic purpura (TTP)	Precaution in label for hemolysis Postmarketing surveillance by ODS for serious hemolysis, hemolytic anemia, TTP, ITP, and pancytopenia

Vascular Reactions: Phlebitis, thrombophebitis	Postmarketing surveillance by ODS for serious deep venous thrombosis, arterial thrombosis, pulmonary embolism, mycocardial 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

Memorandum

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

DATE: 31 January 2005

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS), HFD-030

TO: Renata Albrecht, M.D., Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590
Mary Singer, M.D., Medical Reviewer, HFD-590

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation (DDRE), HFD-430; Office of Drug Safety (ODS), HFD-400
Paul Seligman, M.D., Director, (OPSS), HFD-030

SUBJECT: ODS consultation #D040713 regarding hepatotoxicity possibly induced by use of micafungin (MYCAMINE, Fujisawa) for treatment of esophageal candidiasis (NDA 21-754)

Documents reviewed:

1) Consultation request from HFD-590 to OPSS/ODS/DDRE dated 26 October 2004, assigned #D040713 for desired completion date of 25 January 2005
2) Packages of material (37 volumes) from Fujisawa Pharmaceuticals providing:
   a) 120-day safety update to NDA 21-754 submitted 24 August 2004: 17 volumes
   b) Response to September 10 request for information, submitted 22 September: 3 volumes
   c) Clinical protocols for 8 studies for NDA 21-506 and 21-754: 2 volumes
   d) Response to October 13 request for information, submitted 25 October: 1 volume
   e) Response to October 20 request for information, submitted 29 October: 1 volume
   f) Response to October 27 request for information, submitted 12 November: 1 volume
   g) Response to December 14 request for information, submitted 22 December: 12 volumes
3) Medical literature (PubMed) on echinocandin toxicity 21 January 2005
4) DSS, DFS listings for reviews entered to 21 January 2005 for micafungin, NDA 21-754
5) Additional two cases of possible micafungin-induced injury received by fax 24 January 2005

In view of the huge amount of material submitted in the 37 volumes cited above, plus the original New Drug Application (NDA) submission, I asked Dr. Mary Singer what critical questions I should address in this consultation. She suggested on 13 January 2005 that it would be most helpful for me to focus my attention on the cases that were reviewed by a special panel of experts. Division 590 on 27 October 2004 had requested Fujisawa to have a panel of external expert hepatologists review all deaths due to hepatic failure and serious events of hepatic failure in the safety database. That panel included Drs. [redacted]. They were asked to review 19 cases of "liver damage" and "hepatic failure" to assess the relation of the adverse event to study drug administration. Of the 19 patients, 14 had been treated with micafungin, 4 with fluconazole, and 1 with neither ("placebo"),

but panelists were blinded to what treatment the patients had. They were asked to assess whether the adverse hepatic events were not related, possibly related, or related to study drug, as follows:

Not Related	Adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has much more likely alternative etiology).
Possibly Related	Adverse event has a strong temporal relationship to study drug and another etiology is equally or less likely.
Related	Adverse event has a strong temporal relationship to study drug or recurs on rechallenge, and another etiology is unlikely or significantly less likely.

Fujisawa assembled information on the 19 cases, including for each a patient profile and narrative, plus laboratory, radiology, liver biopsy and autopsy reports if available. Treatment with micafungin, fluconazole, or neither was not stated. The 19 cases, along with a copy of the current Investigator Brochure, were sent to each of the panelists during the week of 8 November. They reviewed the cases individually, and then "met" by telephone conference on 23 November 2004 to discuss each of the cases and to reach their consensus on the association of study drug with the occurrence of the hepatic events, with their reasons for arriving at the decisions. Their final report of the review was sent to the sponsor that day by Dr [redacted] who said that, from their review and deliberations, there appeared to be no clear signal of hepatotoxicity from micafungin, but they emphasized that the underlying medical conditions in these patients were extraordinarily complex. The patients were receiving many other types of medications, were immuno-compromised, and had serious underlying diseases including AIDS, malignancies, and pre-existing end-stage liver disease. Of the 19 cases, they felt that 13 were not related, 6 possibly related, and none probably related to study drug. The report of the external panel of expert hepatology reviewers was then forwarded to HFD-590 on 1 December 2004, which. then requested on 14 December additional information, including as item 10 a request for a copy of the package of information given to the expert panel, exactly as sent, with e data on the 19 patients and the Investigator Brochure. Fujisawa responded on 22 December, and sent the material requested as volume 8 of a total of 12 volumes.

Comment: The accurate attribution of causality of adverse events as drug-induced has been one of the most difficult problems in medicine to resolve, despite many attempts over the past 35 years or so. Most of the initial attempts considered the problem in general, for any drug-induced adverse reaction (Irey, 1971; Feinstein, 1974; Karch and Lasagna, 1975; Kramer, et al., 1979; Naranjo, et al., 1981), but special efforts were subsequently undertaken in France (Danan, et al., 1987, 1988; Bénichou, et al., 1990, 1993) to address the question of drug-induced liver injury (DILI), and soon after in other European countries (Maria and Victorino, 1997; Aithal, et al., 2000; Lucena, et al., 2001). More recently, with the formation of the Drug-Induced Liver Injury Network (DILIN) funded by the National Institutes of Health (NIH) in 2003, particular attention has been aimed at moving beyond simply opinion-based overview decisions as to the quantitative likelihood of drug-induced causality of the liver reactions. It has been recognized for many years (Goodman, 2002) that there are no pathognomonic histologic changes to make a certain diagnosis that an hepatic disorder is caused by exposure to a drug, as opposed to being caused by a non-drug or disease etiology. At most it can be said that a given set of findings on liver biopsy or autopsy may be "compatible with"

or "consistent with" drug causation. There are no laboratory tests that are diagnostic, either. The diagnosis of DILI therefore is one of exclusion, requiring that other possible causes be ruled out, before concluding that it may have been the drug that caused the problem. Time relationships of exposure to drug are critical, for the reaction must follow the exposure, although by how much time is still debatable. Generally, it is widely believed that if the reaction subsides when exposure to drug is stopped (dechallenge), that is some evidence in favor of drug-causation; even stronger evidence is reappearance of the reaction if drug administration is resumed (rechallenge), but that is less and less frequently done intentionally because of the danger of a more severe, irreversible reaction, as well as for ethical and legal liability reasons. To go beyond what the expert panel of hepatologists did when reviewing the 19 cases, let us consider in more detail the semi-quantitative methods developed initially in France, and now widely used throughout the world (Lee, 2000; Kaplowitz, 2001; Kaplowitz, et al., 2003) and under active investigation by the DILIN group.

French investigators (Danan and Bénichou, 1987-1993) worked for years to develop national and international consensus on what information would be needed and how to weight that information to make a reasonably certain diagnosis of DILI. They developed a method for typing a given liver reaction as principally hepatocellular or cholestatic, or mixed, based on the ratio (R) of relative rise in serum activity of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) at the time of onset of the hepatic reaction, or first set of clearly abnormal laboratory findings, both expressed as multiples of the upper limit of the normal range for each measure.

DETERMINING THE TYPE OF ACUTE LIVER INJURY
International Consensus (1990), *J Hepatol* **11**: 272-6.

Ratio (R) of serum activities of ALT/ ALP, in xULN, measured together at time liver injury first recognized	
Hepatocellular	**R** ≥ 5, OR (ALT >2xULN and ALP in normal range)
Cholestatic	**R** ≤ 2, OR (ALP > 2xULN and ALT in normal range)
Mixed	2 < **R** < 5 AND (ALT > 2xULN and ALP > ULN)

Note: ALT, alanine amonotransferase; ALP, alkaline phosphatase; xULN, multiples of the upper limit of the normal range.

They then assembled teams of experts from Europe and the Unites States to define terminology, establish standards and definitions, and decide what clinical information was critical to making the best decisions about drug causality. The time of drug exposure and course of the hepatic reaction were agreed to be essential factors, with positive weight for reaction following drug exposure, then subsiding when exposure was stopped, and reappearance if drug exposure was resumed. Negative weights were applied if the timing was wrong. Other possible causes for acute liver injury were important to determine, including acute viral hepatitis A or B (much less often acute hepatitis C), ischemic hepatitis following shock or heart failure, recent heavy alcohol consumption, acute cholelithiasis, autoimmune hepatitis, and less often other disease causes such as acute onset of Wilson's disease, infections with other viruses (cytomegalic, herpes simplex, Ebstein-Barr). Also considered were other drugs that might have been taken concomitantly, and the known history of hepatotoxicity of the drugs, both the one in question and the concomitant medications. Weights for each factor, ranging from +3 to -3 points were assigned, by consensus of the experts, resulting in a total score that could range from -8 to +14. Scores of 0 or less were taken to exclude the possibility of drug-induced injury, 1 or 2 unlikely, 3-5 possible, 6-8 probable, and 9-14 as highly probable.

Because both Danan and Bénichou at that time were employed by the pharmaceutical firm of Roussel-Uclaf, the system of scoring was called "RUCAM," Roussel-Uclaf Causality Assessment Method. The simplified RUCAM scoring system, as published in 1993 (Danan, et al.; Bénichou, et al.), and still in use ten years later (Danan, 2003):

Criteria for Causal Assessment of Drug-induced Hepatocellular Liver Injury

1. Temporal relationship of start of drug to start of illness	
Initial treatment: onset in 5-90 days; subsequent treatment course: 1-15 days	+2
Initial treatment <5 or >90 days; subsequent treatment course: > 15 days	+1
After stopping drug: onset within 15 days, or within 15 days after subsequent treatment	+1
Otherwise	0
2. Course	
ALT decreases ≥ 50% from peak within 8 days	+3
ALT decreases ≥ 50% from peak within 30 days	+2
If the drug is continued or decrease ≥ 50% from peak >30 days, or inconclusive	0
Against causative role for drug	-2
3. Risk factors	
Alcohol use, 1; No alcohol use, 0	0 or 1
Age ≥ 55 years, +1; Age < 55 years, 0	0 or 1
4. Concomitant drug	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
5. Non-drug causes: *Six are primary: recent hepatitis A, B, or C, acute alcoholic hepatitis (AST ≥2x ALT), biliary obstruction, recent hypotension (especially if heart disease). Secondary group: Underlying other disease; possible CMV, EBV or HSV infection*	
All primary and secondary causes reasonably ruled out:	+2
All 6 primary causes ruled out	+1
4 or 5 primary causes ruled out	0
Fewer than 4 primary causes ruled out (*maximum negative score for items 4 and 5: -4*)	-2
Non-drug cause highly probable	-3
6. Previous information on hepatotoxicity of the drug in question	
Package insert or labeling mention	+2
Published case reports but not in label	+1
Reaction unknown	0
7. Rechallenge	
Positive (ALT doubles with drug in question alone)	+3
Compatible (ALT doubles with same drugs as given before initial reaction)	+1
Negative (Increase in ALT but ≤2 X ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0

Total (range of algebraic sum: -8 to +14)

Note: Item 4 and 5 cannot exceed a score of -4

Interpretation: Highly probable, >8; Probable, 6-8; Possible, 3-5; Unlikely, 1-2; Excluded, ≤0

Applying the RUCAM to a given case still requires experience and skill, as well as a consistent approach to how the items are defined. One of the problems in scoring the likelihood that a given hepatic abnormality is a DILI has been the amount and quality of information available to whomever is attempting to judge possible causality. This led the DILIN Causality Committee to list information that is needed in order to exclude non-drug causes of a given hepatic reaction. Items felt to be critical were:

DILIN DATA COMPLETENESS CHECKLIST
CRITICAL INFORMATION FOR DECIDING ON CAUSE OF LIVER INJURY

1	Were details of drug exposure including dose, drug start and stop date recorded?	No ___	Yes ___	
2	Was lifetime history of medication use from the same therapeutic class of agents recorded?	No ___	Yes ___	
3	Was timing of clinical liver disease recorded?	No ___	Yes ___	
4	Were key history and PE data present?	No ___	Yes ___	
5	Was assessment for prior liver disease performed?	No ___	Yes ___	
6	Were doses, start and stop dates of competing prescription medications recorded?	No ___	Yes ___	
7	Were doses, start and stop dates of OTC and complementary/alternative agents recorded?	No ___	Yes ___	
8	Was baseline EtOH history known?	No ___	Yes ___	
9	Was baseline ALT recorded?	No ___	Yes ___	
10	Were serial ALT values recorded?	No ___	Yes ___	
11	Was baseline total bilirubin recorded?	No ___	Yes ___	
12	Were serial total bilirubin values recorded?	No ___	Yes ___	
13	Was baseline AP recorded?	No ___	Yes ___	
14	Were serial AP values recorded?	No ___	Yes ___	
15	Was baseline PT (INR) recorded?	No ___	Yes ___	
16	Were serial PT (INR) values recorded?	No ___	Yes ___	
17	Were data for anti-HAV IgM recorded?	No ___	Yes ___	
18	Were data for HBsAg recorded?	No ___	Yes ___	
	If HBsAg was positive for >6 months, please be sure to also answer questions 30 and 31.			
19	Were data for anti-HBc IgM recorded?	No ___	Yes ___	
20	Were data for HCV RNA recorded?	No ___	Yes ___	
	If HCV RNA was positive for >6 months, please be sure to also answer question 32.			
21	Were data for autoimmune hepatitis (ANA, immunoglobulins) recorded?	No ___	Yes ___	
22	Was serum ceruloplasmin, if under 50, recorded?	No ___	Yes ___	
23	Was history of hypotension or CHF recorded?	No ___	Yes ___	
24	Were liver ultrasound, CT, or MRI data recorded?	No ___	Yes ___	
25	Was ERCP performed, and if so, are data available?	No ___	Yes ___	
26	Were liver biopsy data present?	No ___	Yes ___	
27	Were data on rechallenge available?	No ___	Yes ___	
	Data related to chronic HIV, HBV or HCV:			
28	If the patient had a history of HIV disease, was baseline CD4 recorded?	No ___	Yes ___	NA ___
29	If HIV was positive, were serial CD4 and HIV RNA values recorded?	No ___	Yes ___	NA ___
30	If HBsAg positive >6 months, prior HBV DNA, HBeAg, anti-HBe, treatment recorded ?	No ___	Yes ___	NA ___
31	If HBsAg was positive for >6 months, were data on anti-HDV available?	No ___	Yes ___	NA ___
32	If HCV RNA positive >6 months, were prior HCV RNA, ALT, and treatment recorded?	No ___	Yes ___	NA ___

Note: PE, physical examination; ALT, alanine transaminase, ; ALP, alkaline phosphatase; ; PT, prothrombin time; INR, international ratio; Serious = hospitalized, disabling, life threatening, or fatal; HAV, hepatitis A virus; IgM, immunoglobulin M; HBV, hepatitis B virus; ; HCV, hepatitis C virus; RNA, ribonucleic acid assay for HCV; ANA, antinuclear antibodies; EtOH, , ethanol; CHF, congestive heart failure; CT, computed tomography; MRI, magnetic resonance imaging.

Comment: Several of these items contain two or more questions, which cannot be well answered by a simple yes or no, and the quality of information for each is not assessed, just whether or not some information was available or recorded. Nevertheless, it is valuable for scoring the RUCAM to have as much information as possible. It may be unlikely that many cases will have all the information listed above, but it is perhaps useful to make some effort to quantitate how much information was indeed available for each of the cases to be adjudged. It has been the experience of all who attempt

to use spontaneously reported data, such as reports to MedWatch, that there is much information missing. The DILIN group recently (January 2005) called Dr. Danan, now working at —— *— to resolve some questions of definition, so that in the future they can apply the method to scoring putative DILI cases in both retrospective review of cases associated with drugs known to cause hepatotoxicity of different types (isoniazid, phenytoin, Augmentin: clavulanic acid + amoxicillin), and valproic acid), and to prospective study of DILI cases from any drug. Use of the RUCAM is still something of an art, and obtaining accurate and reproducible results both within raters at different times and between raters at any time is still a work in progress. Proper use of the RUCAM requires that considerable amounts of good information be gathered. Simple failure to rule out 3 or more of the 6 primary disease causes of acute liver injury generates a -2 score for item 5, which will negate a +2 score for initial onset within 5-90 of first drug exposure. If nothing is known about the course after stopping the drug (dechallenge), and if there are no risk factors of age 55 or more or use of alcohol, no rechallenge is done, no concomitant drug likely to have caused the reaction was known to have been given, and no labeling or literature information available, then a RUCAM score of 0 will be generated, which is taken as excluding DILI. The RUCAM demands that adequate information be obtained, and allows an interpretation of "excluded" simply by failing to gather and record adequate information. This will need to be borne in mind as we proceed.*

Finally, after assessing the quantity of information available, and using that information to score the likelihood that a DILI has occurred, a global assessment can be attempted, using a five-point scale:

Based on your assessment of the information available and RUCAM scoring, how likely do you assess the hepatic abnormalities to be drug-induced?

□	Definite	More than 95%
□	Very likely	>75-95%
□	Probable	>50-75%
□	Possible	25-50%
□	Unlikely	<25%

Therefore, we shall try to apply these methods to assessing the apparent likelihood of causation of the selected cases as drug-induced injury, and then compare the findings to the consensus arrived at by the expert panel. As requested by Dr. Singer on 13 January 2005, we shall start by considering cases #1008, 10665008, 10745035, 063786, 262780, 262788, 287679, 0203501, and 474177, cases thought to be relatively less confounded, or in younger patients. Then, I shall consider the other 10 cases of the 19 reviewed by the special panel of experts.

In the tables below, I shall summarize patient identification information, acute liver disease, other concomitant or underlying diseases, concomitant medications, quantity and quality of information available, the RUCAM score, and my global assessment as an estimated percent likelihood that the drug may have caused the liver injury observed or diagnosed. This will not be an estimation of whether the drug may have caused the death of the patient, only the acute liver disease. I shall use the DILIN 32-question checklist of data completeness, and apply the information available in the patient profile and narrative provided for each case by the sponsor, as reviewed by the expert panel of external hepatologists. Finally, after reviewing all 19 cases, I shall compare the consensus report by Dr. [redacted] sent on 23 November 2004, and comment on agreements or disagreements.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	HIV: asthenia, diarrhea,	micafungin	9 +	+2 onset	
#1008	-3 40 19 125 0.35	cachexia. CD4 = 290/μL	— (14)	20 -	-2 <3 R/Os	50%,
M48b	7 49 19 132 0.76	inv esophageal candidiasis.		3 NA		possible
	14 2068 322 122 0.76	tuberculosis	cotrimoxazole	very poor	= 0	
	hepatocellular injury		betaclopramide		inadequate	
South	nausea (7), vomiting (8),	died — , of	loperamide		information	
Africa	confusion (13), hepatorenal	aggravated tuberculosis	flumazenil			
	failure (13)					
Comment: death may have resulted from the advanced underlying disease, but did micafungin cause the acute terminal liver failure?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	HIV: severe cachexia.	fluconazole —	8 +	+2 onset	
#10665008	-1 47 28 103 0.29	CD4 = 34/μL	— (21)	21 -	-2 <3 R/Os	30%,
F31b	7 49 22 163 0.23	inv esophageal candidiasis.		3 NA	-1 other drug	possible
	16 44 15 128 0.76	reactivated tuberculosis	**Voltaren**		= -1	
	21 4002 1274 294 3.74		**Panadol**	very poor	inadequate	
South	**hepatocellular injury**	died — of	Cifran		information	
Africa	nausea (16), anxiety (16),	pneumonia - Pneu. carinii	**Rifafour**			
	hepatic failure (21)		Maxolon			
Comment: death may have resulted from the tuberculosis, but did fluconazole or other drug cause the acute terminal liver failure?						

Note: F, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	HIV: lymphadenopathy,	micafungin —	6 +	+2 onset	
#10745035	-3 121 65 264 0.94	cachexia, diarrhea, anemia	— (5), stop	22 -	-2 <3 R/Os	25%,
M34b	5 66 29 208 8.25	CD4 = 97/μL	because liver failure	4 NA	+1 alcohol	possible
/		inv esophageal candidiasis.	**Rifinah**		-1 other drug	
	?? **alcoholic hepatic injury**	reactivated tuberculosis	DS-24	very poor	= 0	
South	jaundice (5), severe hepatic	alcohol abuse	**Voltaren**		inadequate	
Africa	failure (4-21)	died — of	Bactrim		information	
		reactivated tuberculosis	herbal cough syrup			
Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced alcoholic liver disease?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4, R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	end-stage liver disease,	micafungin —	7 +	+2 onset	
#063786	1 158 102 332 30.5	corticosteroid therapy	— (7)	20 -	-2 <3 R/Os	15%,
M58c	7 266 132 472 43.0	invasive lung aspergillosis.	Solumedrol	5 NA	-1 other drug	unlikely
—	?? **previous liver disease**	died — of	Prevacid		= -1	
location not	jaundice (5), severe hepatic	hepatic failure from	**Ambisome**	very poor	inadequate	
stated	failure (4-21)	unknown liver disease	Haldol		information	
Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced unknown liver disease?						

Note: M, male, c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	leukemia, bone marrow	micafungin —	10 +	+2 onset	
#262780	1 32 38 335 1.70	transplant	— (29)	17 -	-2 <3 R/Os	25%,
M4c	9 25 35 345 2.40	invasive lung aspergillosis.		5 NA	-1 other drug	possible
—	16 20 33 236 4.10		**ABELCET**		= -1	
location not	23 35 57 314 2.20	died — of	**itraconzole**	poor	inadequate	
stated	30 196 178 581 9.80	interstitial pneumonia,	**Tylenol**		information	
	cholestatic liver disease	with multiorgan failure	Foscarnet			
	nausea (5), vomiting (5), itch		Zithromax			
	(18), bilirubin elevation (24),		Actigall			
	hepatic failure (27)		Many, many others			
Comment: death may have resulted from tuberculosis, but did micafungin cause or aggravate cholestatic liver disease?						

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number, NA, not applicable..

patient	acute liver disease					underlying diseases	medications	information	RUCAM	Global
	Sday	AST	ALT	ALP	TBL	acute myelogenous leukemia,	micafungin —	10 +	-2 <3 R/Os	
#262788	-2	87	58	156	5.7	allogenic marrow transplant	— (10)	17 –	-1 other drug	<5%,
M16b	9	118	49	279	21.1	invasive lung aspergillosis.		5 NA	= -3	very
	10	134	56	353	24.8	probable liver candidiasis	**fluconazole**		inadequate	unlikely
	cholestatic liver disease						Mycelex	poor	information	
TN	bilirubin elevation (2),					die —), of	**Ambisome**			
	hepatic failure (2), renal					respiratory distress syndrome	many others			
	failure (4)					autopsy confirmed				
Comment: death may have resulted from lung disease, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.										

Note: M, male; b,Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	pancreatic carcinoma	micafungin —	11 +	-2 <3 R/Os	
#287679	1	50	59	946	7.08	Candida albicans septicemia.	— (19)	16 –	-3 panc. CA	<1%,
F51c	7	57	26	1217	9.65			5 NA	-1 other drug	ruled
—	14	134	63	2601	11.7		**amphotericin B**		= -6	out
location	20	159	112	3188	19.6	died —), of hepatic	vancomycin	fair	inadequate	
not stated	**cholestatic liver disease**					failure secondary to spread of	**Panadol**		information	
	pre-existing disease; pain(13),					pancreatic cancer	Tazocin			
	ascites (19), jaundice (30)						others			
Comment: death resulted from pancreatic cancer, and cholestatic liver disease preceded micafungin, so very unlikely M-DILI.										

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	acute myelogenous leukemia,	fluconazole —	13 +	+2 onset	
#0203501	1	37	43	81	0.9	allogenic marrow transplant	— (15)	14 -	-2 <3 R/Os	40%
F36o	4	27	37	65	0.6			5 NA	-1 other drug	possible
—	12	20	17	69	1.5	no fungal infection proved	IV heparin (?flush)		= -1	
	16	5970	754	173	10.5	mitral regurgitation	**acetaminophen**	fair	inadequate	
	hepatocellular liver injury					resistant bacteremia	Ativan		information	
,	anorexia (6), liver large (10),						Halcion			
	confusion and renal failure					died — of gastro-	tobramycin			
MN	(15), coagulation disorder					intestinal hemorrhage, after	many others			
	(16), liver failure(16), cardiac					liver failure with coagulation				
	arrest (17), GI bleed (18)					disorder				
Comment: death resulted from GI bleeding, but did fluconazole cause the acute liver failure and coagulation disorder?.										

Note: F, female; o,Oriental; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	leukemia, unspecified	micafungin —	10 +	-2 <3 R/Os	
#474177	1	85	66	696	5.17	probable lung aspergillosis.	— (34)	17 –	-1 other drug	<5%,
M40c	7	79	29	638	11.9			5 NA	= -3	very
/	14	99	52	691	14.5	alcohol abuse	amphotericin B		inadequate	unlikely
	21	134	66	657	19.4		Distranervin	poor	information	
Germany	28	444	510	1680	25.0	died — , of	cyclophosphamide			
	34	419	381	1470	40.4	leukemia	Cytarabine			
	35	363	298	1442	41.8		Haldol			
	cholestatic liver disease						**Ambisome**			
	jaundice (5), pruritus (16),						**Caspofungin**			
	renal failure (33), shock,						many others			
	coma, hepatic failure (36),									
Comment: death may have resulted from terminal bleed, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.										

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Comment: For these 9 cases, chosen by Dr. Mary Singer for me to review first, there are none that show a RUCAM score that suggests even possible drug causation of the liver disease, but mainly because the data available to insert into the RUCAM system are so inadequate. Without sufficient data, the RUCVAM can yield misleading interpretations that the likelihood of DILI is excluded. On

the other hand, the exercise of examining carefully just what information is and is not available may allow better-informed global assessments that may lead to different conclusions with higher levels of likelihood that the drugs in question may have at least aggravated severely any pre-existing liver disease or may have induced liver disease in otherwise very sick people With these thoughts clearly in mind, let us now consider the other 10 cases of the 19 reviewed by the expert panel.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	Hodgkin's lymphoma	no antifungal agent	10 +	onset before	
#384301	1	25	33	163	17.9		("placebo") —	17 -	-2 <3 R/Os	<1%,
M52c	4	24	23	387	25.8	no fungal infection proved.	— , (8)	5 NA	-3 other cause	not
	7	45	28	188	21.5	renal insufficiency, Cr 3.15			= **not DILI**	DILI
	8	66	33	134	24.2	sepsis, V tach (3), severe	cefotaxime	poor	**incompatible**	
ON CA	**cholestatic liver disease**					acidosis (6),	vancomycin			
	jaundice, liver failure (-??),						acyclovir		inadequate	
	hemorrhage (8), hepatic					Died — ·f hepatic	Ativan		information	
	failure (9)					failure. Autopsy confirmed dx	many others			
Comment: death resulted from lymphoma infiltration of the liver, preceding administration of "placebo", so not-DILI.										

Note: M, male; c, Caucasian, Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out, (#), study day number; NA, not applicable

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	massive blood loss, aortic	micafungin —	10 +	onset before	
#2194007	1	546	117	25	2.0	aneurysm repair (-1)	— ,(13)	17 -	-2 <3 R/Os	<1%,
M77c	5	234	17	66	2.9	no fungal infection proved.		5 NA	-3 other cause	not
	8	113	17	95	8.1	renal insufficiency, Cr 3,	Kefzol		= **not DILI**	DILI
/	12	116	22	149	16.3	diabetes, respiratory distress.	midazolam	poor	**incompatible**	
	hepatocellular disease						dopamine			
CA	shocked liver failure (-??),					Died — in shock,	insulin		inadequate	
	hemorrhage (8), hepatic					with hepatorenal, respiratory	many others		information	
	failure (9)					failure				
Comment: death resulted from hypotensive shock, ischemic liver disease, preceding administration of micafungin, so not-DILI.										

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin, R/Os, diseases ruled out; (#), study day number, NA, not applicable

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	acute myelogenous leukemia,	micafungin —	12 +	+2 onset	
#20785	8	32	30	236	0.7	post marrow transplant	— (77)	15	-2 <3 R/Os	<10%,
F30c	15	35	38	257	0.7	probable lung aspergillosis.		5 NA	-1 other drug	unlikely
	28	35	26	257	0.6		**amphotericin B**		-3 other cause	
	54	16	12	150	2.5	died — of veno	**itraconazole**	fair	= -4	
/	66		27	203	3.4	occlusive disease, sepsis, liver	**Percocet**			
	80		44	244	34.6	failure, renal failure	**Tylenol**		inadequate	
MN	93		64	844	51.3		Ativan		information	
	cholestatic liver disease						Dilantin			
	abd. pain (18), confusion (37)						CellCept			
	hepatic failure (78)						Many others			
Comment: death may have resulted from veno-occlusive disease, but did micafungin aggravate the terminal liver failure?										

Note: F, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out, (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	duodenal carcinoid tumor	micafungin —	10 +	+2 onset	
#33885	-1	44	41	652	2.7	septicemia, Candida glab.	— (13)	17	-2 <3 R/Os	40%,
F62b	7	82	55	540	2.3	diabetes, cachexia, sepsis,		5 NA	-1 other drug	possibly
—	14	5836	783	1155	3.2	pancreatitis, hypotension,	**fluconazole**		-3 other cause	worsened
location	**hepatocellular injury added**					renal failure, cholestatic	APAP propoxyphen	poor	= -4	
not	ascites (6), confusion (14),					liver disease from carcinoid	cefoxitin			
stated	vomiting (15), renal failure					died — sepsis,	vancomycin		inadequate	
	(15), hypotension (15)					multiorgan failure	many others		information	
Comment: death may have resulted from sepsis, but did micafungin add hepatocellular injury to carconoid cholestatic liver disease?										

Note: F, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase, TBL, total bilirubin; R/Os, diseases ruled out, (#), study day number, NA, not applicable

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	mantle cell lymphoma,	micafungin —	8 +	+2 onset	
#585271	1	36	19	112	0.72	chemotherapy	← (8)	19 -	-2 <3 R/Os	<10%,
M73c	5	29	16			pulmonary aspergillosis and		5 NA	-1 other drug	unlikely
	8	439	118	928	2.18	candidiasis, pneumonia	metformin		-3 other cause	
	mixed liver injury					diabetes, coronary disease	**fluconazole**	very poor	= -4	
Poland	severe liver damage (8), renal					Died — heart	Ambroxol			
	insufficiency (8)					failure. Autopsy confirmed.	many others		inadequate information	
Comment: death resulted from cardiac failure, which may have caused ischemic liver injury										

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	acute myelogenous leukemia,	micafungin —	9 +	+2 onset	
#059777	-1	10	9	135	5.7	chemotherapy	— (114)	16 -	-2 <3 R/Os	25%,
M0.7h	3	18	9	115	23.3	Klinefelter syndrome		5 NA	-1 other drug	possibly
/	10	52	3	305	51.1	sinus aspergillosis, sinusitis	**Ambisome**			made
	17	101	81	290	8.9	fever, pancytopenia, failure to	Nystatin	poor	= -1	worse
	24	202	232	330	6.4	thrive, systolic murmur	**Tylenol**			
	31	61	146	315	2.9		Ativan		inadequate	
	46	54	78	284	1.5	survived , recovered	Midazolam		information	
	84	37	58	218	0.7		Bactrim			
	98	27	10	91	0.3		RBCs, platelets			
	116	10	33	163			dopamine			
	162	26		153	1.1		**itraconazole**			
	?cholestatic liver injury						many, many others			
	jaundice, hepatomegaly (2),									
	renal insufficiency (11), acute									
	hemolysis? (9)									
Comment: infant, 8 months, with preexisting jaundice, possibly increased markedly by micafungin, but adapted and recovered										

Note: M, male; h,Hispanic; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	Lymphoma chemotherapy	micafungin —	10 +	+2 onset	
#287674	1	22	18	74	0.59	Candida rugosa septicemia	— (27)	17 -	-2 <3 R/Os	30%,
M48c	7	51	26	87	0.59	hypotension (13), Afib (14),		5 NA	-1 other drug	possible
/	14	257	356	110	8.42	anemia and renal failure (14),	warfarin (-4 to 14)		= -1	
	21	54	65	117	25.7	pneumothorax (17), bleeding	Panadol	poor	inadequate	
South	**hepatocellular injury**					gastric ulcer, hematemesis,	Amphotericin B		information	
Africa	vomiting (3), jaundice (15),					edema (28)	Mycostatin			
	hepatic failure (14)					died — heart failure	many others			
Comment: death resulted from hypotensive shock, ischemic liver disease,.										

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	acute biphenotypic leukemia	fluconazole —	14 +	+2 onset	
#372501	3	31	37	62	0.47	marrow transplant (6)	— (26): LE	15 -	-2 <3 R/Os	<1%,
M39c	8	35	59	58	0.64			3 NA	-2 neg dechall	not
/	16	17	24	45	5.08	HBsAg carrier	cyclophosphamide		-1 other drugs	F-DILI
	19	21	18	51	14.3	possible fungal infection (26)	ciprofloxacin	fair	-3 other cause	
Canada	24	58	35	64	28.7	persistent leucopenia, anemia,	methotrexate		= -6	
	26	60	45	62	36.9	thrombocytopenia (21-35)	acyclovir			
	33	118		110	53.9	renal insufficiency (27-43)	ceftazidime		limited	
	39	129		226	65.5		vancomycin		information	
	veno-occlusive disease					died — hepatic	Abelcet (26-34)			
	jaundice (13), veno-occlusive					failure, venooclusive disease	dopamine			
	disease (16), liver failure (32)						many others			
Comment: death resulted from veno-occlusive liver disease, probably from chemotherapy; liver disease not from fluconazole										

Note: M, male, c, Caucasian; Sday, days since first dose, AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	chronic myelogenous	fluconazole —	10 +	+1 onset	
#423004	-1	39	55	177	0.6	leukemia	— (17): LE	17 –	-2 <3 R/Os	25%,
F40c	3	122	289	171	0.7	marrow transplant		5 NA	-1 other drugs	
"	6	91	134	120	1.6	pulmonary Candida albicans	ursodiol		= -2	possible
	12	110	110	81	1.6	and Aspergillus sp.	cyclophosphamide	poor		
Oregon	17	33	25	111	2.4		Decadron		inadequate	
	hepatocellular injury					chest pain (8), lung edema (9)	acetaminophen		information	
	abdominal pain, asthenia (7), anorexia (12),'hepatic failure' (17), abnormal thinking (18-34)					pericardial effusion (9), heart failure, congestive (10), renal failure (13), GVHD (32)	ciprofloxacin methotrexate vancomycin Solumedrol			
						died — pulmonary mycosis	dobutamine many others			
Comment: death resulted from cardiopulmonary disease, probably from chemotherapy; liver injury relatively mild (not liver failure)										

Note:F, female; c, Caucasian; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy, R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL	HIV,	micafungin —	9 +	incompatible	
#3103	-2	27	30	312	0.9	non-Hodgkins lymphoma	— (14)	18 –		<1%
F26c	1	27	20	140	0.8			5 NA	**excluded**	not
"___"	7	24	18	190	1.1	esophageal Candida alb.	**acetaminophen**(-1 to 24)			M-DILI
	14	16	17	152	0.8	fever, cough	**isoniazid** (2-24)	very poor	inadequate	
location	28	18	9	163	0.8	many liver abscesses(15),	metronidazole		information	
not	**? obstructive liver disease**					liver bx(42), non-Hodgkins	ceftriaxone			
stated	nausea (5), 'liver damage' (11), vomiting (16), liver biopsy, laparoscopy (42)					lymphoma in hilar nodes	many others			
						survived				
Comment: no significant liver disease; isolated elevated alklaline before micafungin given										

Note: F, male; c, Caucasian; Sday, days since first dose; AST, ALT,serum aspartate, alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Comment: In the majority of these cases (10 of the 19), there did not seem to be clear causation of the hepatic injury by the administered antifungal treatment, which in 8 of the cases was micafungin (#3103, 20785, 63786, 262788, 287679, 474177, 585271, 2194007), in 1 case was fluconazole (#372501) and in 1 case none (#384301). Nine other cases seem possibly to have had liver injury caused or aggravated by the drug, 6 by micafungin (#1008, 33885, 262780, 287674, and 10745035) and 3 by fluconazole #203501, 423004, 10665008). There were no cases in this series in which it can be stated with confidence that the antifungal drug definitely or even probably caused the liver injury, mainly because of multiple confounding possible other causes from underlying or concomitant diseases, or by the plethora of other drugs that were given. This was further made difficult by the generally inadequate provision of sufficient clinical information to make the differential diagnosis of drug-induced, as opposed to disease-induced, other drug-induced, and certainly no information at all on the possibilities of drug-drug interactions that might have caused the problems. Many of the patients considered were actually dying of terribly serious diseases when antifungal treatment was started, and there are almost no data on effects of withdrawing the drug to see if improvement in the liver injury might follow, and no patients were observed long enough for rechallenge effects to be observed.

We are stuck, therefore, with relying upon opinions as to whether the hepatic injuries seen were related to drug administration or not, and even experts do not always agree, as we have seen, and will now consider more closely. After considering independently the data provided, I rated each case for adequacy of information to make a diagnosis of DILI, an estimate of the RUCAM score, and my estimated likelihood that the hepatic reaction was drug induced, before looking at the panel consensus ratings. In the following table, I list my ratings and the expert panel's:

COMPARISON OF CAUSALITY ATTRIBUTION RATINGS BY JRS AND THE EXPERT PANEL

Note: M, micafungin; F, fluconazole; N, neither; NR, not related; P, possibly related; R, related; U, unlikely

Case #	Underlying diseases	Liver Disease/Injury	Drug	JRS	Panel
# 1008, M48b, South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Hepatocellular injury without jaundice, 14 days, moderately severe	M	P 50% *concur*	PR
# 3103, F26c, location not stated	Non-Hodgkin's lymphoma Esophageal candidiasis	Obstructive liver disease, hilar lymphoma, elevated ALP before micafungin given	M	U <1% *concur*	NR
# 20785, F30c, MN	Acute myelogenous leukemia; Probable lung aspergillosis	Cholestatic liver disease, before drug given, but worse after 80 days, ?leukemic infiltrate	M	U <10% *concur*	NR
# 33885, F62b, location not stated	Duodenal carcinoid tumor; Candida septicemia	Hepatocellular injury, at 14 days, added to carcinoid cholestatic disease	M	P 40% *disagree**	NR
**Comment: Panel thought NR, but JRS noted preexisting liver disease, probably worsened by micafungin*					
# 59777, M 0.7h —	Acute myelogenous leukemia; Sinus aspergillosis ; survived	Cholestatic liver injury, transient, aggravating mild preexisting abnormality, recovered	M	P 25% *disagree**	NR
**Comment: Panel thought data inadequate, but JRS noted preexisting liver disease, probably worsened by micafungin.*					
# 63786, M58c location not stated	End-stage liver disease ???; Invasive lung aspergillosis	Previous liver disease of unknown type, with slight increase in jaundice, 7 days	M	U 15% *concur*	NR
# 262780, M4c location not stated	Leukemia, marrow transplant; Lung aspergillosis	Cholestatic liver injury or aggravation, some preexisting cholestasis	M	P 25% *concur*	PR
# 262788, M16b —: TN	Acute myelogenous leukemia; Lung aspergillosis; liver C alb	Cholestatic liver injury aggravation, 9 days, some preexisting cholestasis	M	U <5% *concur*	NR
# 287674, M48c, South Africa	Lymphoma chemotherapy; Candida rugosa septicemia	Hepatocellular injury with jaundice, 14 days, Liver tests normal before	M	P 30% *concur*	PR
# 287679, F51c location not stated	Pancreatic CA, metastases; Candida alb septicemia	Cholestatic liver disease, pre-existing, before drug given	M	U <1% *concur*	NR
# 474177, M40c — Germany	Leukemia, NOS Probable lung aspergillosis	Alcoholic liver disease, with cholestasis, somewhat worsened after 21 days on drug	M	U <1% *disagree**	PR
**Comment: Panel thought PR, but JRS noted preexisting liver disease, probably worsened by drugs given for leukemia.*					
# 585271, M73c — , Poland	Mantle cell lymphoma Lung aspergillosis & candida	Mixed liver injury, probable tumor in liver, preexisting before micafungin given	M	U <10% *concur*	NR
# 2194007, M77c , CA	Massive blood loss, aneurysm Repair; no fungal infection	Hepatocellular disease, probably ischemic liver injury	M	U <1% *concur*	NR
#10745035, M34b South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Aggravation of prior alcoholic liver disease, with jaundice and hepatic failure, 5 day	M	P 25% *concur*	PR
FLUCONAZOLE CASES					
# 203501, F36o — MN	Acute myelogenous leukemia; No fungal infection proved	Hepatocellular injury with jaundice, 16 days coagulation disorder, gastrointestinal bleeding	F	P 40% *disagree**	NR
**Comment: Panel divided, maybe aggravation, but data unreadable; JRS thought fluconazole may have caused liver failure*					
# 372501, M39c, — , Canada	Acute biphenotypic leukemia Possible fungal infection	Veno-0cclusive disease, from chemotherapy, with progressive liver failure	F	U <1% *concur*	NR
# 423004, F40c, - OR	Chronic myelogenous leukemia Pulmonary aspergillus sp.	Hepatocellular injury, perhaps added to Leukemic infiltrate before drug	F	P 25% *disagree**	NR
** Comment: Panel thought NR; JRS thought quite possibly fluconazole-induced aggravation, not liver failure*					
#10665008, F31b South Africa	HIV severe cachexia, tbc; Esophageal candidiasis	Hepatocellular injury with jaundice, 21 days Severe	F	P 30% *concur*	PR
NEITHER MICAFUNGIN OR FLUCONAZOLE					
# 384301, M52c — Canada	Hodgkin's lymphoma No fungal infection proved	Cholestatic liver disease before drug given, due to tumor in liver, not DILI	N	U <1% *concur*	NR

Comment: It may be seen that my independent assessments concurred with the consensus of the panel of experts in 5 of 6 cases in which they thought the liver abnormalities were possibly related to administration of study drug. The exception was #474177, the 40-year-old German man with a history of alcohol abuse who had significantly abnormal liver tests before starting on micafungin, and then slowly progressed to worsening of all his liver tests as he died of leukemia complications

or the many antineoplastic and other drugs he received. Micafungin was stopped after 34 days, and he lived only 4 days more, so not "dechallenge" effects could be observed. My estimates also were in concurrence in 9 of the 13 cases in which the panel thought the liver reactions were unrelated to study drug, with disagreements for cases #33885, 59777, both of whom received micafungin, and for cases #203501 and 372501 who received fluconazole. It was my thinking in all 4 cases that the antifungal treatment had added to or aggravated pre-existing liver disease, with some degree of likelihood, but insufficient information to be more certain.

The concept of drug-induced injury adding to or aggravating pre-existing liver disease was seen in some of the cases in which there was concurrence of our thinking (#262780), although this is not a widely held view. There is considerable controversy about whether or not a relatively uncommon or unpredictable ("idiosyncratic) hepatic injury is more likely to occur in patients with previous liver disease, or whether it simply appears so because such people are less well able to withstand or to recover from additional liver injury if it is induced by a drug.

Another point that was noted in review of these cases was that there were several cases of serum bilirubin elevations that seemed out of proportion to the serum enzyme indicators of liver injury, often in cases in which there was underlying liver disease not likely caused by micafunfin (e.g., see cases #63786, 262788, 474177, 384301, 2194007, 20785, 59777, 287674, and 372501 among the 19 cases summarized above). All of the echinocandins were plagued by some degree of red blood cell hemolysis problems during their development, and molecular manipulations were used to find less hemolytic antifungal compounds. Merck found that L-671,329 was less hemolytic than was aculeacin (Frompting and Abruzzo, 1989); and L-743,872 (MK-0991,(later called caspofungin) less hemolytic than amphotericin B (Bartizal, et al., 1997). Efforts in the Fujisawa laboratories in which FR131535 was found less hemolytic than FR901379 (Fujie, et al., 2001), led to FK-463 (micafungin). In evaluating the cases of possibly micafungin-induced hepatotoxicity, whether in a previously normal liver, or in aggravation of some underlying liver disease, a contribution of micafungin-accelerated hemolysis should be considered as at least partly responsible for rises in serum total bilirubin concentrations.

The finding of significant but rare hepatotoxicty associated with caspofungin, a recently approved member of this new class of echinocandin agents, is of interest and possible pertinence to this consideration of micafungin. The class of echinocandins (caspofungin, anidulafungin, micafungin) all have a central, large, cyclic hexapeptide nucleus with N-terminal fatty acyl and an amino group connecting the 3-OH-proline moiety to the δ-amino-γ-hydroxyornithine to form the ring. The three new drug agents differ mainly in their patterns of hydroxylations, which is extensive and confers the water solubility of the compounds (Wiederhold and Lewis, 2003), and in their α-aminoacyl side chains. The agents were developed to be safer than earlier antifungal agents that caused collateral damage to host cells (amphotericin B) and drug interactions (the –conazoles). Caspofungin (CANCIDAS, Merck) is a large, complex, semisynthetic molecule that inhibits 1,3-β-D-glucan synthase required for fungal cell wall synthesis, approved in January 2001 for treatment of invasive aspergillosis. It is of interest that although 8 cases of caspofungin hepatotoxicity have been reported to AERS, only one case is even mentioned in the published literature, in an acute leukemic patient who had moderate but reversible hepatotoxicity (Aliff, et al., 2003). No cases of micafungin-induced liver injury have been reported as yet.

In addition to the 19 cases discussed above that had been selected for special review, Dr. Mary Singer found two more, patients who had died after being treated with micafungin, and whose test results suggested acute liver injury. She sent copies of the narratives and patient profile summaries of data by fax on 24 January, and requested my opinion about them, in brief for the planned meeting at 4 p.m. that day, and more fully thereafter. On cursory inspection, both cases appeared to show acute rises in serum tests of liver injury and function, and of renal function, after starting treatment with micafungin. The information provided for the two cases is summarized below, in similar format to that used for the 19 cases previously reviewed above.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	HIV: no retroviral therapy,	micafungin	8 +	+2 onset	
#10745031	-3 101 85 217 1.05	CD4 = 148/μL	(9)	21 -	-2 <3 R/Os	50%,
M34b	7 649 305 519 4.27	inv esophageal candidiasis.		3 NA		possible
—		anemia, renal insufficiency	Bactrim	very poor	= 0	
	hepatocellular injury	renal failure worsened (7)	Immodium		inadequate	
South	not stated; lab tests suggest	died — , of	Lasix		information	
Africa	acute liver injury (7)	acute renal failure	others			
Comment: death may have resulted from renal failure, but did micafungin cause the acute terminal liver injury also?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
	Sday AST ALT ALP TBL	HIV: no retroviral therapy,	micafungin	8 +	-1 onset ?	
#10445008	-1 50 74 547 0.41	cachexia, CD4 = 13/μL	(14)	21 -	-2 <3 R/Os	15%,
M45c	8 179 227 646 0.82	inv esophageal candidiasis.		3 NA		unlikely
—	14 43 81 741 1.18	neurotoxoplasmosis	Cisapride (3)	very poor	= -3	
	26 5670 1760 249 4.05	disseminated tuberculosis;	Oxaciline (13)		inadequate	
Brazil	**hepatocellular injury**		Riphampacine (20)		information	
	mild transient injury (8), then	died , of	Isoniazide (20)			
	more severe acute liver injury	reactivated tuberculosis	Pyrazinamide (20)			
	(26) when tbc therapy started		many, many others			
Comment: death may have resulted from tuberculosis, but did micafungin cause mild liver injury, anti-tbc therapy severe injury?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT,serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

Comment: The first case (#10745031) had findings 3 days before micafungin was started of modest serum ALT, AST, and ALP elevations but top-normal serum bilirubin, plus definite evidence of renal insufficiency (both UN and creatinine were elevated). After 7 days of micafungin, the renal indicators had worsened, but the serum AST, ALT, ALP and TBL were dramatically increased. It seems likely that the patient had some degree of tuberculous infiltrate in his liver, and that it is quite possible that micafungin induced an cute aggravation of the mild underlying liver problem, which clinically seemed overshadowed by the renal failure to which his death was attributed by the clinical staff. The data are insufficient for any more probable attribution of the acute liver injury to micafungin administration. The second case (#10445008) is interesting in the timing of the treatments. After micafungin was started, he showed a moderate mixed hepatocellular and cholestatic liver injury without rise in serum bilirubin, which subsided except for the cholestasis by Day 14 when the micafungin was stopped. After treatment with Oxaciline for phlebitis on Day 13, and initiation of anti-tuberculosis therapy with isoniazide, rifampin, and pyrazinamide on Day 20, he showed a dramatic rise in the serum transaminase activities suggesting acute superimposed hepatocelluar injury with probable jaundice (bilirubin 4.05 mg/dL) on Day 26. Either the Oxaciline or the anti-tuberculosis regimen weremore likely responsible for the severe hepatocellular injury noted on Day 26, 2 days before his death. The information available is inadequate to infer more.

Recommendations:

1. These cases in which there appear to be possible causation of liver injury following use of micafungin cannot be entirely dismissed, even though many of the cases can be "thrown out" as not related. As noted by the expert panel, these are extremely difficult cases to assess and there were many confounding factors, both other drugs and concurrent diseases. To make matters worse, drug-induced liver injury is a diagnosis of exclusion, and lack of good information to exclude other causes is not proof that they may be excluded.

2. Other cases must be looked for in patients treated with this micafungin, as well as the other two echinocandins, caspofungin and anidulafungin. Systemic fungal diseases usually occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or less able to recover from additional liver injury that may be caused by agents such as micafungin.

3. The labeling should indicate that some cases have been observed, that in the opinion of expert and well known specialists on hepatology may possibly be caused or worsened by micafungin. Caution should be exercised in its use, and the possibility that some patients may show liver injury should be borne in mind by clinicians prescribing echinocandin treatment of systemic or internal fungal infections in immunocompromised patients.

4. It may be shown that more patients are saved by micafungin treatment of their fungal infections than are injured, and the echinocandins may be safer than the previously available agents, but they should not be considered totally safe. Physicians should weigh carefully the relative benefits and risks of them, in managing these extremely serious and complex diseases.

/S/

John R. Senior, M.D.

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R. Albrecht, HFD-590
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Senior JR. ODS consultation #D040163 regarding [redacted]

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John Senior
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MEDICAL OFFICER

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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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Christina Chi
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CSO

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

Office of Drug Safety

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

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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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/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 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

Please find below the comments we have received form 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 blue color to designate the strengths. This blue blends into the background color of the container label and decreases the prominence and legibility of the strength. Please revise.
2. Currently the phrase "FOR INJECTION" appears — , whereas the established name appears in lower case letters. Please revise so that the established name and the phrase "for injection" have the same prominence and case.
3. Please add the statement "Once reconstituted, with xx mL of 0.9% sodium chloride for injection (without bacteriostatic agent), each mL contains xx — /mL".

B. CARTON LABELING — 50 mg/vial – — 10 vials per carton)

1. Please add the statement "Discard unused portion" following "Single vial use".
2. Increase the prominence of the statement "For Intravenous Infusion Only".

C. PACKAGE INSERT LABELING

1. Dosage and Administration

   - Please remove the '

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

   - The current presentation is difficult to follow.

2. Storage of Mycamine

   Under " , 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 reach .

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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: 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

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: 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

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 "Dormicum".

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

) *(Division/Office)*: DMETS Request
HFD-400
Parklawn Bldg/Room 15B-03
Attention: Sammie Beam, Project Manager

FROM: Division of Special Pathogens
HFD-590
9201 Corporate Blvd.
Attention: Anne Marie Homonny-Weikel

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/25/04		21-506		8/24/04

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Mycamine (micafungin) for Injection		Standard	1/25/05 (PDUFA date = 2/25/04)

NAME OF FIRM: Fujisawa Healthcare, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Please re-evaluate the trade name "Mycamine" since the application may be approved on 2/25/05. This name was found to be previously acceptable by DMETs.**

Thank You

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
ne Marie Homonnay-Weikel	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Anna-Marie Homonnay
10/25/04 02:37:20 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 21, 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 21-506

Total no. of pages including cover: 1

1. Please provide clinical narratives of the patients with proven and probable fungal infections from Study 98-0-050, including the results of any diagnostic tests. You do not need to provide clinical narratives for the two patients who died (133-502 and 405-3601), as they are already included in the original study report, but we would like to see copies of the autopsy reports, if available.
2. Please provide a clinical narrative for Patient 123-3502 in Study 98-0-050. This patient also died following treatment with micafungin.
3. Please provide a narrative summary for patient 466171 (study 98-0-046) whose death was previously reported in NDA 21-506 as possibly related to micafungin.

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/s/

Anna-Marie Homonnay
10/22/04 10:34:36 AM
CSO

Anna-Marie Homonnay
10/22/04 10:36:34 AM
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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2003

To: Robert Reed	**From:** Susan Peacock
Compan y: Fujisawa	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	**Fax number:** (301) 827-2475
Phone number(847) 317-8985	**Phone number:** (301) 827-2173

Subject: Comments from Product Quality Microbiology Reviewer

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

Date: March 26, 2003

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

From: Susan Peacock
Regulatory Project Manager, HFD-590

Through: Mark Seggel, Ph.D. Chemistry Reviewer
Norm Schmuff, Ph.D. Chemistry Team Leader

Subject: Comments from the Product Quality Microbiology Reviewer

Dear Mr. Reed:

The Product Quality Microbiology Reviewer had the following comments after reviewing NDA 21-506. — — for Mycamine (micafungin sodium):

1.

2.

3.

4.

5. The drug product should be tested for —
— as part of the stability protocol.

6. The drug product is not preserved and no data was provided to demonstrate the ability of the reconstituted drug product to resist the growth of microorganisms, inadvertently introduced during reconstitution, over the proposed in-use holding

period (room temperature, up to —

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
3/26/03 08:40:03 AM
CSO

Susan Peacock
3/26/03 08:43:23 AM
CSO

NDA 21-506

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2004

To: Robert Reed	**From:** Susan Peacock
Company: Fujisawa Healthcare, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 847-317-7286	**Fax number:** 301-827-2475
Phone number: 847-317-8985	**Phone number:** 301-827-2127

Subject: Information Request in preparation for March 8, 2004 meeting.

Total no. of pages including cover: 2

Comments: R. Albrecht, M. Cavaillé-Coll, E. Ibia, K. Higgins, L. Tracy

Document to be mailed: ☐ YES ☑ NO

We have reviewed your briefing package submitted on February 18, 2004, for the March 8, 2004 meeting to discuss the next steps for the approval of NDA 21-506. In preparation for the March 8, 2004 meeting, the Review Division requests that you note the following comments and provide the needed information:

1. The Division is very interested in the rates of relapse or sustained response after end of therapy. In the March 28, 2003 meeting, you provided summary data tables up to end of

therapy for study FG-463-09. For the face-to-face meeting scheduled for Monday, March 8, 2004, the Division would like you to present similar data tables/summaries up to and including the 2 week post-treatment visit for study FG-463-09 and any additional follow-up data. Similarly, the Division would like to see follow-up data tables for the dose ranging study 97-7-003, if possible.

2. The Division has reviewed your analyses of the incidence of proven *Candida* infection in study 98-0-050. Since you relied on incidence rates from prior conducted trials, mainly the Goodman *et al.* study [1992] and the Slavin *et al.* study [1995], please provide rationale for comparability of these two trials to study 98-0-050 in terms of patient population, study endpoints, and study designs. The Division will consider this analysis when reviewing your proposed re-submission for the indication of prophylaxis of *Candida* infection in patients undergoing hematopoietic stem cell transplantation. However, please note that the primary analysis as stated in the protocol will remain the same.

Please provide this information before the meeting by email or at the time of the meeting.

Susan Peacock, M.S.
Regulatory Project Manager

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/s/

Susan Peacock
3/4/04 01:04:44 PM
CSO

Susan Peacock
3/4/04 01:06:00 PM
CSO

NDA 21-506

MEETING AGENDA / MINUTES

MEETING DATE:	March 28, 2003
TIME:	11:30 A.M. – 12:30 P.M.
LOCATION:	9201 Corporate Blvd, Conference Room S400
IND/NDA	NDA 21-506
REQUEST SUBMISSION DATE:	February 27, 2003
BRIEFING DOCUMENT SUBMISSION DATE:	March 13, 2003
DRUG:	MYCAMINE (micafungin sodium)
SPONSOR/APPLICANT:	Fujisawa Healthcare, Inc.
TYPE of MEETING:	Type A meeting
PROPOSED INDICATION:	—

FDA PARTICIPANTS:

Renata Albrecht, M.D.	Division Director
Edward Cox, M.D., M.P.H,	Deputy Director, Office of Drug Evaluation IV
John Powers, M.D.	Lead Medical Officer for Antimicrobial Drug Development and Resistance Issues
Ekopimo Ibia, M.D., M.P.H.	Medical Reviewer
Marc Cavaillé-Coll, M.D., Ph.D.	Medical Team Leader
Karen M Higgins, Sc.D	Statistics Team Leader
LaRee Tracy, M.A.	Statistics Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacologist and Biopharmaceutics Team Leader
Jang-Ik Lee, Pharm.D., Ph.D.	Clinical Pharmacologist and Biopharmaceutics Reviewer
Mark Seggel, Ph.D.	Chemistry Reviewer
Norman Schmuff, Ph.D.	Chemistry Team Leader
Kalavati Suvarna, Ph.D.	Microbiology Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Ellen Frank, R.Ph.	Chief, Project Management Staff
Susan Peacock, M.S.	Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Fujisawa Pharmaceutical Company, Ltd

Noriaki Inamura, Ph.D	Global Project Coordinator

Fujisawa Healthcare, Inc

Ira Lawrence, M.D.	Senior Vice President of R&D
William Fitzsimmons, Pharm. D.	Senior Vice President of Business Development
Jerry Johnson, Ph.D.	Vice President of Regulatory Affairs, Quality Assurance, and Safety
Don Buell, M.D.	Senior Medical Director
William Zhao, Ph.D.	Senior Director - Biostatistics
James Keirns, Ph.D.	Senior Director - Biopharmaceutical Sciences
Dave Facklam	Director - Clinical Studies

NDA 21-506

Wendi Lau	Manager - Clinical Studies
Shobha Dhadda, Ph.D.	Manager - Biostatistics
Gwen Barlow, JD	Assistant Director - DDPM
Robert Reed	Associate Director - Regulatory Affairs
Christian Redondo-Mueller	Senior Manager - Development Planning Management - Fujisawa GmbH

Consultant

Thomas Walsh, M.D.	Chief Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute

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. In the approvable letter, the Agency suggested that Fujisawa meet with the Agency before resubmitting this NDA. Fujisawa agreed and provided the Agency with a background package on February 27, 2003, which addressed the deficiencies outlined in the approvable letter and contained questions regarding their future plans for this NDA. In addition, at the request of the Agency, Fujisawa provided electronic copy of tables of exposure to micafungin by dose.

QUESTIONS PROPOSED BY THE SPONSOR for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the Agency concur that the FG-463-21-09 study, in addition to the data submitted in NDA 21-534, would be sufficient to support the approval of a new indication for first line treatment of esophageal candidiasis (EC)?

    - Following introductions and a brief remark by Fujisawa on Study FG-463-21-09 as it relates to NDA 21-506, the Agency informed Fujisawa that Study FG-463-21-09 supports filing of an NDA for treatment of EC but pointed out that determination on approvability would be based on a review of the study data. In addition, the agency informed Fujisawa that the EC treatment indication will rely on the controlled study (Study FG-643-21-09) as well as noncomparative data on EC and candidemia in the original submission. The Agency further expressed difficulty in determining the number of subjects who received 150 mg/day of micafungin after reviewing the tables provided by Fujisawa. The Agency then asked Fujisawa to supply another table clearly identifying the number of subjects receiving 150 mg/day of micafungin for 14 days. The Agency also stated that they would want to see data on at least 300-500 subjects, who received 150mg/day of micafungin for 14 days, to evaluate safety. Fujisawa questioned the Agency on the justification for the 300-500 subjects. The Agency explained that these numbers were based on a consideration of a number of factors including risk-benefit profile, seriousness of the targeted condition, and availability of alternative therapies. The Agency further noted that if a particular adverse event is not observed in a database of 300 patients this excludes a rate of that adverse event of 1% (1 in 100). In addition, the Agency informed the sponsor that while quantity was important, the quality of the safety database was equally important. In that regard, the Agency noted that safety data obtained from a randomized controlled trial would be more valuable than additional data from a larger

uncontrolled treatment cohort. With the treatment of esophageal candidiasis indication, the Division clarified that there must be clear evidence of the benefit of the drug over placebo.

- The Division also clarified that this indication would need to be submitted as a new NDA.
- In response to Fujisawa's question about the Agency's attitude to a product that fails to meet a predefined delta in a non-inferiority trial, the Agency clarified the crucial components of what the Agency assesses in such trials. Firstly, the magnitude of the product's benefit over placebo is considered and secondly the magnitude of product's benefit or loss of benefit over an active comparator is considered. The Agency further pointed out that factors considered in such determinations include the severity of the targeted indication and the availability of alternative therapies for that indication.

2. Fujisawa Healthcare, Inc. believes that Study FG-463-21-09 addresses the need for an additional well-controlled study to support approval of micafungin for the indication "prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplantation". Does the Agency concur?

- The Division began by saying that the Sponsor originally wanted [redacted], and are now asking only for prophylaxis due to *Candida* which is more limited. The Division further clarified that the label would probably state that [redacted] The Division gave the example of casponfungin and how that Sponsor only studied refractory/intolerant *Aspergillus*. In that particular case, the Division explained, the caspofungin label stated that it was not studied as initial therapy.
- The Division explained that Fujisawa must show evidence of efficacy in *Candida* treatment and that the esophageal candidiasis study would need a favorable review showing support of safety and efficacy to support the prophylaxis indication. The Division further discussed that the EC indication and the prophylaxis indication are considered two separate NDAs but the data from each would not be able to stand alone for a favorable action. The Division further discussed that the prophylaxis indication data is supported by the EC study and the EC study data supports the prophylaxis data. The Division explained that the submission of these data would be considered a complete response to the NDA 21-506 approvable letter and would constitute a resubmission with a 6-month review clock. The Agency further noted that it would be more appropriate to concurrently review efficacy of treatment and prophylaxis indications but that there could be exceptions.

- Fujisawa expressed concern about the possible non-favorable review of the EC data based on inadequate numbers of patients receiving the 150mg/day dose. Fujisawa questioned the Agency on whether the EC efficacy data could be used to support the prophylaxis indication if the number of patients were not adequate to assess safety at the proposed dose of 150 mg/day for 14 days.

- The Agency explained that they could not answer this question at this time and agreed to have further internal discussion followed by a response to Fujisawa at a later time. The Agency expressed to the Sponsor the hope that the EC review would be favorable and that the sponsor would have adequate numbers of patients for a safety evaluation at the 150 mg/day dose.

- Fujisawa referenced the approvable letter and explained that their understanding of the letter was that Fujisawa would need more efficacy data to support an approval of the prophylaxis indication, not more safety data.

- Fujisawa agreed to the idea of conducting another study for the treatment of EC to increase their numbers of patients receiving the 150 mg/day dose. However, Fujisawa does not want a new study to delay the approval of the prophylaxis indication.

- Fujisawa wanted to know if they should resubmit the NDA now or wait until the Division has further internal discussion.

- The Division explained that they would need to discuss the regulatory issues surrounding the precedence of the submissions.

- The Agency reiterated that the only data received so far (not counting this data on EC) on the activity of micafungin against clinically documented *Candida* infections comes from open label non-comparative studies.

ACTION ITEMS:

- The Division asked Fujisawa to provide safety data tables for the EC indication.
- The Division also asked Fujisawa to provide a table showing the number of patients who received 150 mg/day or higher of micafungin for the 14 day duration.
- The Division agreed to further discuss the idea of reviewing the EC efficacy data in support of the prophylaxis indication, even if the number of patients are not adequate to assess safety at the proposed dose for EC. The Division agreed to contact the Sponsor for further discussion at a later time.

_____/_____ Concurrence Chair: _____/_____

(Susan Peacock) Date — (Renata Albrecht) Date

Project Manager — Division Director

Minutes preparer

Attachments:

cc:

Original NDA 21-506

HFD-590/Div File

MEETING MINUTES

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/s/

Renata Albrecht
4/8/03 04:22:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 5 2003

Voravit Ratanatharathorn, M.D.
1500 East Medical Center
Ann Arbor, Michigan 48109

Dear Dr. Ratanatharathorn:

Between July 9 and 22, 2002, Ms. Lisa Oakes, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigaton (protocol #98-0-050 entitled, "A Phase 3, Randomized, Double-Blind, Comparative Trial of FK463 Versus Fluconazole For Prophylaxis of Fungal Infections in Patients Undergoing a Hematopoetic Stem Cell Transplant") of the investigational drug FK463, performed for Fujisawa Healthcare. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Oakes presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

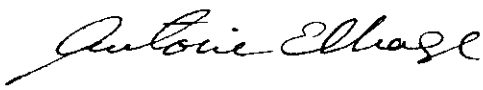
1. You did not promptly report to your Institutional Review Board (IRB) the deaths of two subjects (21 CFR 312.66). Subjects 841004 and 842001 died on [redacted] and [redacted] respectively. You did not notify your IRB of these deaths until [redacted], more than 19 and 21 weeks after the deaths.

2. You did not conduct the study in accordance with the approved protocol (21 CFR 312.60) in that subject 843003 received fluconazole 14 hours before receiving the first dose of study medication. The protocol excluded subjects administered systemic antifungal agents within 72 hours of starting study drug.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Oakes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,



Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: 1831525
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X__failure to adhere to protocol (05)
__X__failure to notify IRB of changes, failure to submit progress reports (15)
Deficiency Codes: **5, 15**

cc:
HFA-224
HFD-590 Doc.Rm. NDA# 21-506
HFD-590 Review Div.Dir. Albrecht
HFD-590 MO Ibia
HFD-590 PM Kong
HFD-46/47 GCP Reviewer Shibuya
HFD-46/47 CSO Storms
HFR-CE-750 DIB Dempster
HFR-CE-750 Bimo Monitor Bellamy
HFR-CE-750 Field Investigator Oakes
GCF-1 Seth Ray

r/d: (RS/8/2/02):
reviewed:aeh:8/16/02
f/t:**ml:8/16/02; 2/27/03**

o:\RS\NDA21-506\Ratanatharathorn.doc

Reviewer Note to Rev. Div. M.O.

- This site randomized 54 subjects, discontinued 5, and completed 49.
- Sixteen of 54 subject's records were inspected in detail; all were alive and available as reported in the case report forms. One minor protocol violation and 1 record keeping deficiency were documented.
- All subjects received adequate informed consent.
- Data appear acceptable.

TELECON MINUTES

DATE:	January 13, 2003
TIME:	3:30-4:00 PM
LOCATION:	S440, 9201 Corporate Blvd.
NDA#	21-506, ___
DRUG:	Mycamine (micafungin sodium)
SPONSOR/APPLICANT:	Fujisawa Healthcare, Inc.
CONTACT NAME:	Robert Reed
FAX NUMBER:	(847) 317-7286
PHONE NUMBER:	(847) 317-8985
PROJECT MANAGER:	Susan Peacock, MS
DIVISION OF:	Special Pathogen and Immunologic Drug Products, HFD-590
FORMAT:	Teleconference

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Renata Albrecht, M.D., Division Director
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Ellen Frank, R.Ph., Chief, Project Management Staff
Susan Peacock, M.S., Regulatory Project Manager

INDUSTRY PARTICIPANTS AND TITLES:

Donald Buell, M.D., Senior Medical Director
David Facklam, Director, Clinical Studies
Robert Reed, Associate Director of Regulatory Affairs

DISCUSSION WITH RESPONSES AND DECISIONS REACHED:

SUBJECT: **Fujisawa's proposal to amend pending NDAs with data from esophageal candidiasis study** (FG463-21-09)

Background: On January 10, 2003, Fujisawa Healthcare, Inc., submitted a briefing document in preparation for a January 14, 2003, telecon with the Division. At this January 14, 2003, telecon, Fujisawa planned to present the following:

> Protocol for Study FG463-21-09 (esophageal candidiasis study) with protocol amendments
> A brief summary of data from patients with esophageal candidiasis
> Synopses for Studies 98-0-047 (An Open-Label, Non-Comparative Study Of FK463 In The Treatment Of Candidemia Or Invasive Candidiasis) and 97-7-003 (A Phase II Study to Determine the Minimal Effective Dose of FK463 in the Treatment of Esophageal Candidiasis in HIV Positive Patients.

The Agency quickly scanned the material submitted and decided that the questions proposed by Fujisawa could be answered in a short telecon. The questions from Fujisawa and the Division's responses are found below:

Questions:

Question 1: As part of amending NDA — with Study FG463-21-09, Fujisawa Healthcare, Inc. intends to amend the indication. Fujisawa Healthcare, Inc. believes the data from Study FG463-21-09, in conjunction with data submitted in NDA — will support an amended indication for micafungin (FK463) of "treatment of patients with esophageal candidiasis". Does the Agency agree?

Division's Response: Based on the Prescription Drug User Fee Act , the Agency is subject to the review of complete applications in a predefined timeframe. These applications are filed for the indication(s) included in them at the time of submission. In the original submission of administrative NDA the indication was for —— —— Data intended to support an esophageal candidiasis indication cannot be used to amend the current NDA. Esophageal candidiasis is a new indication and would constitute the submission of a new NDA (if no NDA is already approved at the time of submission). The Division suggested Fujisawa ask for a pre-NDA meeting following the meeting MaPP and PDUFA performance goals. They may wish to ask for a Type A meeting if they feel it applies.

Question 2: Fujisawa Healthcare, Inc. believes that the data contained in amended NDA — will provide evidence of the efficacy of micafungin adequate to support micafungin for the prophylaxis of — , in patients undergoing hematopoietic stem cell transplantation (NDA 21-506). Therefore, Fujisawa Healthcare, Inc. believes that amended NDA — , and the data already submitted in NDA 21-506 are adequate to support the prophylaxis indication for micafungin. Does the Agency agree?

Division's Response: The Division suggested that Fujisawa ask for a pre-NDA meeting. At that meeting, the Division could discuss the study more fully and advise Fujisawa on what additional information would be needed.

Question 3: Fujisawa Healthcare, Inc. intends to amend NDA — , providing a final study report for Study FG463-21-09, an amended package insert, and a revised CTD Module 2.7.3 (integrated summary of efficacy in esophageal candidiasis). Is this acceptable to the Agency?

Division's Response: Based on the Division's response to Questions 1 and 2, it was no longer necessary to address this question. The Division also suggested that the telecon scheduled for January 14th be cancelled because all of the questions had been answered.

Fujisawa accepted the Division's responses to the 3 questions and agreed to take advantage of meeting with the Division to discuss the protocols before amending the applications. Fujisawa asked what the next steps would be regarding the NDAs. The Division told Fujisawa that they plan to take action on all NDAs on January 29, 2003. Upon receipt of the letter, the Division explained that Fujisawa would have 10 days to respond letting the Division know whether they plan to amend the applications. A 6-month review clock would start once the Division received a complete response to the action letter.

Susan Peacock, Regulatory Project Manager
Minutes Preparer

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
2/11/03 08:04:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506

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

Dear Mr. Reed:

We received your February 27, 2003, correspondence on February 28, 2003, requesting a meeting to discuss your proposed action plan to address the deficiencies identified in the action letter. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type A meeting. The meeting is scheduled for:

Date: March 28, 2003
Time: 11 A.M. - 12:30 P.M.
Location: Room S-400, 9201 Corporate Blvd., Rockville, MD 20850
CDER participants(tentatively):
Renata Albrecht, M.D., Division Director
John Powers, M.D., Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives
Edward Cox, M.D., M.P.H, Deputy Director, Office of Drug Evaluation IV
Mark Seggel, Ph.D., Chemistry Reviewer
Norman Schmuff, Ph. D. Chemistry Team Leader

Phil Colangelo, Pharm.D., Ph.D., Acting Clinical Pharmacology and Biopharmaceutics Team Leader
Ekopimo Ibia, M.D., Medical Officer Reviewer
Sary Beidas, M.D., Medical Officer Reviewer
Marc Cavaillé-Coll, M.D., Medical Team Leader
Kalavati Suvarna, Ph.D., Microbiology Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Owen McMaster, Ph. D., Pharmacolgy Reviewer
Kenneth Hastings, Dr. P.H., Pharmacology/ToxicologyTeam Leader
Karen Higgins, Sc.D., Statistics Team Leader
Ellen Frank, R.Ph., Chief, Project Management Staff
Susan Peacock, M.S., Regulatory Project Manager

Please provide the background information for this meeting at least two weeks prior to the meeting. If we do not receive it by March 14, 2003, we may need to reschedule the meeting.

If you have any questions, call me at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Susan Peacock, M.S.
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Susan Peacock
3/10/03 03:07:01 PM

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

NDA ACTION PACKAGE CHECKLIST

NDA 21-506 NDA ✓ NDA (	Efficacy Supplement Type SE-	Supplement Number
Drug:Mycamine (micafungin sodium)	Applicant:Fujisawa Healthcare, Inc.	
RPM:Susan Peacock	HFD-590	Phone # 301-827-2173
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	January 29, 2003 NDA 21-506 February 28, 2003 NDA ✓ NDA
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**Filing Review 7/15/02**
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA **(X)** AE **(X)** NA **AE NDA 21-506** **NA NDA /** **NA NDA**
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 8/9/02, 9/20/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	September 10, 1999
• Pre-NDA meeting (indicate date)	June 28, 2001 Clinical/Non-Clinical

• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	~~N/A~~ Draft Med. TL
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	DRAFTS, 1-28-03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	12/23/02, 1/22/03
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	12/13/02 ODS
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	~~Draft~~ 1/31/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1/23/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	10/22/02
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	DRAFT, 1-28-03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See Chemistry Review
• Review & FONSI *(indicate date of review)*	See Chemistry Review
• Review & Environmental Impact Statement *(indicate date of each review)*	See Chemistry Review
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	~~Should be in DFS Tues. or Wed.~~ 1/29/03
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	DRAFT, 1/28/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/a

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 21, 2003

To: Robert Reed	**From:** Susan Peacock
Company: Fujisawa Healthcare	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: 847-317-7286	**Fax number:** (301) 827-2475
Phone number: 847-317-8985	**Phone number:** (301) 827-2173

Subject: Micafungin sodium approval/launch in Japan

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ **YES** ☑ **NO**

Date: **January 21, 2003**

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

From: Susan Peacock, M.S.
Regulatory Project Manager, HFD-590

Subject: **Questions concerning the Micafungin sodium approval/launch in Japan**

Dear Mr. Reed,

The medical reviewers were informed of the approval/launch of micafungin sodium in Japan today. The Review team was wondering if Fujisawa has other applications under review in other jurisdictions? If yes, would you be willing to let us know where those applications have been submitted, if approved, not approved, or decision pending. If approved, where, when, what indications, and what dose. If not approved, what indications were sought and what were the deficiencies. We would appreciate any updates.

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
1/21/03 04:25:18 PM
CSO

Susan Peacock
1/21/03 04:27:52 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 31 2002

Marinella Della Negra, M.D.
Instituto de Infectologia Emilio Ribas
Av. Dr. Arnaldo, 165 – 2nd andar, sala 218
Cequiera Cesar
Sao Paulo, SP BRAZIL
CEP 01246-900

Dear Dr. Della Negra:

Between August 26 and 29, 2002, Mr. Joel Martinez and Drs. Khin Maung U and Robert Shibuya, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol 98-0-047 entitled: "An Open-Label, Non-Comparative Study of FK-463 in the Treatment of Candidemia or Invasive Candidiasis") of the investigational drug FK-463, performed for Fujisawa Healthcare. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

We understand you performed this study under a U.S. Investigational New Drug Application (IND) and that you knew at the time that your data would later be submitted to FDA.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not follow the relevant statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, our inspectors presented and discussed with you the one item listed on Form FDA 483, Inspectional Observations. We have evaluated the inspection report and the documents submitted with that report and agree with their observation.

We wish to emphasize that you did not adhere to the protocol (21 CFR 312.60) in that you enrolled subject 359-493 who met an exclusionary criterion. This subject had a serum alkaline phosphatase level greater than 5 times the upper limit of normal on the initial screening.

Please make appropriate corrections in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown our staff during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003736472
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X_ failure to adhere to protocol (05)
Deficiency Codes: 5

cc:
HFA-224
HFD-590 Doc.Rm. NDA# 21-506
HFD-590 Review Div.Dir. Albrecht
HFD-590 MO Ibia
HFD-590 PM Kong
HFD-47c/r/s/ GCP File #10721
HFD-47 GCP Reviewer Shibuya
HFD-47 CSO Storms
HFR-SW-150 DIB Thornburg
HFR-SW-1540 Bimo Monitor/Field Investigator Martinez
HFC-134 Kadar
GCF-1 Seth Ray

r/d: (RS/10/16/02):
reviewed:AEH:10/17/02;10/18/02;10/21/02
f/t:ml: 10/21/02; 12/31/02

o:**RS\NDA 21-506\DellaNegra.doc**

Reviewer Note to Rev. Div. M.O.
- This site screened 32 subjects and enrolled 24.
- Records for all enrolled subjects were inspected in detail.
- One protocol deviation was noted.
- All subjects were consented.
- Data appear acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Long

Food and Drug Administration
Rockville MD 20857

Leonard S. Sender, M.D.
St. Joseph's Hospital
1100 West Stewart Drive
Orange, California 92865

DEC 31 2002

Dear Dr. Sender:

On September 30-October 11, 2002, Ms. Diane Van Leeuwen and Mr. John Jorgensen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #98-0-046 entitled: "An Open Label, Non-Comparative Study of FK463 for the Treatment of Invasive Aspergillis") of the investigational drug FK463, performed for Fujisawa Healthcare. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your response dated November 12, 2002, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We acknowledge receipt of your letter dated November 12, 2002 and find your response adequate except for the comments noted in this letter. We are aware that at the conclusion of the inspection, our investigators presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not promptly report serious adverse events (SAEs) to the sponsor and your institutional review board (IRB) (21 CFR 312.60, 312.64(b), and 312.66).

Subject	Nature of SAE	SAE Date	Reported to Sponsor*	Reported to IRB
290-771	Thrombocytopenia		11/23/99	10/3/02
290-772	AML		6/12/00	7/3/00
290-772	AML		6/12/00	7/3/00
290-773	GI bleed		10/11/00	10/3/02
290-773	Death		—	10/3/02
290-774	Increasing CLL		10/10/00	10/3/02
290-774	Resp failure/death		—	10/3/02
290-778	Pulmonary Embolus		9/4/01	9/5/01
290-778	Failure To Thrive		11/13/01	10/3/02
249-773	Fever		9/6/00	9/6/00
249-773	Fever		9/6/00	9/6/00
249-775	AML		1/25/02	1/25/02
249-778	GI bleed		10/9/01	10/9/01
249-778	Respiratory failure		10/29/01	10/29/01

*Protocol required sponsor to be notified within 48 hours
**Within acceptable timeframe

2. You did not adhere to the current, approved protocol (21 CFR 312.60).

   a. Subject 290-772 did not receive his baseline physical exam within the protocol specified 72 hours prior to receiving his first dose of study drug.

   b. Subjects 290-772 and 290-776 did not receive their mycological assessments (assessment of eradication of Aspergillis by culture or biopsy of applicable sites) on treatment days 14, 28, and end of therapy.

   c. Subject 290-772 did not have his Clinical Assessments documented on study days 21, 28, 49, 56, 63, 84, 91, 98, 105, and 112.

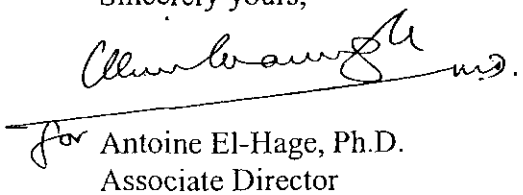
   d. Subject 290-772 was not administered study drug in accordance with the protocol in that drug was placed in a hot water bath prior to administration and the drug was infused over 10 minutes instead of the protocol specified one hour.

3. Informed consents for subjects 249-771, 249-772, 249-773, and 249-774 did not document the date on which the parent/guardian signed the form (21 CFR 50.27(a)).

We trust, as you stated in your written response dated November 12, 2002, that adequate measures will be implemented to ensure compliance with pertinent regulations in current or future studies. Your response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigators Van Leeuwen and Jorgensen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



for Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003811072
Field Classification: OAI
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why: Violations do not meet criteria for an OAI classification.

Deficiencies noted:
__X_inadequate informed consent form (03)
__X_failure to adhere to protocol (05)
__X_failure to notify IRB of changes, failure to submit progress reports (15)
__X_failure to report ADRS (16)
Deficiency Codes: **3, 5, 15, 16**

cc:
HFA-224
HFD-590 Doc.Rm. NDA
HFD-590 Review Div.Dir. Albrecht
HFD-590 MO Ibia
HFD-590 PM Kong
HFD-47c/r/s/ GCP File #10741
HFD-47 GCP Reviewer Shibuya
HFD-47 CSO Storms
HFR-PA-252 DIB Tucker
HFR-PA-2565 Bimo Monitor Koller
HFR-PA-200 Field Investigator Van Leeuwen/Jorgensen
GCF-1 Seth Ray

r/d: (RS112002):
reviewed:AEH:11/25/02
f/t:ml:11/25/02; 12/30/02

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TELECON MINUTES

DATE:	December 19, 2002
TIME:	2:00-3:00pm
LOCATION:	S440, Corp2
NDA#	21-506.
DRUG:	Mycamine (micafungin sodium)
SPONSOR/APPLICANT:	Fujisawa Healthcare, Inc.
CONTACT NAME:	Robert Reed
FAX NUMBER:	(847) 317-7286
PHONE NUMBER:	(847) 317-8985
PROJECT MANAGER:	Susan Peacock, MS
DIVISION OF:	Special Pathogen and Immunologic Drug Products, HFD-590
FORMAT:	Teleconference

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Renata Albrecht, M.D., Division Director
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Ekopimo Ibia, M.D., M.P.H., Medical Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Frederic Marsik, Ph.D., Microbiology Reviewer
Kalavati Suvarna, Ph.D., Microbiology Reviewer

INDUSTRY PARTICIPANTS AND TITLES:

Jerry Johnson, Ph.D., Vice President of Regulatory Affairs, Quality, and Safety
Donald Buell, M.D., Senior Medical Director
David Facklam, Director, Clinical Studies
Robert Reed, Associate Director of Regulatory Affairs

DISCUSSION WITH RESPONSES AND DECISIONS REACHED:

SUBJECT: Discuss December 18, 2002, submission of revised efficacy tables as requested by the Division on December 17, 2002.

Background: This teleconference was convened as a follow-up to the teleconference held with the sponsor on December 6, 2002 during which time the Agency informed the sponsor that data provided in the NDA were inadequate to support the proposed indications. The sponsor had hinted the Agency of the availability of additional data from Studies 98-0-046 and 98-0-047 in the 120-Day Safety Update. The sponsor had then offered to submit these data in further support of the proposed indications. On December 17, 2002 the Agency sent a facsimile to the sponsor with formats for tabular presentation of the updated data to facilitate quick review. The facsimile was followed with a brief teleconference on the same day. During that meeting, the Agency

learned that [redacted] ne sponsor had also asked their independent reviewer to prepare an additional analysis using failure after 7 days of treatment (instead of the 3 days specified in the protocol) as criteria for defining patients with refractory invasive fungal infection at time of initiation of micafungin. In addition to the requested tables, the sponsor also offered to provide flow charts that describe how the groups were partitioned (baseline diagnosis, disposition and outcome). The Agency further learned that the sponsor already had individual patient summaries and longitudinal flow charts that might be helpful if and when the Agency wanted to look at the new data in greater detail. On December 18, 2002, the sponsor submitted an electronic 30-page document in response to the earlier discussions. The current teleconference was convened to discuss the additional data submitted by the sponsor on December 18, 2002.

Division's Response: Following brief introductions, the Agency opened the meeting noting that the additional numbers were unlikely to change the Agency's interpretation of the data. The Agency then reminded the sponsor of deliberation at the December 6, 2002, teleconference that the conclusion might be similar to that reached after reviewing the data submitted with the original NDA. The Agency further

Fujisawa's Response: [redacted]

Division's Response:

NDA 21-506

Fujisawa's Response:

Division's Response:

Fujisawa's Response: Regarding the candidiasis data, the sponsor maintained that they added a large number of nice, well-documented cases of non-esophogeal candidiasis patients.

Division's Response: The Agency pointed out that 58/101 belonged to the non-efficacy failure or De Novo group. 21 belonged to efficacy failure with micafungin plus another drug. Only 12 belonged to the efficacy failure with micafungin alone. The remaining 10 were cases of breakthrough fungal infections. The Agency further noted that the additional patients did not add anything and that the sponsor needed to have patients on micafungin alone. The Agency then reminded the sponsor that they are not seeking a De Novo indication and that for the [redacted] indication, the data was not supportive.

Fujisawa's Response: The sponsor then asked about the prophylaxis indication

Division's Response: The Agency noted that there is not enough strength in the treatment indication data to support the prophylaxis indication.

Fujisawa's Response: The sponsor then sought to know the views of the Agency if sponsor had access to a comparative, blinded study trial for esophageal candidiasis. The sponsor informed the Agency that they have 251 patients with a fluconazole alone arm and 3 different doses of FK463. This trial had just been completed in Europe. The sponsor asked if the data looked favorable versus the

fluconazole arm, whether the Agency would consider it sufficient data to show efficacy of micafungin.

Division's Response: The Agency responded that at a minimum, it would support a resubmission. For the prophylaxis indication, the regulations allow only one major amendment, which had already taken place, so we will need to take an action in January. Regarding the European study, the Agency noted that this data would be reviewed for an esophageal candidiasis indication.

Fujisawa's response: The sponsor then proposed to maintain the January 14th teleconference and promised to prepare a summary of what they plan to do, which would be submitted to the Agency a few days before the teleconference.

Susan Peacock, Regulatory Project Manager
Minutes Preparer

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/s/

Renata Albrecht
2/10/03 06:47:26 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: December 17, 2002

To: Robert Reed	**From:** Susan Peacock
Company: Fujisawa	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	**Fax number:** (301) 827-2475
Phone number(847) 317-8985	**Phone number:** (301) 827-2173

Subject: **Draft tables for population with numbers based on independent reviewer's assessment**

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 21-506
NDA
NDA

Date: December 17, 2002

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

From: Susan Peacock, M.S.
Regulatory Project Manager, HFD-590

Through: Marc Cavaillé-Coll, M.D., Ph.D., Medical Review Team Leader
Sary Beidas, M.D., Medical Reviewer
Ekopimo Ibia, M.D., Medical Reviewer

Subject: **Draft tables for population with numbers based on independent reviewer's assessment.**

Dear Mr. Reed:

Please find below tables provided by the medical reviewers of the aspergillosis and candidiasis studies. They would like to have these tables populated with numbers based on the independent reviewers' assessment. Please populate with both the total data (old plus additional data) and with the old data alone.

Please note in Tables 1 and 2, breakthrough infection refers to patients who developed fungal infection while receiving prophylactic systemic antifungal agent (s).

1. **Primary Site of Fungal Infection at Baseline As Per Independent Reviewers' Assessment**

	De Novo	Efficacy Failure		Breakthrough Infection		Total
		FK463 & Other	FK463 Alone	FK463 & Other	FK463 Alone	
Site of *Candida* Species Infection						
Esophageal						
Blood						
Disseminated*						
proven						
probable						
Abscess						
Peritoneal						
Other*						

*Please specify exact sites involved

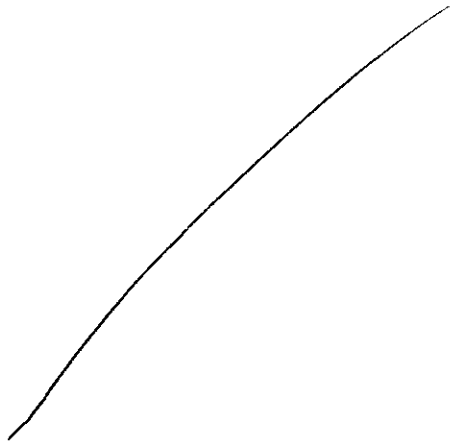
2. Global Assessment of Outcome at End of Therapy by Primary Site of Infection As Per Independent Reviewers' Assessment

	De Novo	Efficacy Failure		Breakthrough Infection		Total
		FK463 & Other	FK463 Alone	FK463 & Other	FK463 Alone	
Blood						
Complete Response						
Partial Response						
Failure						
Not Evaluable						
Esophageal						
Complete Response						
Partial Response						
Failure						
Not Evaluable						
Disseminated						
Complete Response						
Partial Response						
Failure						
Not Evaluable						
Abdominal abscess						
Complete Response						
Partial Response						
Failure, n (%)						
Not Evaluable						

3. Updated efficacy table listing success outcomes at End-of-Therapy (EOT).

Please provide the following information:

- **Column-4**: per protocol success results at EOT and the total number of patients by investigator
- **Column-5**: per protocol success results at EOT and the total number of patients by independent reviewer
- In columns 4 & 5 provide the breakdown numbers for complete response, partial response, and stable



Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
12/17/02 10:08:38 AM
CSO

Susan Peacock
12/17/02 10:09:25 AM
CSO

Marc Cavaille Coll
1/31/03 08:57:30 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: December 9, 2002

To: Robert Reed	**From:** Susan Peacock
Company: Fujisawa	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	**Fax number:** (301) 827-2475
Phone number(847) 317-8985	**Phone number:** (301) 827-2173

Subjec: FDA Response to Fujisawa Healthcare, Inc.'s (FHI) proposal for how to identify outliers in the 97-0-041 and 98-0-043 PK studies.

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-506
NDA
NDA /

Date: December 9, 2002

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

From: Susan Peacock
Regulatory Project Manager, HFD-590

Through: John Lazor, Pharm.D., Director, Division of Pharmacology Evaluation III
Barbara Davit, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Jang Ik-Lee, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Subject: FDA Response to Fujisawa Healthcare, Inc.'s (FHI) proposal for how to identify outliers in the 97-0-041 and 98-0-043 PK studies.

Dear Mr. Reed:

(1) The proposed approach for determining outliers is reasonable. However, we cannot make a final decision about the findings in these two study reports until we completely review all of the revised calculations.

(2) We also ask that the proposed tests be applied to identify low outliers as well as high outliers.

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

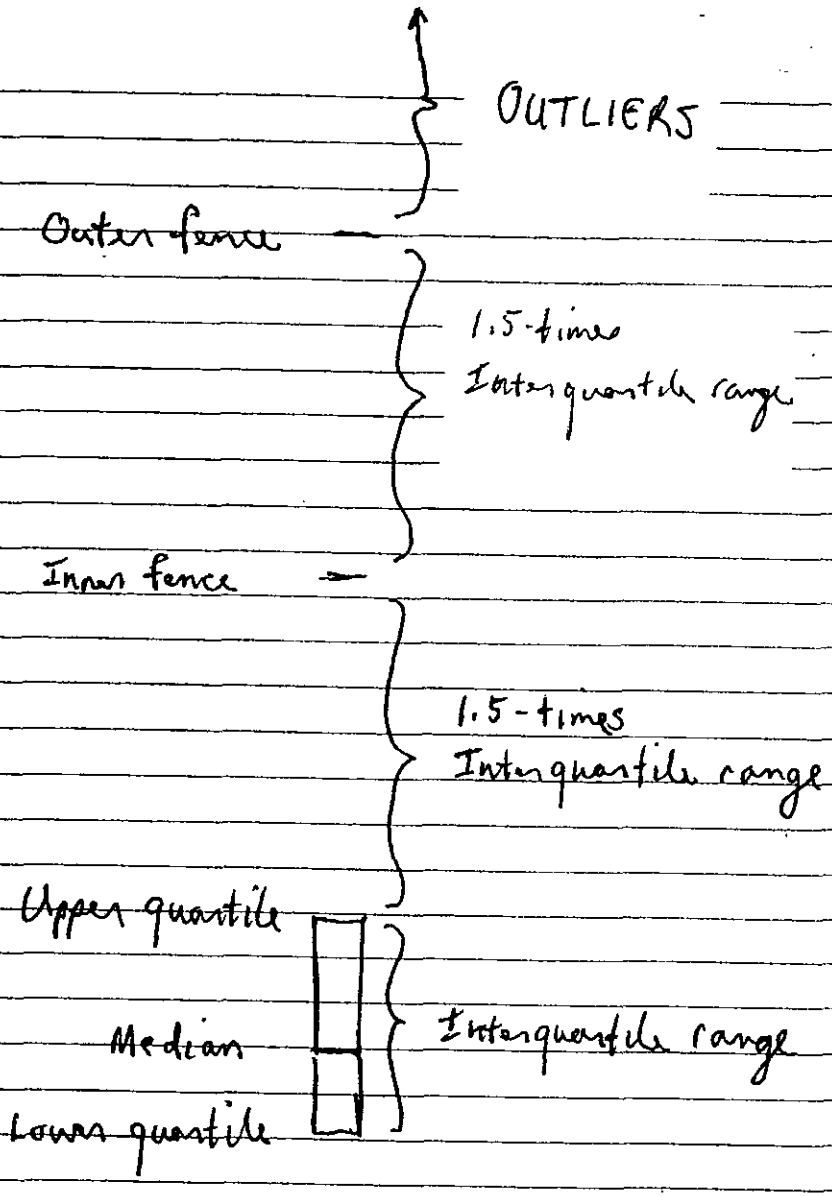
Attachment: Fujisawa Healthcare's proposal for identifying outliers in the FK463 studies 97-0-041 and 98-0-043.

Procedure for identifying outliers in the FK463 studies 97-0-041 and 98-0-043.

Case report forms have been reviewed and provide documentation for excluding five individual samples from study 978-0-041 and three individual samples plus the day one profile of one subject from study 98-0-043. The CRFs do not provide a clear reason to exclude most of the extremely high concentrations in the study.

After excluding the samples for which the CRFs provide a rationale, we plan to use a procedure proposed by Tukey in "Exploratory Data Analysis" (1977, pp. 43-45). Tukey's procedure is based on the median and interquartile range for a set of data. The interquartile range is the difference between the 75th percentile and 25th percentile values of the set of data. Tukey defines an "inner fence" that is 1.5-times the interquartile rang above the upper (75th percentile) quartile and an "outer fence" that is 3-times the interquartile range above the upper quartile. (Please see attached.)

We propose to classify outliers according to this criterion in addition to considering clinical judgement.


OUTLIERS
Outer fence
1.5-times
Interquartile range
Inner fence
1.5-times
Interquartile range
Upper quartile
Median
Lower quartile
Interquartile range

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/s/

Susan Peacock
12/9/02 03:37:15 PM
CSO

Susan Peacock
12/9/02 03:38:13 PM
CSO

Barbara Davit
12/10/02 01:04:12 PM
BIOPHARMACEUTICS

MEETING MINUTES

MEETING DATE:	**December 6, 2002**
TIME:	**1:00-2:00 P.M.**
LOCATION:	**CORP2, S346**
NDA #:	**NDA 21-506,**
DRUG:	**Mycamine (micafungin sodium) for Injection**
SPONSOR/APPLICANT:	**Fujisawa Healthcare, Inc.**
CONTACT NAME:	**Robert Reed, Associate Director, Regulatory Affairs**
FAX NUMBER:	**847-317-7286**
PHONE NUMBER:	**847-317-8985**
PROJECT MANAGER:	**Susan Peacock, MS**
DIVISION OF:	**Special Pathogen and Immunologic Drug Products, HFD-590**
FORMAT:	**Teleconference**

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Renata Albrecht, M.D., Division Director
Marc Cavaille-Coll, M.D., Medical Officer Team Leader
Ekopimo Ibia, M.D., M.P.H., Medical Officer Reviewer
Sary Beidas, M.D., Medical Officer Reviewer
John Powers, M.D., Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives
Shukal Bala, Ph.D., Microbiology Team Leader
Kalavati Suvarna, Ph.D., Microbiology Reviewer
Karen Higgins, Sc.D., Statistics Team Leader
Qian Li, Ph.D., Statistics Reviewer
Barbara Davit, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Susan Peacock, M.S., Regulatory Project Manager

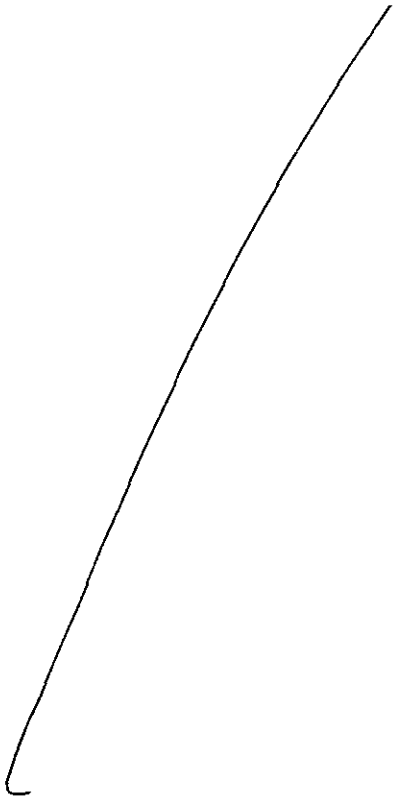
INDUSTRY PARTICIPANTS AND TITLES:

Jerry Johnson, Ph.D., Vice President of Regulatory Affairs, Quality, and Safety
Rebecca Ikusz, Regulatory Affairs Senior Scientist
Donald Buell, M.D., Senior Medical Director
David Facklam, Director, Clinical Studies
Ellen Hodosh, Ph.D., Associate Director, Biopharmaceutical Sciences
James Keirns, Ph.D., Senior Director Biopharmaceutical Sciences
Herman Lilja, Ph.D., Director Biopharmaceutical Sciences

DISCUSSION WITH RESPONSES AND DECISIONS REACHED:

FDA Summary of Issues for Discussion:

1.



- ***Fujisawa Response:*** *Regarding the candidiasis study, what are the Agency's concerns? We still feel the data, although uncontrolled, showed that micafungin was effective in the treatment of candidiasis when added.*

- ***Agency Response:*** *The information on the 30 or so patients that received Micafungin alone was from a non-comparative study. The bulk of the remaining cases were esophageal candidiasis. Limited conclusions could be drawn from these data. A comparative study would have been better.*

- ***Fujisawa Response:*** *A large number had non-albicans candida. We felt the data was very supportive. We were very surprised by the Agency's interpretation of the candidiasis data.*

- ***Agency Response:*** *The bulk of the patients were esophageal candidiasis. The response is hard to interpret due to no controlled therapy. Without a comparator, it is hard to determine efficacy in esophageal candidiasis.*

- ***Fujisawa Response:*** *We closed the study to esophageal candidiasis due to enrollment of so many patients. In the updated safety report, those patients were non-esophageal.*

- ***Agency Response***: *In the 120 day safety update, you did submit additional patients treated for candidiasis with micafungin, right?*

- ***Fujisawa Response:*** *We have a locked database with this information that we could submit. The additional 82 patients were not esophageal candidiasis. These were fairly clear-cut cases of candidemia.*

- ***Agency Response:*** *The Agency would be willing to look at the additional data if submitted but would have to look at the review timeframe due to PDUFA. You would hope this data would change our minds but it may not. We recommend you make a decision for us to look at the additional data or not. If you do decide to submit this additional data, we would like to discuss it with you first.*

- ***Fujisawa Response:*** *We will take all of this into mind and make a decision. We will get back to you by following up with the Project Manager. We have a large database and this is very disappointing news. This database includes over 1500 patients exposed to micafungin. We feel it is the tightest and strongest study ever done. We strongly feel the de novo candidiasis data is very supportive. We will regroup and figure a way to submit this data to the Agency in a clearer manner so that the benefits of micafungin can be seen.*

2. Prophylaxis: NDA 21-506 (running short of time at this point so very brief exchange)

- The lack of substantial evidence of activity was not supportive of efficacy in prophylaxis indication as would be expected for empiric therapy or prophylaxis indication.

- Moreover, results of the single controlled study were marginal and failed to stand up to sensitivity analyses. During the course of development, the Agency had emphasized the need for a robust study result. Results of the prophylaxis study was driven by suspected fungal infection rather than breakthrough fungal infections, which occurred at a rate much lower than expected during the design of the study.

- While the results presented in the NDA may not be sufficient to support the proposed indications, they were sufficiently encouraging to support further investigation. The experience may facilitate the design of some better study (ies).
- For example, in situations of uncertain activity of micafungin combined with existing therapy, it may be reasonable to consider a randomized controlled study.

Fujisawa Response: *the prophylaxis study is controlled and the candidiasis is very microbiologically supported. We still feel strongly of the supportive data regarding candidiasis.*

Agency Response: *We hear your comments and your interpretation of the data. We are willing to work with you addressing your concerns and your interpretation of the data. We are willing to look at the additional information but have the regulatory burden of showing efficacy and safety. We each have a better understanding now of where we stand and need to come up with a plan.*

Fujisawa Response: *We will regroup and get back to the Agency with a proposal for how to proceed.*

Susan Peacock, Regulatory Project Manager
Minutes Preparer

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/s/

Renata Albrecht
1/23/03 09:58:22 AM

MEMORANDUM OF TELECON

DATE: December 4, 2002

APPLICATION NUMBER: NDA 21-506, [redacted]

BETWEEN:

Name: Jerry Johnson, Ph.D., Vice President of Regulatory Affairs, Quality, and Safety
Rebecca Ikusz, Regulatory Affairs Senior Scientist
Donald Buell, M.D., Senior Medical Director
David Facklam, Director, Clinical Studies
Ellen Hodosh, Ph.D., Associate Director, Biopharmaceutical Sciences
Yoichi Satoi, Assistant Director, Research Data Operations
Wayne Wisemandle, Senior Statistician
James Keirns, Ph.D., Senior Director Biopharmaceutical Sciences
Herman Lilja, Ph.D., Director Biopharmaceutical Sciences
Ala Alak, Ph.D., Director of Bioanalytical Sciences, Fujisawa Research Institute of America
Robert Reed, Associate Director of Regulatory Affairs

Phone: 847-317-8985
Representing: Fujisawa Healthcare, Inc.

AND

Name: Renata Albrecht, M.D., Division Director
Sary Beidas, M.D., Clinical Reviewer
Marc Cavaille-Coll, M.D., Medical Team Leader
Barbara Davit, Ph. D., Clinical Pharmacology and Biopharmaceutics Team Leader
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
John Lazor, Pharm.D., Director, Division of Pharmacology Evaluation III
Susan Peacock, M.S., Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products, HFD-590

SUBJECT: Discuss the fax sent 12/3/02 by the clinical pharmacology review team where critical problems in two pivotal pharmacokinetic studies for FK463 conducted in adult BMT/PSCT patients (97-0-041) and neutropenic pediatric patients (98-0-043) were outlined as follows:

1. The clinical part of the two studies appears to be poorly controlled. There are a number of unexplained outlier FK463 concentrations (up to 20 times larger than mean values) and missed blood samplings. Please provide an explanation as to the possible causes of the

outliers. If the outliers were due to contamination of blood specimens by infused micafungin during sampling using FK463 infusion ports, as you speculated, please provide case record forms or other records confirming this. Any samples drawn from the infusion port would likely be contaminated with residual FK463 to some unknown extent. Please reanalyze data excluding all samples that are confirmed as drawn from the infusion ports.

Fujisawa response: They just hired a new head of the Department of Pharmacology and plan to reanalyze the data as requested.

FDA response: Please define the term outlier and the review team would like to see the analysis with and without these outliers.

Fujisawa response: They agreed to define the term and provide reasons why patients are included in the outlier category. The sponsor also agreed to recognize blood samples collected from infusion port by looking at CRFs or other study sheets and removing them from the data analysis.

2. Some pharmacokinetic and statistical analyses appear inconsistent and inappropriate. For example, some outlier FK463 concentrations were excluded in calculating mean concentrations but included in estimating other pharmacokinetic parameters such as AUC. It appears that favorable rather than the most appropriate concentrations were used in the determination of terminal half-life. See Study 98-0-043, patients # 012-530, 059-337, 059-354, etc. for examples. Problems are not limited to these examples. Please reanalyze data excluding all inappropriate values. Also, please keep your calculations consistent and use the actual data in performing calculations.

Fujisawa response: They will do analysis with outliers included and excluded and agree to be more consistent with the analysis.

3. Neither original nor updated reports for the two studies are complete. For example, the reports do not provide individual or spaghetti plots of FK463 concentration-time data. In the study 98-0-043 report, you claim that some pharmacokinetic parameters (e.g., AUC) were correlated with dose and age. However, no regression analysis was submitted in support of such claims. Deficiencies are not limited to these examples. Please provide complete reports.

Fujisawa response: They agreed to include the spaghetti plots and will provide regression analysis.

4. Overall, please provide updated and complete reports accounting for the requests mentioned above. Please keep consistency in pharmacokinetic and statistical analysis and in comparing results across study reports. You may use the report for study FG463-21-03 as a template, since this study report contains acceptable minimum required information.

Fujisawa response: They agreed to provide updated and complete reports and plan to follow the FG463-21-03 template. The sponsor also agreed to provide a completely updated report for Report 2002001040 in addition to reports for Studies 97-0-041 and 98-0-043.

5. Please indicate how soon we can receive the revised reports.

Fujisawa response: They plan to get the above requested information by December 20, 2002.

Susan Peacock
Regulatory Project Manager

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/s/

Barbara Davit
12/6/02 02:14:39 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2002

To: Robert Reed	**From:** Susan Peacock
Compan y: Fujisawa	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	**Fax number:** (301) 827-2475
Phone number(847) 317-8985	**Phone number:** (301) 827-2173
Subject Clinical pharmacology Issues to be discussed at 12/4/02 telecon :	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES ☑ NO

Facsimile

Date: December 3, 2002

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

From: Susan Peacock
Regulatory Project Manager, HFD-590

Through: John Lazor, Pharm.D., Director, Division of Pharmacology Evaluation III
Barbara Davit, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Jang Ik-Lee, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Subject: **Issues to be discussed at 12/4/02 telecon**

Dear Mr. Reed:

The clinical pharmacology review team has found critical problems in two pivotal pharmacokinetic studies for FK463 conducted in adult BMT/PSCT patients (97-0-041) and neutropenic pediatric patients (98-0-0043). Our position on the reports and requests are as follows:

1. The clinical part of the two studies appears to be poorly controlled. There are a number of unexplained outlier FK463 concentrations (up to 20 times larger than mean values) and missed blood samplings. Please provide an explanation as to the possible causes of the outliers. If the outliers were due to contamination of blood specimens by infused micafungin during sampling using FK463 infusion ports, as you speculated, please provide case record forms or other records confirming this. Any samples drawn from the infusion port would likely be contaminated with residual FK463 to some unknown extent. Please reanalyze data excluding all samples that are confirmed as drawn from the infusion ports.

2. Some pharmacokinetic and statistical analyses appear inconsistent and inappropriate. For example, some outlier FK463 concentrations were excluded in calculating mean concentrations but included in estimating other pharmacokinetic parameters such as AUC. It appears that favorable rather than the most appropriate concentrations were used in the determination of terminal half-life. See Study 98-0-043, patients # 012-530, 059-337, 059-354, etc. for examples. Problems are not limited to these examples. Please reanalyze data excluding all inappropriate values. Also, please keep your calculations consistent and use the actual data in performing calculations.

3. Neither original nor updated reports for the two studies are complete. For example, the reports do not provide individual or spaghetti plots of FK463 concentration-time data. In the study 98-0-0043 report, you claim that some pharmacokinetic parameters (e.g., AUC) were correlated with dose and age. However, no regression analysis was submitted in support of such claims. Deficiencies are not limited to these examples. Please provide complete reports.

4. Overall, please provide updated and complete reports accounting for the requests mentioned above. Please keep consistency in pharmacokinetic and statistical analysis and in comparing results across study reports. You may use the report for study FG463-21-03 as a template, since this study report contains acceptable minimum required information.

5. Please indicate how soon we can receive the revised reports.

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
12/3/02 02:10:17 PM
CSO

Susan Peacock
12/3/02 02:11:01 PM
CSO

Barbara Davit
12/3/02 04:21:39 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506

Fujisawa Pharmaceutical Company, Ltd.
Attention: Robert M. Reed
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Reed:

Please refer to your April 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine (Micafungin sodium for injection), 25 mg and 50 mg.

On August 29, 2002, we received your August 28, 2002 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 29, 2003.

If you have any questions, call Yoon Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation ODE IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
10/18/02 11:47:22 AM
NDA 21-506

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 24, 2002

To: Robert M. Reed	**From:** Yoon Kong, Pharm.D.
Company: Fujisawa Healthcare, Inc.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (847) 317-7286	**Fax number:** (301) 827-2475
Phone number: (847) 317-8985	**Phone number:** (301) 827-2127

Subject: NDA 21-506 Micafungin

Total no. of pages including cover: 3

Comments: **Response to Clarifications regarding September 13, 2002, fax**
Alternative Tradename- Mycamine
CMC information request

Document to be mailed: ☐ YES ☑ NO

Date: September 24, 2002

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

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Ekopimo Ibia, M.D., M.P.H., Clinical Reviewer
Marc W. Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Qian Li, Ph.D., Statistical Reviewer
Karen Higgins, Sc.D., Statistical Team Leader
Mark Seggel, Chemistry Reviewer
Norman Schmuff, Chemistry Team Leader

Subject: NDA 21-506
Micafungin (Clarification regarding our 9-13-02 fax, Alternative Tradename- Mycamine, Chemistry Information Request)

Dear Mr. Reed:

I. Please refer to your NDA 21-506 submission dated September 18, 2002 (received September 20, 2002) requesting clarification regarding our fax sent on September 13, 2002. We have the following comments.

General

- Yes, the comments /requests received are in reference to Study 98-050 only.

Item 2

- For the first 4 bullets listed in your September 18, 2002, submission, we concur that our responses are "yes".
- For the 5th bullet, "**used after therapy**" refers to use in patients who have completed randomized study drug treatment vs. "**used after discontinuation of study drug**" refers to use in patients who were prematurely discontinued from randomized study drug treatment".

Item 2 –Formats associated with these datasets

- We would prefer to have the original variables with the format catalog instead of the character variables.
- **CNTLOUT** data set is acceptable.

II. Please refer to your NDA 21-506 submission dated August 26, 2002 (received August 27, 2002) providing an alternative proposed tradename for micafungin, Mycamine as a possible replacement for [redacted] The Division of Medical Errors and Technical Services (DMETS) has reviewed the tradename Mycamine and has found it acceptable. DMETS also has recommended the following carton/container labeling - [redacted] 50 mg strengths [redacted]

Please note that the review division takes into consideration the recommendations made by DMETS, but reserves the right to make an ultimate decision on the drug product (including drug product name).

III. Please provide the following chemistry information.

- Please provide a tabulation of the samples (drug substance, drug product, reference standards, related substances) that will be submitted to the FDA laboratories for methods validation. Lot numbers and quantities should be provided. You can use the attached format provided for your submission.

Samples and any special equipment/reagents that will be provided to FDA laboratories for validation of analytical procedures described in NDA 21-506

ITEM	QUANTITY	CONTROL NUMBERS
Drug Substance:		
Finished Dosage Form:		
Reference Samples:		
Related Substances:		

Please contact me at (301) 827-2127 if you have any questions regarding the facsimile transmission.

Thank you.

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Yoon Kong
9/24/02 02:44:31 PM
CSO

4 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

___✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

CONSULTATION RESPONSE

Mycamine [redacted]

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

DATE RECEIVED: 08/30/02	**DUE DATE:** 09/27/02	**ODS CONSULT #:** 02-0128-1

TO:

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

THROUGH:

Yoon Kong
Project Manager
HFD-590

PRODUCT NAME: **Mycamine** (Micafungin Sodium for Injection) — 50 mg **NDA: 21-506.** —	**NDA SPONSOR:** Fujisawa Healthcare, Inc.

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Special Pathogens and Immunologic Drug Products (HFD-590), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name "Mycamine" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name, "Mycamine". In addition, DMETS recommends implementation of the labels and labeling revision as outlined in section III of this review.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 594-6079

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 17, 2002

NDA: 21-506, —

NAME OF DRUG (S): **Mycamine**
Micafungin Sodium for Injection
— . 50 mg

NDA HOLDER: Fujisawa Healthcare, Inc.

I. INTRODUCTION:

This consult is written in response to a May 31, 2002 request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590) for an assessment of the proposed proprietary name, "Mycamine." The container label and carton labeling were reviewed for possible interventions in minimizing medication errors.

Mycamine is the second proposed proprietary name for this product. The sponsor initially proposed — which was reviewed by DMETS on July 22, 2002. DMETS did not recommend the use of the proposed name —

PRODUCT INFORMATION

Mycamine contains the active ingredient, micafungin, which inhibits the synthesis of 1,3-beta-D-glucan, an essential component of the cell wall of susceptible fungi. Mycamine (micafungin) has demonstrated in vitro activity against a variety of *Candida* and *Aspergillus* species. Mycamine is indicated for the:

- Prophylaxis of — . in patients undergoing hematopoietic stem cell transplantation.

For adults, the usual dose is 50 mg — via intravenous infusion. —
— Mycamine must be reconstituted with 5 mL of 0.9% Sodium Chloride for Injection or 5% Dextrose Injection. The reconstituted Mycamine should be added to 100 mL of 0.9% Sodium Chloride for Injection. Mycamine is available in vials containing —
50 mg of micafungin.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] 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[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies, outpatient and inpatient, and one verbal prescription studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

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 names were also discussed. The expert panel consists of members of DMETS Safety Evaluator Staff and a representative 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. The Expert Panel identified several names that were thought to have the potential for confusion with Mycamine. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC has no objection to the proposed proprietary name Mycamine with regards to promotional claims.

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html

[5] Data provided by Thomson and Thomson' SAEGIS™ Online Service, available at www.thomson-thomson.com.

Table 1 (Mycamine)

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Mycamine	Micafungin Sodium For Injection 50 mg (Rx)	Adults: 50 mg to 100 mg IV infusion daily	
Hycomine Compound	Hydrocodone Bitartrate 5 mg, Chlorpeneramine Maleate 2 mg, Phenylephrine Hydrochloride 10 mg, Acetaminophen 250 mg, Caffeine 30 mg Tablets (C-IV)	1 tablet 4 times daily	LA/SA*
Micrainin	Aspirin 325 mg, Meprobamate 200 mg Tablets (C-IV)	1- 2 tablets every 2-6 hours as needed for pain	LA/SA*
Mylaramine	Dexchlorpheniramine Maleate, USP Tablets	1 tablet every 4-6 hours	LA/SA*
Mysoline	Primidone Tablets 50 mg, 250 mg Oral Suspension: 250 mg/5 mL (Rx)	Slowly titrated up to 250 mg 3 to 4 times daily	SA*
Thiamine	Thiamine Tablets 50 mg, 100 mg, 250 mg (otc) Thiamine Injection 100 mg/mL (Rx)	Varies according to deficiency and disease	SA*

*SA = Sound-alike
*LA = Look-alike
**Identified from the prescription study conducted by DMETS.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

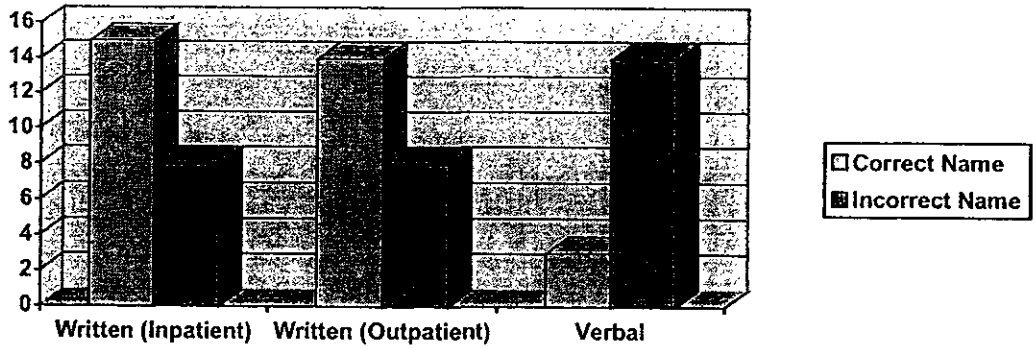
Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Mycamine with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Inpatient and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Mycamine (see page 5). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Mycamine

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: Mycamine 50 mg 1	Verbal Rx: Mycamine 50 mg Use as directed. #1
Inpatient Rx: Mycaumis 50mg IV x 1	

2. Results for Mycamine

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	23(59%)	15 (65%)	8 (35%)
Written Outpatient	35	22 (63%)	14 (64%)	8 (36%)
Verbal	32	17 (53%)	3 (18%)	14 (82%)
Total	106	62 (58%)	32 (52%)	30 (48%)



Among the verbal prescription study participants for **Mycamine**, 14 of 17 (82%) participants interpreted the name incorrectly. Majority of the incorrect name interpretations were phonetic variations of "Mycamine." The incorrect responses were *Micamine (2), Mitomeen, Micomene, Micomine, Mightomean, Mycomine (4), Mitomene, Mycomean, Mytomeen,* and *Mytamin.*

Among the written prescription study participants for **Mycamine**, 16 of 45 (36 %) participants interpreted the name incorrectly. Incorrect responses were misspelled variations of "Mycamine": *Mycainime, Mycannis, Mycamins, Mycaumis, Mycaune, Myamin, Mycanasine, Mycaurno, Mycomine (6), Mysamine,* and *Mycosamine.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Mycamine", the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Mycamine were Hycomine, Micrainin, and Mysoline.

DMETS conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Mycamine and Hycomine, Micrainin or Mysoline. The majority of interpretations from the verbal and written prescription studies were phonetic/misspelled interpretations of the drug name Mycamine.

Each Hycomine Compound tablet contains 5 mg of hydrocodone bitartrate, 2 mg of chlorpheneramine maleate, 10 mg of phenylephrine hydrochloride, 250 mg of acetaminophen and 30 mg of caffeine. Hycomine is indicated for the symptomatic relief of cough, nasal congestion, and discomfort associated with upper respiratory tract infections. Hycomine and Mycamine sound similar as they each contain 3 syllables. The first syllable is somewhat similar differing only in the first letter. The second and third syllables are indistinguishable. The names look similar as well (see below). Although Hycomine and Mycamine look and sound somewhat similar, the names differ in respect to many other characteristics such as dosage form (tablet vs. injection), dosing regimen (4 times daily vs. once daily), prescription drug class (schedule III vs. non-schedule), indications for use (symptoms associated with upper respiratory infections vs. antifungal) and strength (one strength containing multiple active ingredients vs. — 50 mg). Therefore, the potential for confusion between Hycomine and Mycamine should be minimal.

Hycomine Mycamine

Micrainin contains the active ingredients aspirin and meprobamate. Micrainin is indicated as an adjunct in the short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease or tension headache. Micrainin and Mycamine may look somewhat similar as they share the first letter "M" and contain a similar ending (crainin vs. camine). The names may sound similar, sharing an identical first and second syllable. The names both end with an "n" sound as well. Although Mycrainin and Mycamine look and sound somewhat similar, the names differ in respect to many other characteristics such as dosage form (tablet vs. injection), dosing regimen (every 2 to 6 hours as needed vs. once daily), prescription drug class (schedule IV vs. non-schedule), indications for use (analgesia vs. antifungal) and strength (one strength containing two active ingredients vs — . 50 mg). Therefore, the potential for confusion between Micrainin and Mycamine should be minimal.

Micrainin Mycamine

Mysoline contains the active ingredient primidone and is indicated for control of grand mal, psychomotor, or focal epileptic seizures, either alone or with other anticonvulsants. Mysoline and Mycamine sound somewhat similar as the names share the prefix "My" and end with an "n" sound. However, the names are distinguishable in sound because the second syllable and beginning of the third syllable are completely different. Although the drug products share an overlapping strength (50 mg), they differ in dosage form (tablet and oral suspension vs. injection). The drug products also differ in dosing regimen (3 to 4 times daily vs. once daily). The likelihood of confusion between Mysoline and Mycamine is low given the differences described above and a lack of convincing sound-alike potential.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container label and carton labeling of Mycamine, DMETS has focused on safety issues relating to possible medication errors. We have identified one area of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (— 50 mg)

B. CARTON LABELING (— 50 mg)

See comment under A.

IV. RECOMMENDATIONS:

A. DMETS has no objections to use of the proprietary name Mycamine.

B. DMETS recommends implementation of the labels and labeling revision as outlined in section III of this review.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

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/s/

Alina Mahmud
9/19/02 01:46:00 PM
PHARMACIST

Carol Holquist
9/20/02 03:23:03 PM
PHARMACIST

Jerry Phillips
9/20/02 03:46:20 PM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **HFD-400**
Office of Pharmacoepidemiology and Statistical Science-Office of Drug Safety

FROM: **HFD-590**
Division of Special Pathogen and Immunologic Drug Products
Yoon Kong, Regulatory Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 30, 2002	**55,322**	**21-506**	**Original NDA submission**	**April 29, 2002** **August 16, 2002**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Micafungin sodium (FK-463)	**Priority**	**7030410 (Antifungal Agent-Systemic)**	**September 16, 2002**

NAME OF FIRM: **Fujisawa Healthcare, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*.

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW).	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Request for review of sponsor's proposed alternative tradename "Mycamine".
Background- Sponsor originally proposed the tradename of ' — . Division submitted a tradename consult to DMETS. DMETS in their consult response did not recommend the use of the primary proprietary name, ' — . Subsequently, the sponsor has provided an alternative proprietary name, "Mycamine". If you have any questions, please contact Yoon Kong @ (301) 827-2195.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Yoon Kong, May 31, 2002	■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Yoon Kong
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____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

Applications: NDA 21-506

Requested Tradename:

Generic Name and Strengths: micafungin sodium for injection, — 50 mg

Applicant: Fujisawa Healthcare, Inc.

Date of Application: April 29, 2002

Date of Receipt: April 29, 2002

Date of Filing Meeting: June 14, 2002

Filing Date: June 28, 2002

Indications requested:

1. NDA 21-506: prophylaxis of — in patients undergoing hematopoietic stem cell transplantation.

Type of Applications: **Full NDAs** ___X___ Supplement _____
(b)(1) ___X___ (b)(2) _____

Therapeutic Classification: **NDA 21-506** S_____ P__X____

Resubmission after a withdrawal or refuse to file: ___NA___

Chemical Classification: **NDA 21-506** ___1___**(NME)**

Other (orphan, OTC, etc.): ___NA____

Has orphan drug exclusivity been granted to another drug for the same indication? YES ___ **NO** **X**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: **Paid** **X** Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: **YES** **X** NO _____

User Fee ID#: **4327**

Clinical data? **YES** **X** NO _____ Referenced to NDA# **NA**

Date clock started after UN: **NA**

User Fee Goal dates: **NDA 21-506** **October 29, 2002**

- **Does the submission contain an accurate comprehensive index?** **YES** **X** NO _____
- **Form 356h included with authorized signature?** **YES** **X** NO _____
  If foreign applicant, the U.S. Agent must countersign.
- **Submission complete as required under 21 CFR 314.50?** **YES** **X** NO _____
  If no, explain:
- **If electronic NDA, does it follow the Guidance?** **YES** **X** NO _____ NA _____
  If an electronic NDA: all certifications must be in paper and require a signature.
- **If Common Technical Document, does it follow the guidance?** **YES** **X** NO _____ NA _____
- **Patent information included with authorized signature?** **YES** **X** NO _____
- **Exclusivity requested?** **YES;** **5** **years** NO _____
  Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.
- **Correctly worded Debarment Certification included with authorized signature?** **YES** **X** NO _____
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- **Financial Disclosure included with authorized signature?** YES __X__ NO _____
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- **Has the applicant complied with the Pediatric Rule for all ages and indications?** YES __X__ NO _____
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- **Field Copy Certification (that it is a true copy of the CMC technical section)?** YES __X__ NO _____
  Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES __X__ NO _____

Drug name/Applicant name correct in COMIS? YES __X__ NO _____

List referenced IND numbers: 55,322

End-of-Phase 2 Meeting? Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meetings: **Non-clinical/Clinical** **June 8, 2001**
CMC **June 28,2002**

Project Management

Copy of the labeling (PI) sent to DDMAC? YES __X__ NO _____

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
(consult dated May 31, 2002 in DFS) YES __X__ NO _____

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES _____ NO _____ NA __X__

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES _____ NO _____ NA __X__

Advisory Committee Meeting needed? YES, date if known _____ NO _____
To be determined as review progresses __X__

Clinical

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

Chemistry

- **Did sponsor request categorical exclusion for environmental assessment?** **YES** __X__ NO _____
  If no, did sponsor submit a complete environmental assessment? YES NO

  If EA submitted, consulted to Nancy Sager (HFD-357) **YES** __X__ NO _____

  Establishment Evaluation Request (EER) package submitted? **YES** __X__ NO _____

- **Parenteral Applications Consulted to Sterile Products (HFD-805)?**
  YES _____ NO _____ NA __X__

ATTACHMENT

MEMO OF FILING MEETING

Date of Filing Meeting: June 14, 2002

Background

NDA 21-506 was submitted on April 29, 2002 for use of — (micafungin sodium) for injectior —
— 50 mg, for the following — indications:

1. prophylaxis of — n patients undergoing hematopoietic stem cell transplantation,

The reference IND for this NDA is IND 55,322 (FK-463).

Fujisawa submitted NDA 21-506 as a Common Technical Document (CTD) in an electronic format. In the April 29, 2002 cover letter, Fujisawa requested a priority review for NDA 21-506.

Attendees:

Mark Goldberger, M.D., M.P.H.	Office Director, Office of Drug Evaluation IV, HFD-104
David Roeder, M.S.	Associate Director of Regulatory Affairs, ODE IV, HFD-104
Renata Albrecht, M.D.	Actin Division Director, HFD-590
Marc W. Cavaille-Coll, M.D., Ph.D.	Team Leader/Medical Officer, HFD-590
Epokima Ibia, M.D., M.P.H.	Medical Officer, HFD-590
Robert Shibuya, M.D.	Medical Officer/DSI, HFD-47
Kalavati Suvarna, Ph.D.	Microbiologist, HFD-590
Shukal Bala, Ph.D.	Team Leader/Microbiology, HFD-590
Qian Li, Ph.D.	Statistician, HFD-725
Karen Higgins, Sc.D.	Team Leader/Statistics, HFD-725
Mark Seggel, Ph.D.	Chemist, HFD-590
Norman Schmuff, Ph.D.	Team Leader/Chemistry, HFD-590
Joette Meyer, Pharm.D.	Clinical Pharmacology & Biopharmaceutics Reviewer, HFD-880
Barbara Davit, Ph.D.	Clinical Pharmacology & Biopharmaceutics/Team Leader HFD-880
Owen McMaster, Ph.D.	Pharmacologist/Toxicologist, HFD-590
Kenneth Hastings, Ph.D.	Pharmacology/Toxicology/Team Leader, HFD-590
Ellen Frank, R.Ph.	Chief, Project Management Staff, HFD-590
Diana Willard	Regulatory Project Manager, HFD-590

Assigned Reviewers:

Discipline	**Reviewer**
Clinical	Ekopima Ibia, M.D., M.P.H.
Statistics	Qian Li, Ph.D.
PharmacologyToxicology	Owen McMaster, Ph.D.
Chemistry	Mark Seggel, Ph.D.
Environmental Assessment (if needed):	Nancy Sager, Ph.D. Florian Zielinshi, Ph.D.
Clinical Pharmacology & Biopharmaceutics	Joette Meyer, Pharm.D.
Microbiology, sterility:	
Microbiology/clinical	Linda Gosey
DSI	Robert Shibuya, M.D.
Project Manager	Yoon Kong, Pharm.D.
Other Consults: DDMAC	James Rogers, Pharm.D.
ODS (Tradename)	

- **Per reviewers, all parts in English, or English translation?** **YES__X__** NO___

Fileability:

Clinical:	**File __X__**	Refuse to file _____
Clinical site inspection needed:	**YES__X__**	NO_____
Microbiology (efficacy)	**File__X__**	Refuse to file_____
Statistical	**File __X__**	Refuse to file _____
Biopharmaceutics	**File __X__**	Refuse to file _____
Biopharm. inspection Needed:	YES_____	**NO __X__**
Pharmacology	**File __X__**	Refuse to file _____

Chemistry **File** ___X___ Refuse to file _____
Establishment(s) ready for inspection? **YES**__X__ NO____

Discussion

During the Filing Meeting, a decision was made to separate the indications into separate NDAs to reflect the review status of the different indications. The NDA numbers, the indication for each application, and the priority review status are as follows:

NDA Number	Indication	Review Status
21-506	prophylaxis of fungal infections in patients undergoing hematopoietic stem cell transplantation	priority

Regulatory Conclusions

__X__ **The applications, on their face, appear to be well organized and indexed. The applications appear to be suitable for filing.**

_____ The application is unsuitable for filing. Explain why:

_____
Diana Willard, Regulatory Project Manager, HFD-590 for
Yoon Kong, Regulatory Project Manager

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

/s/

Yoon Kong
7/15/02 01:22:34 PM

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8985 / Telefax (847) 317-7286

Fujisawa

April 29, 2002

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

Re: NDA #21-506
— (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 — (micafungin sodium) FOR INJECTION, — 50 mg.

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 3.5 gigabytes) and has been confirmed to be virus-free by Norton Antivirus software (Version 7.0). A detailed roadmap of the electronic submission is provided in **Attachment 1**.

At the request of the Division, some sections of the NDA are being provided as desk copies (i.e., hard copy format). The desk copies were printed from the electronic archive "pdf" files and, therefore, are identical to the electronic archive copies. A detailed description of those portions of the NDA submission that are provided as desk copies can be found in **Attachment 2** of this cover letter.

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 also provided in **Attachment 2**. The CTD roadmap serves as the table of contents for the desk copy submission.

Included as **Attachment 3** and **4** of this cover letter are the relevant Patent Information (Section 13) and Patent Certification (Section 14) for micafungin sodium drug substance.

Provided as **Attachment 5** and **6** 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 7** and the Financial Disclosure Information (Section 19) is included as **Attachment 8**.

Chemistry, Manufacturing and Controls administrative information is located in **Attachment 9** of the cover letter. The following information has been included:

- DMF Authorization Letter for (DMF #
- DMF Authorization Letter for (DMF
- cGMP Certification for Takaoka Manufacturing Facility
- Environmental Assessment – Request for Categorical Exclusion
- Stability Commitment for Drug Product
- Certificate of Quality Assurance for CMC Documents in NDA

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.

This submission supports the safety and efficacy of — (micafungin sodium) FOR INJECTION for the following indications:

- prophylaxis of — in patients undergoing hematopoietic stem cell transplantation.
-
-

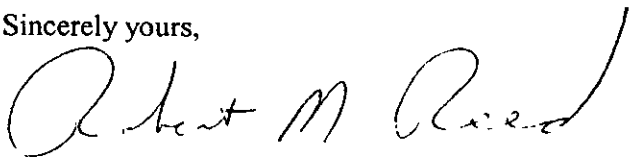
Based on the data presented in this submission, FHI believes — (micafungin sodium) FOR INJECTION is as safe as, and potentially more effective than, fluconazole for the prophylaxis of — n patients undergoing hematopoietic stem cell transplantation. —

— (micafungin sodium) FOR INJECTION is effective as a single agent and in combination with other antifungal agents and can be safely used regardless of age, race, gender, underlying disease, or use of concomitant medication in a diverse patient population.

Based on the efficacy of — in comparison to fluconazole along with the medical need for safer alternatives for the treatment of — we believe that a "Priority Review" is warranted.

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 Jerry D. Johnson, Ph.D. at **847/317-8898**.

Sincerely yours,



Robert M. Reed

Associate Director, Regulatory Affairs

cc: Yoon Kong

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

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

2. TELEPHONE NUMBER *(Include Area Code)*

(847) 317-8872

3. PRODUCT NAME

— .nicafungin sodium) for Injection

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N 21-506

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ 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:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4327

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ 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.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(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

and

Food and Drug Administration
CDER, HFD-94
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	DATE
[signature]	Senior Director, Regulatory Affairs	4/23/02

FORM FDA 3397 (4/01)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):
ODS

FROM: **Qian Li/Karen Higgins/Yoon Kong**
HFD-590 (Division of Special Pathogen and Immunologic Drug Products)

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
June 20, 2002		**21506**	**NDA**	**April 30, 2002**

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
(micafungin)		**Anti-Fungal**	**September 16, 2002**

NAME OF FIRM: **Fujisawa Healthcare Inc. (FHI)**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

Electronic NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This NDA, recently submitted to the Division, contains two historically controlled, based on literature review, studies for the indications of [redacted]. We would like the following questions answered:

1. Have the usual biases associated with using a historical control been adequately addressed in this submission?

2. Are the study populations in studies 98-0-046 and 98-0-047 and their respective historical controls based on

literature review comparable? What conclusions can be drawn regarding efficacy in these two indications? The Division appreciates ODS's willingness to assist us in analyzing these historically controlled studies. An epidemiologist's perspective would greatly enhance our ability to interpret the data. Should ODS's epidemiologist have any specific questions, please don't hesitate to contact:

Qian Li (Statistician Reviewer) 301-827-2204
Karen Higgins (Statistics Team Leader) 301-827-2171
Ekopimo Ibia (Medical Officer reviewer) 301-827-2365
Marc Cavaille-Coll (Medical Officer Team Leader) 301-827-2414

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): **E-Mail**
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Appears This Way
On Original

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

/s/

Leo Chan
6/20/02 03:43:58 PM

Fujisawa Healthcare, Inc. CHECK NO. 611659

VENDOR NUMBER	VENDOR NAME		CHECK DATE	CHECK NUMBER
210113	FOOD & DRUG ADMINISTRATIO	FDA (360909)	4/19/02	611659

MEMO INFORMATION	INVOICE IDENTIFICATION	INVOICE DATE	INVOICE AMOUNT	TERMS DISCOUNT	AMOUNT PAID
NDA 21-506 ID# 4327	CR45377	4/18/02	313320.00	.00	313320.00
					313320.00

Fujisawa Healthcare, Inc.
PARKWAY NORTH CENTER
THREE PARKWAY NORTH
DEERFIELD, ILLINOIS 60015-2548

70-2328
719

611659

PAY THREE HUNDRED THIRTEEN THOUSAND THREE HUNDRED TWENTY AND 00/100

DATE 4/19/02

PAY EXACTLY $313,320.00

TO THE ORDER OF
FOOD & DRUG ADMINISTRATIO
FDA (360909)
MELLON CLIENT SERV CTR
ROOM 670, 500 ROSS STREET
PITTSBURGH PA 15262-0001

Bank of America Illinois
Commercial Disbursement Account
Northbrook, IL

K. Fukumoto
Kyoko F. Ford
TWO SIGNATURES REQUIRED OVER $25,000

⑈611659⑈ ⑆071923284⑆ 87654⑈63238⑈