CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-506

CHEMISTRY REVIEW(S)

NDA 21-506
NDA 21-754

MYCAMINE™ (micafungin sodium) For Injection

Fujisawa Healthcare, Inc.

Mark R. Seggel
Division of Special Pathogen and Immunologic
Drug Products, HFD-590

Table of Contents

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Chemistry Review Data Sheet

1. NDA 21-506
   NDA 21-754

2. REVIEW #: 2

3. REVIEW DATE: 28-FEB-2005

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA 21-506	29-APR-2002
BC	29-AUG-2002
BC	03-SEP-2002
BC	05-SEP-2002
BC	27-SEP-2002
BL	19-NOV-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 21-754	23-APR-2004
NDA 21-506 / AZ	24-AUG-2004
NDA 21-506 / BC	20-OCT-2004
NDA 21-754 / BC	20-OCT-2004
NDA 21-506 / BC	03-FEB-2005 (Patent info.)
NDA 21-754 / BC	03-FEB-2005 (Patent info.)

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name: Fujisawa Healthcare, Inc.

Address: Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548

Representative: Robert M. Reed
Associate Director, Regulatory Affairs

Telephone: 847-317-8985

Telefax: 847-317-7286

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MYCAMINE
b) Non-Proprietary Name (JPN, INN): micafungin sodium
c) Non-Proprietary Name (USAN): micafungin sodium
d) Code Name/#: FK463, FR179463
e) Chem. Type/Submission Priority:
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: systemic antifungal

11. DOSAGE FORM: lyophilized powder for injection

12. STRENGTH/POTENCY: 50-mg/vial

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: X Rx ___OTC

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

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Systematic Chemical Names:

Sodium 5-[(1S,2S)-2-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate (IUPAC)

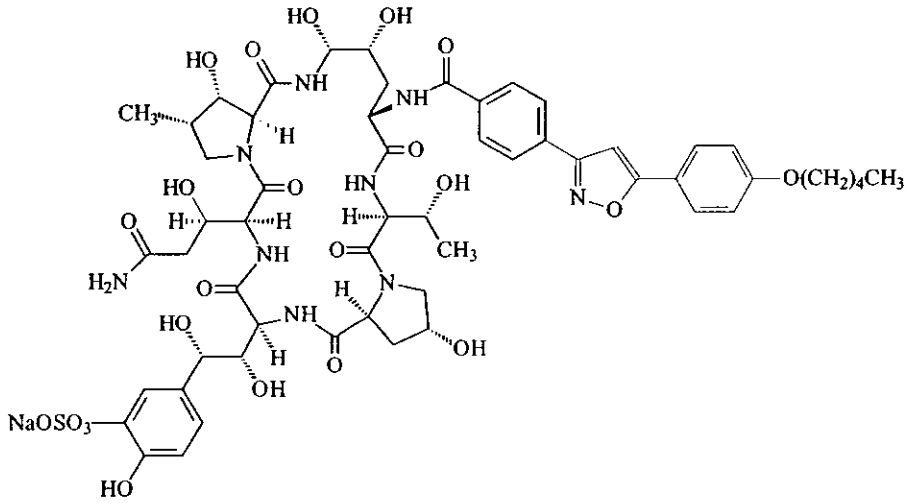
(*4*R,*5*R)-4,5-dihydroxy-N^2 -[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]-benzoyl]-L-ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl-(*4*S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)-phenyl]-L-threonyl-(*3*R)-3-hydroxy-L-glutaminyl-(*3*S,*4*S)- 3-hydroxy-4-methyl-L-proline cyclic(6→1)-peptide

Nomenclature per 'Statement on a Nonproprietary Name Adopted by the USAN Council', July 30, 2003:

Pneumocandin A0, l-[(4R,5R)-4,5-dikydroxy-N^2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt

5-[(1S,2S)-2-[(2R,6S,9S,11R,12R,14aS,15S,16S,20S,23S,25aS)-20-[(1R)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(1R)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25- hexaoxo-9-[[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]benzoyl]amino]-tetracosahydro-1H-dipyrrolo-[2,1-c:2',1'-l][1,4,7,10,13,16]bexaazacycolohenicosin-23-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sodium sulfate

Molecular Formula: $C_{56}H_{70}N_9NaO_{23}S$
Molecular Weight: 1292.27
CAS Registry: 208538-73-2 (sodium salt) [previously reported as 179165-70-9]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]	[redacted]	3	Adequate	27-NOV-2001	
[redacted]	2	Fujisawa	Drug Substance CMC	1	Adequate as amended	29-JAN-2003, 28-FEB-2005	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND Application, Amendments and Reports	IND 55,322	Fujisawa Healthcare, Inc. IND for FK463

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable Acceptable	07-JAN-2003 14-FEB-2005	S. Adams, HFD-324 S. Adams, HFD-324
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	Philadelphia recommends adjustments to — — methodology. St. Louis pending.	11-AUG-2003	E. Murphy, HFR-CE160
DMETS	— unacceptable; other comments to FHI. Mycamine: acceptable	09/AUG/2002 20/SEP/2002	Hye-Joo Kim, Pharm.D., HFD-420 Mahmud, R.Ph., HFD-420
EA	Categorical exclusion acceptable		M. Seggel
Microbiology	Approvable pending resolution of product quality micro deficiencies Approval recommended	29-JAN-2003 23-FEB-2005	B. Riley B. Riley

The Chemistry Review for NDA 21-506 and NDA 21-754

The Executive Summary

Note: For administrative purposes, NDA numbers 21-506, — were assigned to each of the proposed indications originally submitted in NDA 21-506. NDA 21-506 was issued an AE letter based on clinical deficiencies. — — An application, NDA 21-754, for a new indication for Mycamine was submitted on April 23, 2004. This application cross-references NDA 21-506 for non indication-specific information, including an update to the CMC section. Application NDA 21-506 was resubmitted on August 24, 2004.

Reference Number	Indication
NDA 21-506	Prophylaxis of — , in patients undergoing hematopoietic stem cell transplantation. APPROVABLE 29-JAN-2003
Resubmission	Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.
NDA —	
NDA —	
NDA 21-754	

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective the New Drug Applications are recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

MYCAMINE (micafungin sodium) For Injection is a sterile, lyophilized powder for reconstitution and intravenous infusion, which is proposed for the [redacted] The formulation is relatively straightforward as is the manufacturing process. During formulation development studies, it was determined that the [redacted], a relatively stable drug product is produced. The drug product consists of 50 mg of the drug substance, 200 mg of lactose [redacted] and citric acid and/or sodium hydroxide to adjust the pH. [redacted] product was described in original NDA 21-506, but will not be marketed at this time under NDA 21-506 or NDA 21-754. The components are [redacted] and filled into [redacted] glass vials. [redacted] The product is formulated with [redacted] overage to compensate for unwithdrawable material due to foaming upon reconstitution.

Product quality is controlled with several tests including [redacted]

The stability of the drug product has been assessed under long-term storage conditions (25°C/60% RH), accelerated conditions (40°C/75% RH) and stress conditions. The primary stability data were obtained on batches of drug product manufactured by [redacted] Subsequent to the manufacture of the primary stability batches, product manufacturing was transferred back to Fujisawa. Additional long-term and accelerated site-specific data were submitted in support of this product manufacturing operation. The product is stable when stored at 25°C/60% RH and protected from light. Because micafungin sodium is light sensitive, the drug product vials are wrapped with an UV-blocking [redacted] film, [redacted] tainer label. The stability of the reconstituted solution has also been evaluated. The transfusion bag containing the reconstituted infusion solution must also be protected from light.

Micafungin sodium (FK463) is a semi-synthetic lipopeptide (echinocandin) consisting of cyclic hexapeptide with a fatty acyl side chain. It is structurally related to the approved antifungal agent caspofungin acetate (Cancidas®; Merck). Presumably micafungin exerts its antifungal activity through inhibition of the synthesis of 1,3-β-D-

glucan, an integral component of the fungal cell wall. FK463 is synthesized by the chemical modification of a fermentation product produced by *Coleophoma empetri* F-11899 (— . FK463 is amorphous solid that is freely soluble in water, slightly soluble in — and insoluble in ether. The drug substance is hygroscopic. It — under exposure to light, so all formulations must be protected from light. The chemistry, manufacturing and controls of FK463 is detailed in Fujisawa Pharmaceuticals Co., Ltd.'s Type II Drug Master File — , although much of that information has been provided in the NDA as well.

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

The drug product may be stored for 36 months at controlled room temperature when protected from light. For the proposed indications, the adult dose is 50 - 150 mg/day. The current clinical studies do not support pediatric dosing. The content of the 50-mg vials is dissolved with 5 mL of 0.9% Sodium Chloride for Injection or 5% Dextrose for Injection. To minimize excessive foaming upon reconstitution, the product should be gently swirled, and not vigorously shaken. It has been determined that with the — overfill the amount of solution that can typically be withdrawn contains 50 mg micafungin sodium, thus supporting the use of an overage. The solution is aseptically transferred to an infusion solution. Because of the light-sensitivity of FK463, the diluted infusion solution should be protected with a light-resistant resistant cover.

C. Basis for Approvability or Not-Approval Recommendation

Original NDA 21-506 was found approvable from the chemist's perspective. The revised and updated application(s) remain approvable from the chemist's perspective.

The chemistry, manufacturing and controls for the drug substance and drug product is generally well documented. Fujisawa's drug substance and drug product manufacturing facilities all have acceptable cGMP status based on recent pre-approval inspections and profile updates. The chemistry of FK463 and of the formulated drug product have been thoroughly characterized. The manufacturing processes have been adequately defined. The product specification provides further assurance of the identity, quality, purity and potency of the product. Acceptance criteria for related substances have tightened at our request. A second — test (— —) has been added as requested.

A — expiration dating period was supported in original NDA 21-506. A longer expiration dating period of 36 months for drug product stored at controlled room temperature and protected from light is supported by the updated full shelf-life (— months at 25°C/60% RH) and accelerated (— at 40°C/75% RH) data obtained on the primary stability batches, and by the available site-specific stability data.

Analytical methods validation by two FDA laboratories was requested. Validation has only been completed by one laboratory, however this is not an approvability issue. The applicant's continued cooperation to resolve any problems that may be identified is expected.

Several issues identified in the OPS microbiology review of the original application have been satisfactorily addressed by the applicant.

From the clinical perspective, NDA 21-506 and NDA 21-754 are approvable. Labeling negotiations have been completed. The originally proposed trademark, was found unacceptable by DMETS. The alternative trademark MYCAMINE was found acceptable. Container and carton labels have been revised. The nonproprietary name, micafungin sodium, has been adopted as JPN and INN. At our request, Fujisawa submitted the name to the USAN Council. They have recently adopted micafungin sodium as the USAN name.

III. Administrative

A. Reviewer's Signature

{see appended electronic signature page}

B. Endorsement Block

Chemist Name/Date (draft): Mark Seggel, 28-FEB-2005
Chemistry Team Leader Name/Date:
DNDCIII Division Director Name/Date:
Project Manager Name/Date:

C. CC Block

34 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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/s/

Mark Seggel
3/3/05 04:05:42 PM
CHEMIST

Norman Schmuff
3/7/05 11:11:09 AM
CHEMIST

NDA 21-506

MYCAMINE® (micafungin sodium) For Injection

Fujisawa Healthcare, Inc.

Mark R. Seggel
Division of Special Pathogen and Immunologic
Drug Products, HFD-590

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 21-506

2. REVIEW #: 1

3. REVIEW DATE: 29-JAN-2003

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	29-APR-2002
BC	29-AUG-2002
BC	03-SEP-2002
BC	05-SEP-2002
BC	27-SEP-2002
BL	19-NOV-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Fujisawa Healthcare, Inc.

Address: Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548

Representative: Robert M. Reed
Associate Director, Regulatory Affairs

Executive Summary Section

Telephone: 847-317-8985

Telefax: 847-317-7286

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MYCAMINE
b) Non-Proprietary Name (JPN, INN): micafungin sodium
c) Non-Proprietary Name (USAN): *pending*
d) Code Name/#: FK463, FR179463
e) Chem. Type/Submission Priority: N21-506

- Chem. Type: 1 / 6 / 6
- Submission Priority: P / S / S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: systemic antifungal

11. DOSAGE FORM: lyophilized powder for injection

12. STRENGTH/POTENCY: – 50-mg/vial

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

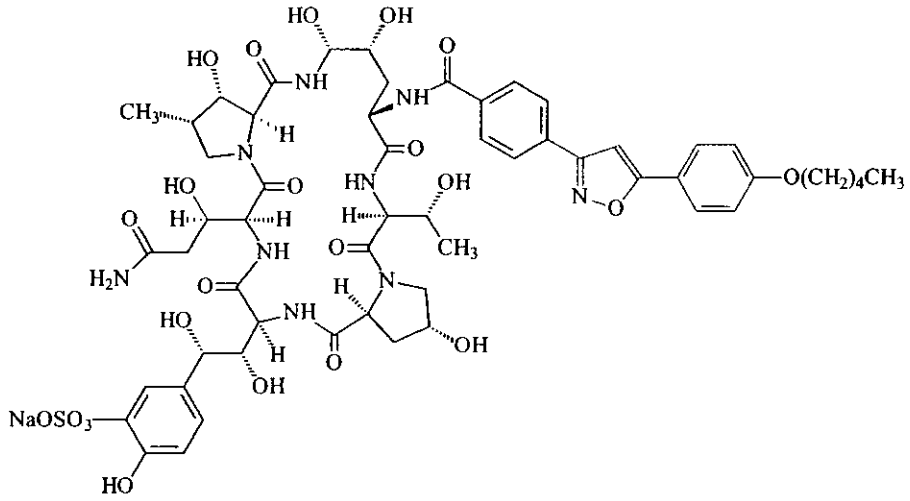
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Systematic Chemical Names:

Sodium 5-[(1S,2S)-2-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate (IUPAC)

(*4*R,*5*R)-4,5-dihydroxy-N^2 -[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]-benzoyl]-L-ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl-(*4*S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)-phenyl]-L-threonyl-(*3*R)-3-hydroxy-L-glutaminyl-(*3*S,*4*S)- 3-hydroxy-4-methyl-L-proline cyclic(6→1)-peptide

Molecular Formula: $C_{56}H_{70}N_9NaO_{23}S$
Molecular Weight: 1292.27
CAS Registry: 208538-73-2 (sodium salt) [previously reported as 179165-70-9]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	3	/	/	3	Adequate	27-NOV-2001	
—	2	Fujisawa	Drug Substance CMC	1	Adequate as amended	29-JAN-2003	

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
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3 - Reviewed previously and no revision since last review
4 - Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND Application, Amendments and Reports	IND 55,322	Fujisawa Healthcare, Inc. IND for FK463

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	07-JAN-2003	S. Adams, HFD-324
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	pending		
DMETS	unacceptable; other comments to FHI. Mycamine: acceptable	09/AUG/2002 20/SEP/2002	Hye-Joo Kim, Pharm.D., HFD-420 Mahmud, R.Ph., HFD-420
EA	Categorical exclusion acceptable		M. Seggel
Microbiology	pending as of 1/29/03		

The Chemistry Review for NDA 21-506, NDA [redacted] and NDA [redacted]

The Executive Summary

Administrative Note: For administrative purposes, NDA numbers as listed below were assigned to each of the proposed indications originally submitted in NDA 21-506. Once a final action is taken on NDA [redacted], these NDA numbers will be retired and all future correspondence will refer to NDA 21-506.

Reference Number	Indication
NDA 21-506	Prophylaxis of [redacted] is in patients undergoing hematopoietic stem cell transplantation

[redacted]

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective these New Drug Applications are recommended for approval.

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

None at this time.

II. Summary of Chemistry Assessments

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

MYCAMINE (micafungin sodium) For Injection is a sterile, lyophilized powder for reconstitution and intravenous infusion, which is proposed for the [redacted]

The formulation is relatively straightforward as is the manufacturing process. During formulation development studies, it was determined that , a relatively stable drug product is produced. The drug product consists of 50 mg of the drug substance, 200 mg of lactose and citric acid and/or sodium hydroxide to adjust the pH. The components are and filled into glass vials. . The product is formulated with a overage to compensate for unwithdrawable material due to foaming upon reconstitution.

Product quality is controlled with several tests including

The stability of the drug product has been assessed under long-term storage conditions (25°C/60% RH), accelerated conditions (40°C/75% RH) and . The primary stability data were obtained on batches of drug product manufactured by Subsequent to the manufacture of the primary stability batches, product manufacturing was transferred back to Fujisawa. Additional long-term and accelerated site-specific data were submitted in support of this product manufacturing operation. The product is stable when stored at 25°C/60% RH and protected from light. Because FK463 is light sensitive, the drug product vials are wrapped with an UV-blocking film. The stability of the reconstituted solution has also been evaluated. The transfusion bag containing the reconstituted infusion solution must also be protected from light.

Micafungin sodium (FK463) is a semi-synthetic lipopeptide (echinocandin) consisting of cyclic hexapeptide with a fatty acyl side chain. It is structurally related to the approved antifungal agent caspofungin acetate (Cancidas®; Merck). Presumably micafungin exerts its antifungal activity through inhibition of the synthesis of 1,3-β-D-glucan, an integral component of the fungal cell wall. FK463 is synthesized by the chemical modification of a fermentation product produced by *Coleophoma empetri* F-11899; . FK463 is amorphous solid that is freely soluble in water, slightly soluble in , and insoluble in ether. The drug substance is hygroscopic. It under exposure to light, so all formulations must be protected from light. The chemistry, manufacturing and controls of FK463 is detailed in Fujisawa Pharmaceuticals Co., Ltd.'s Type II Drug Master File , although much of that information has been provided in the NDA as well.

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

The drug product may be stored for at controlled room temperature when protected from light. For the proposed indications, the adult dose is 50 - 100 mg/day,

while in pediatric patients the dose is 1 - 2 mg/kg/day. The content of the — 50-mg vials is dissolved with 5 mL of 0.9% Sodium Chloride for Injection or 5% Dextrose for Injection. To minimize excessive foaming upon reconstitution, the product should be gently swirled, and not vigorously shaken. It has been determined that with the — overfill the amount of solution that can typically be withdrawn contains — 50 mg micafungin sodium, thus supporting the use of an overage. The solution is aseptically transferred to an infusion solution. Because of the light-sensitivity of FK463, the diluted infusion solution should be protected with a light-resistant resistant cover.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing and controls for the drug substance and drug product is generally well documented. Fujisawa's drug substance and drug product manufacturing facilities all have acceptable cGMP status based on recent pre-approval inspections. The chemistry of FK463 and of the formulated drug product have been thoroughly characterized. The manufacturing processes have been adequately defined. The product specification provides further assurance of the identity, quality, purity and potency of the product. However acceptance criteria for related substances should be tightened in accordance with the available release and stability data. A second — test, e.g., — should be added.

The proposed — expiration dating period for drug product stored at controlled room temperature and protected from light is supported by the full shelf-life — at 25°C/60% RH) and accelerated (— , at 40°C/75% RH) data obtained on the primary stability batches, and by the available site-specific stability data.

Analytical methods validation by two FDA laboratories was requested. Validation has not been completed at this time, however this is not an approvability issue. The applicant's continued cooperation to resolve any problems that may be identified is expected.

Any issues related to sterility assurance that are identified in the OPS microbiology review should also be addressed by the applicant.

From the clinical perspective, NDA 21-506 is approvable while NDAs — are not approvable at this time. Labeling negotiations have not been initiated at this time because the major clinical deficiencies have not yet been resolved. The originally proposed trademark — , was found unacceptable by DMETS. The new trademark MYCAMINE was found acceptable. Container and carton labels have been revised accordingly. The nonproprietary name, micafungin sodium, has been adopted as JPN and INN. USAN approval of this name has not yet been requested by Fujisawa. Fujisawa should do so as soon as possible.

III. Administrative

A. Reviewer's Signature

{see appended electronic signature page}

B. Endorsement Block

Chemist Name/Date (draft): Mark Seggel, 29-JAN-2003
Chemistry Team Leader Name/Date:
DNDCIII Division Director Name/Date:
Project Manager Name/Date:

C. CC Block

78 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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

/s/

Mark Seggel
7/22/03 01:06:33 PM
CHEMIST
N21506, N21533 and N21534

Norman Schmuff
7/22/03 02:07:47 PM
CHEMIST

13 Page(s) Withheld

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

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