CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050740

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Consult #628 (HFD-530)

AMBISOME

amphotericin B liposome for injection

A review revealed one name which sounds like or looks like the proposed name:ambazone. Since ambazone is an INN name for a topical antiseptic, the Committee does not believe there is a significant potential for confusion involving these two names.

The Committee has no reason to find the proposed name unacceptable.

/S/

8/1/96, Chair

CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

NEXSTAR
Pharmaceuticals, Inc. 650 Cliffside Drive San Dimas, California 91773 Phone 909.394.4000 Fax 909.592.8530

The following patent information and certification are supplied in compliance with 21 CFR 314.50:

Patent Certification:

AmBisome (liposomal amphotericin B for Injection) and its constituent raw materials and intermediates are not protected by any U.S. or other patents, except as noted below.

Paragraph II Certification;

Amphotericin B, the active ingredient in AmBisome was protected under U.S. patent 2,908,611, issued to Owen Matheson Chemical Corporation. Patent 2,908,611 was issued October 13, 1959 and expired on October 13, 1976.

Stephen A. Campbell
Director, Regulatory Affairs

October 31, 1996
Date

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 50-740 SUPPL # _____

Trade Name AmBisome Generic Name (amphotericin B) liposome for injection

Applicant Name Fujisawa, USA HFD # 590

Approval Date If Known 11-Aug-97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?

   YES / ✔ / NO / __ /

   b) Is it an effectiveness supplement?

   YES / __ / NO / ✔ /

   If yes, what type? (SE1, SE2, etc.)

   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 / ✔ / 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.

_____

_____

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:

_____

_____

Revised 5-90
cc: Orig NDA Div File HFD-85

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /__/ NO /_✔_/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strengths, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /_✔_/* NO /__/ *for "second-line" treatment **only**

If yes, NDA # 50-724 Drug Name Abelcet
NDA # 50-729 Drug Name Ampotec

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

yes /__/ NO /_✔_/

IF THE ANSWER TO QUESTION 3 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 /__/

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

NDA # 50-724 Abelcet

NDA # 50-729 Amphotec

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 /__/ N/A

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. 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?

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 investigations, 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 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 FDA 1571 as the sponsor?

Investigation #1

IND YES /_✔_/ NO /___/ Explain: _94-0-002__

_____

Investigation #2

IND YES /_✔_/ NO /___/ Explain: ___104-12__

_____

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 _____ N/A

_____ _____

_____ _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____ N/A

_____ _____

_____ _____

(c) Not withstanding 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: _____

_____

/S/

Signature

11-Aug-97

Date

Title: Regulatory Management Officer

APPEARS THIS WAY ON ORIGINAL

/S/

Signature of Division Director

11-Aug-97

Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-740 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-590 Trade and generic names/dosage form: AmBisome (amphotericin B) liposome for injection Action: **AP** AE NA

Applicant Fujisawa, USA Therapeutic Class Anti-fungal agent/systemic

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate N/A inadequate __

Indication in this application Empirical therapy, Visceral Leishmaniasis, Candida/Aspergillus/Cryptoccocus infections when amphotericn B deoxycholate use is precluded (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

✓ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

Labeling is adequate for infants, children, and adolescents but not neonates.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/

Regulatory Management Officer — 7 Aug 97

Signature of Preparer and Title — Date

cc: Orig **NDA**/PLA/PMA # 50-740
HFD-590 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 8/10/97)

Debarment Certification

Dear Dr. Freeman:

Fujisawa USA, Incorporated certifies that it did not use in any capacity the services of any person debarred under sections 306 (a) or (b) in connection with this New Drug Application.

By: Jerry D. Johnson, Ph.D
Vice President
Regulatory Affairs, and R&D
QA/QC

November 3, 1996
Date

APPEARS THIS WAY
ON ORIGINAL

NEXSTAR
Pharmaceuticals, Inc. 650 Cliffside Drive San Dimas, California 91773 Phone 909.394.4000 Fax 909.592.8530

October 18, 1996

Fujisawa USA
NDA file: 50,740

Subject: Debarment Certification

NeXstar Pharmaceuticals, Inc.(NeXstar) certifies that NeXstar did not use in any capacity, the services of any person debarred under sections 306 (a) or (b) in connection with this New Drug Application.

In addition, NeXstar certifies that the U.S. contractor providing services used in preparation of reports contained in this New Drug Application has, as part of the written agreement between the companies, provided similar certification, which is on file at NeXstar.

By: Stephen A. Campbell
Director, Regulatory Affairs
NeXstar Pharmaceuticals, Inc.

10/18/96
Date

APPEARS THIS WAY
ON ORIGINAL

NDA 50-740

JAN - 7 1997

Fujisawa USA, Inc.
Attn: Robert Reed, Manager
Regulatory Affairs
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

Dear Mr. Reed:

Please refer to your new drug application (NDA) submitted on November 8, 1996, for AmBisome for Injection (liposomal amphotericin B).

In addition, please refer to your request for a meeting with this Division to discuss the organization and documentation of your NDA submission during a post-NDA conference. Please also refer to the December 3, 1996, agreement with this Division to have a teleconference instead of a face-to-face meeting.

Attached is a summary of the December 20, 1996, teleconference held to discuss your NDA.

In accordance with the CDER Manual of Policy and Procedure (MAPP 4512.1), we are providing you with a summary of the December 20, 1996, teleconference. Please note any significant discrepancies in your understanding of the meeting outcome as reflected in the minutes by submitting a letter to the NDA file.

If you have any questions, please contact Ms. Ellen Frank, Project Manager, at (301) 827-2335.

Sincerely yours,

/S/

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment

NDA 50-740

MAR 10 1997

Fujisawa, USA
Attention: Robert Reed
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Reed:

Please refer to your pending November 12, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AmBisome (amphotericin B liposome) for injection.

To complete our review of the statistical, clinical and pharmacology/toxicology sections of your submission, we request the following:

1. Please submit corrected data sets LAB410.SD2, LAB413.SD2 and LAB414.SD2 on disk. These should be accompanied by a list of the changes made and the supporting case report form pages for changes other than decimal point placement.

2. When analyses are performed with the corrected data, please compute two-sided 95% confidence intervals for the difference in success rates between AmBisome and control. The confidence intervals should employ the Cochran-Mantel-Haenszel method, stratifying by site in trials 104-13 and 104-14. If more than one definition of success is used, then this should be done for each separate definition.

3. Please submit revised response data sets on disk for trials 104-14 and 104-13 (similar to the one prepared for trial 104-10).

4. Please provide a detailed description of the algorithm used to generate the revised response data sets.

5. Please submit case report forms related to outcome for the subjects in trial 104-10 who were randomized as belonging to the CM stratum but who may be eligible for analysis as part of stratum FUO.

6. Please submit case report forms for all patients that experienced emergent fungal events (both systemic infections and colonizations) in trials 104-10 and 104-14. We will advise you which forms we would like from trial 104-13.

7. Please submit case report forms for the randomly generated list of patients requested by FDA via facsimile February 19, 1997.

8. Please submit a summary of study 94-0-002 including analyses recommended by FDA via facsimile February 19, 1997. Please note that the Division may identify this as a major amendment and extend the review clock by ninety days.

9. Please submit final study reports for trials 104-05 and 105-09.

10. Please submit the pharmacology/toxicology information on disk. The format used for the ninety-one day study is acceptable.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ellen C. Frank, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

/S/ 3/31/97

Donna J. Freeman, M.D.
Acting Director
Division of Anti-Viral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 50-740

APR - 8 1997

Fujisawa, USA
Attention: Robert Reed
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Reed:

We acknowledge receipt on March 31, 1997 of your March 28, 1997 amendment to your new drug application for AmBisome (liposomal amphotericin B) injection.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is August 11, 1997.

If you have any questions, please contact Ellen C. Frank, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

/S/ 4-7-97

Donna J. Freeman, M.D.
Acting Director
Division of Anti-Viral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 10, 1996

Fujisawa USA, Inc.
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

Attention: Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs and Pharmacovigilance

Dear Dr. Johnson:

Reference is made to your orphan drug application of May 16, 1996 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of AmBisome® (liposomal amphotericin B) as an orphan drug

Also please be advised that if AmBisome® were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 827-0991.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-530/V.Kinsey NDA 50-740
HFD-85/M.A.Holovac
HF-35/OP
HF-35/chron
HF-35/P.Vaccari 12/10/96 dsg.996

APPEARS THIS WAY
ON ORIGINAL