

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-740/SE1-002

ADMINISTRATIVE DOCUMENTS



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.

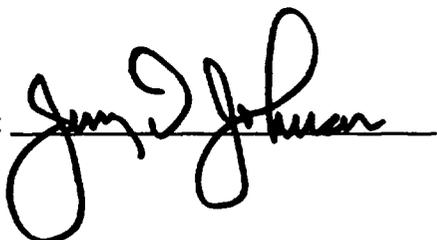
Stephen A. Campbell
Director, Regulatory Affairs

October 31, 1996
Date

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:

A handwritten signature in black ink, appearing to read "Jerry D. Johnson", written over a horizontal line.

Date:

29 June '99

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

The original NDA for AmBisome was submitted under section 507 of the Food, Drug, and Cosmetic Act. This efficacy supplement was submitted under 505(b)(1) and is subject the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997. As such, no exclusivity summary is needed for this supplement.



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Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

September 1, 1999

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

**Re: NDA 50-740, Supplement 2
AmBisome (amphotericin B) liposome for injection**

**REQUEST FOR A CATEGORICAL EXCLUSION OF THE REQUIREMENT TO
SUBMIT AN ENVIRONMENTAL ASSESSMENT**

Dear Dr. Goldberger:

Please find attached a copy of the cross reference letter for the August 31, 1999 amendment to [redacted] for AmBisome for Injection in which [redacted] requests a categorical exclusion of the requirement to submit an environmental assessment for NDA 50-740 – Supplement 2.

This letter also certifies that the electronic submission is identical to the hard copies (desk copies) that were included with the July 6, 1999 submission.

Please feel free to contact me at 847/317-8985 or Jerry D. Johnson, Ph.D. at 847/317-8898 if you have any questions or concerns.

Sincerely yours,

Robert M. Reed
Assistant Director, Regulatory Affairs
cc: Matthew Bacho

*Acceptable.
See ED
6/16/2000*



MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

Date: October 21, 1998

To: Robert Reed
Regulatory Affairs

Address: Fujisawa, USA
Fax: (847) 317-7286
Phone: (847) 317-8985

From: Ellen C. Frank, R.Ph., Chief, Project Management Staff

Through: Marc Cavallé-Coll, M.D., Ph.D., Medical Team Leader
Joyce Korvick, M.D., Medical Officer
Nancy Silliman, Ph.D., Statistical Team Leader
Aloka Chakravarty, Ph.D., Statistical Reviewer

IND/NDA: [redacted] NDA 50-740
AmBisome® (amphotericin B) liposome for injection

Subject: Statistical analysis of protocol 94-0-013 ("A Randomized, Double-Blind, Comparative Trial of Two Doses of AmBisome vs. Amphotericin B, Followed by Fluconazole in the Treatment of Acute Cryptococcal Meningitis in AIDS Patients")

Please refer to your submission 149 dated April 21, 1998 and to your correspondence of September 30, 1998 regarding your "Draft Statistical Analysis Plan for Cryptococcal Meningitis Study" (including second version).

The following comments are provided via facsimile for your convenience:

1. The null hypothesis for this trial is "AmBisome is at least 20% worse than Amphotericin B" and the alternate hypothesis is "AmBisome is less than 20% worse than Amphotericin B." The delta of 20% might be reasonable because we may be willing to consider a drug with lower efficacy if it is less toxic than the standard therapy (Amphotericin B). However, based upon the severity and prevalence rate of this indication, a smaller delta would be more desirable and would lead to less ambiguous statistical inference. Given that it may not be practical to assume that the delta

could be satisfied in this case, the totality of the information will be considered and expert opinion from Advisory Committee members may be sought if results are borderline (i.e., if the lower bound of the confidence interval is below 15%).

2. The step-down approach in testing of hypothesis outlined in the protocol is acceptable. However, if no statistical difference is shown for the combined AmBisome arm (3mg/kg/day and 6 mg/kg/day) against Amphotericin B, it is expected that the individual test drug regimens will not be tested against the active control arm.
3. The second version of the analysis plan states "assuming the efficacy results of the two AmBisome dose groups are similar, the above testing procedure will be applied to the combined AmBisome group." Please clarify how you plan to determine whether the two arms are similar.
4. The sample size computation and the power calculation are based on one-sided tests with alpha of 0.05. Historically, we have used two-sided tests with alpha of 0.05 or one-sided with alpha of 0.025. If one-sided tests are indeed appropriate, the alpha should be set at 0.025. Please note that this is essentially the opinion voiced by Dr. Blackwelder, Workshop on Clinical Trial Design Issues on Liposomal Antifungal Agents, FDA, April 20, 1994, page 20.
5. The analysis plan states that if lower bound of the one-sided 95% CI is over -0.20, then AmBisome is not inferior to Amphotericin B. If the lower bound is over 0, superiority will be claimed. We find that a superiority claim on a one-sided test, without characterization of the upper bound of the confidence interval, will not be appropriate. A one-sided test was considered adequate only for a non-inferiority claim.
6. For treatment by center interaction, Breslow-Day chi-square at alpha of 0.10 is planned. Historically, we have used an alpha of 0.15 in these situations.
7. Your plan states "Mycological success at 10 weeks will be defined for the subset of patients completing the study therapy. For those without a week-10 culture result, both a negative culture prior to week 10 with no subsequent LP and a clinical success at week 10 are needed for a week-10 mycological success." This endpoint is acceptable to us with the addition of the following comment: Any patients who die during this period (2-10 weeks) should be counted as clinical failures regardless of the cause of death.

Please contact me at (301) 827-2127 if you wish to schedule a teleconference to discuss the above comments.

/s/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products

**Record of Teleconference****Date of Teleconference:** March 31, 1999**IND/NDA:** [redacted] NDA 50-740**Drug:** AmBisome® (amphotericin B liposome)**Sponsor/Applicant:** Fujisawa Healthcare, Inc.**Indication:** Antifungal**Subject:** Supplemental NDA to add a "first-line" cryptococcal meningitis indication**FDA Attendees, Titles, and Offices:** Joyce Korvick, M.D., Acting Medical Team Leader
Aloka Chakravarty, Ph.D., Statistical Reviewer
Ellen Frank, R.Ph., Chief, Project Management Staff**External Constituents and Titles:** Don Buell, Medical Director
Boyd Roloff, Biostatistician
James Sayre, Clinical
Robert Reed, Manager, Regulatory Affairs

Background: Protocol 94-0-013 ("A Randomized, Double-Blind, Comparative Trial of Two Doses of AmBisome® vs. Amphotericin B, Followed by Fluconazole in the Treatment of Acute Cryptococcal Meningitis in AIDS Patients") was submitted to the Division of Antiviral Drug Products on December 29, 1994. Comments were provided via teleconference on January 27 and April 14, 1995. An amended protocol incorporating DAVDP comments was submitted on June 29, 1995. NDA 50-740 was received on December 12, 1996. [redacted] NDA 50-740 were transferred to the Division of Special Pathogen and Immunologic Drug Products when the division was formed May 11, 1997. AmBisome® was approved August 11, 1997 for febrile neutropenia, for leishmaniasis and for second-line treatment of candidiasis, cryptococcus and aspergillus. Fujisawa contacted DSPIDP in late 1997 because enrollment for this trial had tapered off and they did not expect to meet the projected sample size. A teleconference was held January 23, 1998 between representatives of DSPIDP and Fujisawa. During this teleconference Fujisawa agreed to revise the statistical plan and share it with DSPIDP to provide comments prior to unblinding. Fujisawa submitted a revised statistical plan April 21, 1998 and a second revised plan September 30, 1998. DSPIDP provided comments via facsimile October 21, 1998. Fujisawa responded to these comments via facsimile October 31, 1998. A teleconference was held November 2, 1998 and a third revised plan was submitted December 3, 1998. Fujisawa was notified via telephone January 28, 1999 that the third revised plan had incorporated all DSPIDP advice and was acceptable.

Objectives/Issues: To discuss an upcoming Supplemental NDA (Efficacy Supplement) to add a "first-line" cryptococcal meningitis indication planned for Fall 1999 submission.

Discussion/Topics:

1. Fujisawa described the anticipated content/format of the sNDA which would include:
 - Information from European studies previously submitted in the original NDA

March 31, 1999

- Pivotal study 94-0-013 ("A Randomized, Double-Blind, Comparative Trial of Two Doses of AmBisome® vs. Amphotericin B, Followed by Fluconazole in the Treatment of Acute Cryptococcal Meningitis in AIDS Patients")
 - Integrated Summary of Safety including all studies
 - Integrated Summary of Efficacy including all studies
 - Electronic database (for each study, NOT integrated)
 - Clinical Microbiology (Section 7) including cryptococcus experience
 - Clinical Pharmacology (Section 6) including cerebrospinal fluid sample data.
2. DSPIDP noted that they are currently working with their first Electronic Regulatory Submissions (ERS). There have been a variety of problems including files that are too large to open. DSPIDP suggested that the review team looks at the ERS for the pending Supplemental Labeling Revision for AmBisome and then provides feedback to help Fujisawa prepare the ERS for this supplement.
 3. Fujisawa noted that they would also like to revise the AmBisome label to include information in the OVERDOSAGE section on adult and pediatric patients that have tolerated doses of up to 15 mg/kg/day and 10 mg/kg/day respectively. They will provide two clinical reports and two clinical pharmacology reports. They noted that they would like to submit these to the IND for AmBisome and cross-reference them in the supplement. DSPIDP noted that this would be acceptable, but emphasized that the material should be available when the supplement is first submitted not when the 120-day safety update is provided.
 4. Fujisawa reported that they are working on other Phase 4 commitments that should be completed toward the end of the year.
 5. DSPIDP noted safety reports of back pain/fever/chills and inquired whether there had been an increase. Fujisawa reported that these reports had come from [redacted] site and one other site during a voriconazole vs. AmBisome study. Fujisawa sent the batches back to [redacted] to have them analyzed and no problem was found. They also sent a team to [redacted] to investigate. Fujisawa noted that they had not seen a problem in Study 94-0-013 (cryptococcal meningitis) or 97-0-034 (AmBisome vs. Abelcet) or in postmarketing. DSPIDP requested that Fujisawa carefully observe this Adverse Event and write a brief summary of their findings. DSPIDP also suggested that they obtain copies of spontaneous reports through MedWatch's program for sponsors.

Outcome/Action:

1. The review team will look at the ERS for the pending Supplemental Labeling Revision for AmBisome and then provide feedback to help Fujisawa prepare the ERS for this supplement.
2. Fujisawa will carefully observe reports of back pain/fever/chills and write a brief summary of their findings.



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: June 6, 2000
TO: Robert Reed
Regulatory Affairs
ADDRESS: Fujisawa Healthcare
Parkway North Center, Three Parkway North
Deerfield, IL 60015-2548
Phone (847) 317-8985
Fax (847) 317-7286
FROM: Leo Chan, Regulatory Project Manager
NDA/DRUG: 50-740, SE1-002 AmBisome[®] (amphotericin B) liposome for injection
SUBJECT: Proposed Labeling Changes

We have reviewed your May 22, 2000 labeling submission, submitted on May 26, 2000, and we have provided the following comments:

1. INDICATIONS AND USAGE:

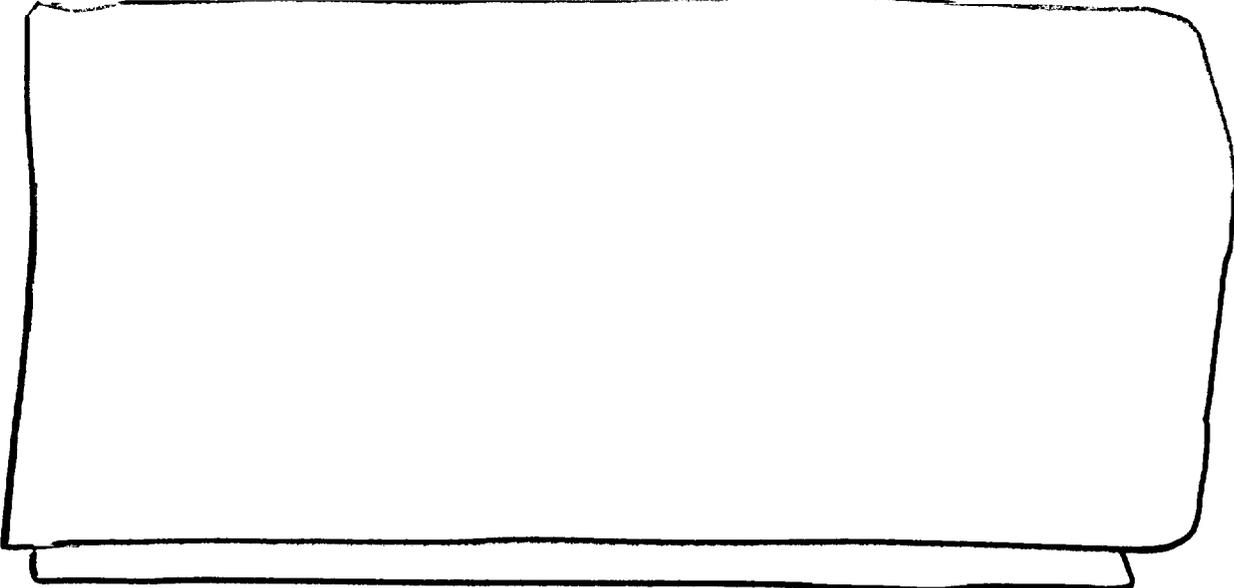
- On page 6, line 22, the FDA suggests that the following indication sentence reads:

Treatment of Cryptococcal Meningitis in HIV infected patients (see **DESCRIPTION OF CLINICAL STUDIES**).

2. DESCRIPTION OF CLINICAL STUDIES:

- On page 7, line 12, the FDA notes that the number of pediatric and adult patients should be 302 and 978 respectively.
- On page 9 line 21, to page 10 line 6, the FDA suggests that the paragraph be replaced with:

Study 94-0-013, a randomized, double-blind, comparative multi-center trial, evaluated the efficacy of AmBisome at doses (3.0 and 6.0 mg/kg/day) compared with amphotericin B deoxycholate (0.7 mg/kg/day) for the treatment of cryptococcal meningitis in adult and pediatric HIV positive patients. Patients received study drug once daily for an induction period of 11 to 21 days. Following induction, all patients were switched to oral fluconazole



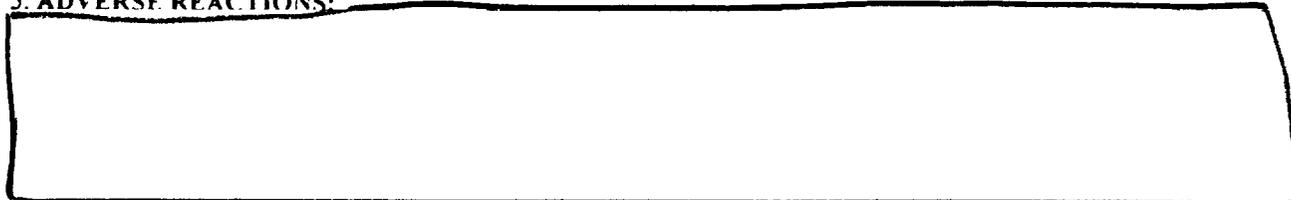
3. PEDIATRIC USE

- On page 15, line 2 to 11, the number of pediatric patients should not be changed since the one pediatric patient who was enrolled in study 94-0-013 received amphotericin B.

4. ELDERLY PATIENTS

- On page 15, line 13 to 16, the proposed change of elderly patients from 71 to 72 is acceptable.

5. ADVERSE REACTIONS:



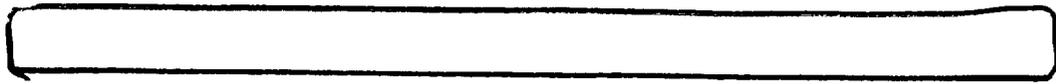
6. LESS COMMON ADVERSE EVENTS

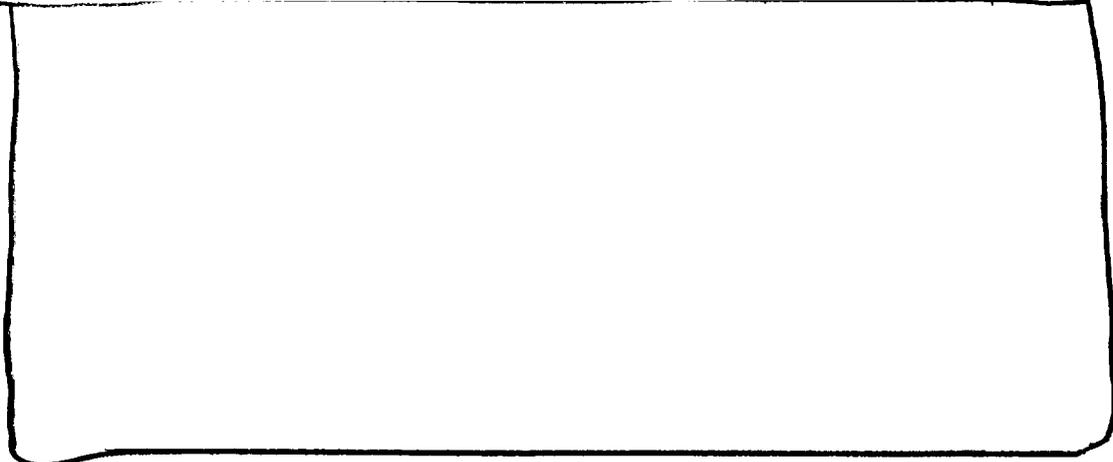
- Since study 94-0-013 did not involve patients receiving chemotherapy or bone marrow transplantation, the FDA suggests that the paragraph on page 22, line 23 to 26, reads:

The following adverse events also have been reported in 2% to 10% of AmBisome-treated patients receiving chemotherapy or bone marrow transplantation, or had HIV disease in six comparative, clinical trials.

7. CLINICAL LABORATORY VALUES

- The FDA suggests that the **Laboratory Evidence of Nephrotoxicity Study 94-0-013** table be changed to the following:



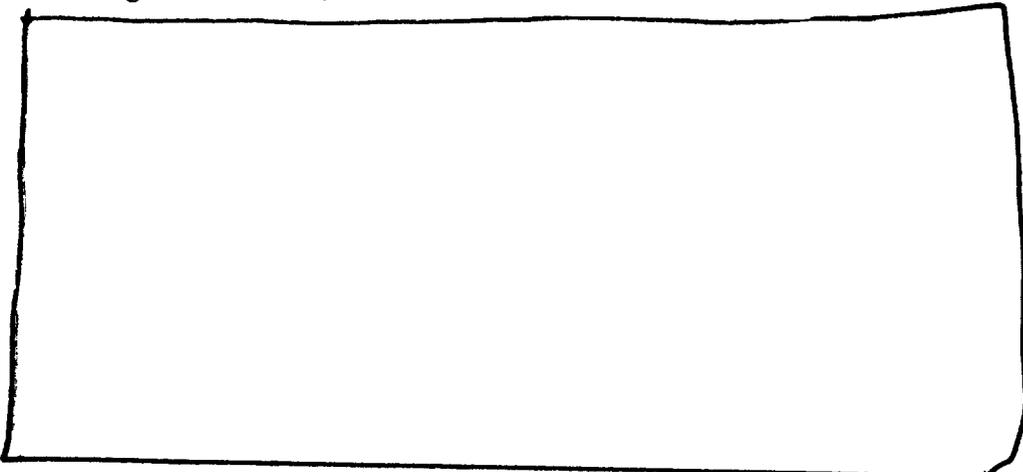


8. OVERDOSAGE:

- On page 27, line 3 to 9, the FDA notes that 7.5 mg/kg should be replaced with 10 mg/kg

9. DOSAGE AND ADMINISTRATION:

- On page 28, line 1 to 3, the FDA suggests adding a row for the dosage in cryptococcal meningitis. Therefore, the table would read:



10. The FDA finds the following addition at the end of the label acceptable as long as the revised date reflect the date of the final revision.

Abelcet® is a registered trademark of The Liposome Company, Inc. Revised: May 2000

If you have any questions, please don't hesitate to contact Leo Chan at (301) 827-21127.

 /S/ , R. Ph.

Leo Chan, R.Ph.
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products