CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-740/SE8-001

CORRESPONDENCE

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

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

March 26, 1999

Food and Drug Administration
P. O. Box 360909
Pittsburgh, PA 15251-6909

Re: NDA 50-740
Application Fee for AmBisome®
(Amphotericin B) liposome for injection
Labeling Supplemental Application
User Fee Identification Number 3690

Dear Sir:

Fujisawa Healthcare, Inc. (FHI) intends to submit to the FDA's Division of Special Pathogens and Immunologic Drug Products, a labeling supplement to NDA 50-740 AmBisome for proposed revisions to the Package Insert along with information supporting these changes.

The labeling supplemental application for AmBisome (amphotericin B) liposome for injection will provide additional clinical and statistical information for the indication of empirical therapy in febrile neutropenic patients and provides comparative data to Abelcet® (amphotericin B lipid complex).

Enclosed please find check number [redacted] in the amount of [redacted] as payment in full for the assessed FY1999 application fee.

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

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

enclosure
cc: Mr. Michael Jones - CSO

A:\BAKER\Usefprog.doc

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

March 26, 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
AmBisome (amphotericin B) liposome for injection

SUBMISSION OF AMBISOME LABELING SUPPLEMENT

Dear Dr. Goldberger:

We are herewith submitting a supplemental new drug application (sNDA) for AmBisome® (amphotericin B) liposome for injection. The supplement provides additional clinical and statistical information for the indication of empirical therapy in febrile neutropenic patients and provides comparative data to Abelcet® (amphotericin B lipid complex) from Clinical Study No. 97-0-034, *A Randomized, Double-Blind Comparative Trial of AmBisome® versus Abelcet® in the Empirical Treatment of Febrile Neutropenia.*

This sNDA is entirely in electronic format on one CDROM (approximately 300 megabytes). The electronic submission was checked with Norton Antivirus (version 4.04) and is virus-free. A description of those portions of the submission that have been submitted as a hard copy desk copy can be found in **Attachment I** of this letter.

A User Fee is required for this submission. A copy of the User Fee Cover Sheet (Section 18) can be found in **Attachment II** of this cover letter. Included, as **Attachment III** of this cover letter, is our debarment certification (Section 16).

AmBisome is also the subject of [redacted] Information pertaining to all other sections of NDA 50-740 and the above referenced IND is unchanged from that originally submitted. Please note that a field copy certification (NDA Section 17) is not required for this submission. Information pertaining to lot numbers of clinical batches utilized in clinical study 97-0-034 can be found in the clinical summary report. We look forward to a collaborative review of this sNDA.

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,

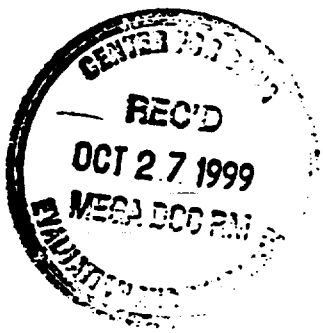
Robert M. Reed

Robert M. Reed
Assistant Director, Regulatory Affairs
cc: Ellen Frank

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel (847) 317-8800 • Telefax (847) 317-7295

Fujisawa

NDA SUPPL RECEIVED
SE8-001
BM



October 26, 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 / S-001
AmBisome® (amphotericin B) liposome for injection

SUBMISSION OF REQUESTED INFORMATION FROM CLINICAL REVIEWER

Dear Dr. Goldberger:

Please find below an explanation as to why the incidence of chills/rigors in the summary report for Study 97-0-034 differs from that calculated by the statistical reviewer. This information was requested by Matthew Bacho in an October 20, 1999 teleconference.

Fujisawa Healthcare. Inc. (FHI) has been able to reproduce the Day 1 chills/rigors results obtained by the FDA statistical reviewer. The variable STARTDAY is defined as the day on which an IRR starts calculated from the first dose day. Thus the variable, STARTDAY=1, is the day of first dose. It is believed that the FDA statistical reviewer selected the variable STARTDAY=1 and merged the variable with the COSTART code for chills/rigors (0990), thus obtaining what appeared to be the patients with Day 1 infusion-related chills/rigors. However, due to the fact that some patients received infusion of study drug just prior to midnight, it is possible to have a Day 1 infusion-related reaction on STARTDAY=2 (i.e., an IRR that started just after midnight). This "Day 2" IRR is really associated with the Day 1 infusion.

FHI used the derived variable DAY1IRR, which examines the time information to determine if an IRR is associated with Day 1 or Day 2. If the FDA statistician uses the variable DAY1IRR. the results should match the values in the study report.

It should be noted that the IRR data set includes multiple counts per patient. For example, patient number 205101 has two chills/rigors recorded for day 1. It is believed that the difference in the results between the FDA statistician and FHI resulted from the duplicate counts for patient number 205101. FHI believes that there are only 16 patients with

chills/rigors on Day 1 for AmBisome 3.0 mg/kg/day treatment group.

FHI has included the original SAS code (see Attachment 1 of this letter) used to produce the variables (IRR1.SAS). Several time variables and derivations are included in this program. The date variables do not have attached the time portion of the SAS formats, which has required FHI to adjust the time variables by multiplying them by [redacted]. FHI provided a data set (Listing 1) that has the unformatted date and time variables to illustrate what is used in the calculations for Day 1 chills/rigors (Attachment 2 of this letter). Also included is Listing 2 (Attachment 3 of this letter) that illustrates the results of the calculations and the accuracy of the derived variable, DAY1IRR (as compared to STARTDAY of IRR). Listing 3 includes all mismatches between IRR STARTDAY=1 and DAY1IRR=YES for chills/rigors (See Attachment 4 of this letter). This listing includes the second chills/rigors recorded for patient number 249151 thus this patient does not effect the overall count.

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

Robert M. Reed
Assistant Director, Regulatory Affairs

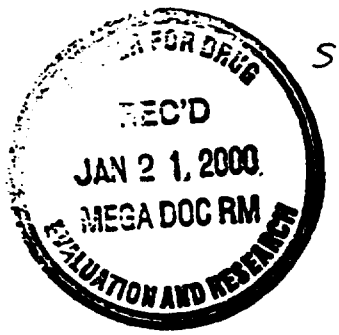
cc: Matthew Bacho

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7295

Fujisawa

NDA

SE8-001/E



January 20, 2000

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 / S-001
AmBisome® (amphotericin B) liposome for injection

SUBMISSION OF REVISED PACKAGE INSERT (FINAL DRAFT)

Dear Dr. Goldberger:

Please find enclosed a copy of the final draft of the AmBisome package insert (Attachment 1) and an updated red-line/strike-out version of the approved AmBisome package insert (Attachment 2). The January 20, 2000 version of the package insert contains all revisions discussed during our January 20 teleconference.

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

Robert M. Reed
Assistant Director, Regulatory Affairs

cc: Matthew Bacho

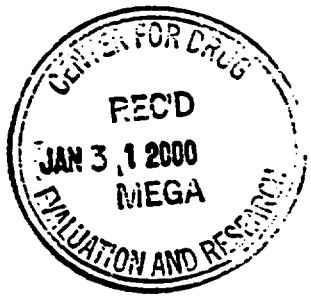
Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7295

Fujisawa

NDA SUPPL AMEND ARCHIVAL
SE8-001

January 28, 2000

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 / S-001
AmBisome® (amphotericin B) liposome for injection

SUBMISSION OF REVISED PACKAGE INSERT (FINAL DRAFT)

Dear Dr. Goldberger:

Please find enclosed a copy of the final draft of the AmBisome package insert that is dated January 21, 2000 (Attachment 1) and an updated red-line/strike-out version of the approved AmBisome package insert (Attachment 2). The January 21, 2000 version of the package insert contains the revision discussed during our January 21 teleconference.

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

Robert M. Reed
Assistant Director, Regulatory Affairs

cc: Matthew Bacho