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APPLICATION NUMBER:
50-740/SE1-002

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA: 50,740 (SE1-002)

Submission Date: 7/6/99

Generic Name: Amphotericin B Liposome for Injection

Brand Name: AmBisome®

Final Review Date: 6/6/00

Applicant: Fujisawa

Reviewer: Kofi A. Kumi, Ph.D.

Type of Submission: Efficacy Supplement

Background

The applicant submitted a supplemental new drug application for the use of AmBisome in the treatment of cryptococcal meningitis in immunocompromised patients based on data from one pivotal clinical study (No. 94-0-013) entitled "A Randomised, Double-Blind Comparative Trial of Two Doses of AmBisome (Liposomal Amphotericin B) versus Amphotericin B, Followed by Fluconazole in the Treatment of Acute Cryptococcal Meningitis in AIDS patients". In this study amphotericin B concentrations were determined in serum and cerebrospinal fluid (CSF) at specified time periods. In addition, two reports from adult and pediatric maximum tolerated dose studies were included in this submission. The adult maximum tolerated dose study was conducted in patients with proven or presumptive aspergillosis or infections due to other filamentous fungi. The pediatric study was conducted in immunocompromised children. This review provides a summary of the evaluation of these studies, serum and CSF concentrations in the pivotal clinical trial.

Summary of Pharmacokinetic Information Submitted in Application

Question: Is amphotericin B concentrations detected in CSF after administration of AmBisome to AIDS patients with Cryptococcus Meningitis?

To address this question, the applicant collected spinal fluid at week 2 of the treatment period in the pivotal clinical trial, study 94-0-013.

Title of Study: A Randomized, Double-Blind, Comparative Trial Of Two Doses Of Ambisome® (Liposomal Amphotericin B) Versus Amphotericin B, Followed By Fluconazole In The Treatment Of Acute Cryptococcal Meningitis In Aids Patients (Protocol 94-0-013)

Objectives: The objective of this study was to compare the safety, tolerability, and efficacy of two doses of AmBisome versus amphotericin B, followed by fluconazole, for treatment of acute cryptococcal meningitis in AIDS patients.

Study Design: This was a randomized (1:1:1), three-arm, double-blind, multicenter, parallel-comparative phase 3 trial. AIDS patients with confirmed cryptococcal meningitis received either 3.0 or 6.0 mg/kg amphotericin B as AmBisome or the conventional formulation of amphotericin B (amphotericin B deoxycholate, Fungizone®) at 0.7 mg/kg once daily via a 2-4 hour infusion during an 11-21 day induction phase. This was followed by daily

consolidation therapy with fluconazole (400 mg, p.o. or i.v.) to complete a total of 10 weeks of therapy. In the pharmacokinetic analysis subsection, serial blood samples to obtain a concentration-time profile of amphotericin B were not taken in this study. However, single blood samples for serum amphotericin B concentration measurement were collected within 72 hours prior to the first dose of study drug and at weeks 1 and 2 at unspecified times relative to dosing. Additional blood samples were collected at weeks 5, 6, 9, and 10 in some patients. CSF samples were collected at week 2 for the determination of amphotericin B concentration.

Data analysis:

Results: Mean amphotericin B concentrations detected in serum and cerebrospinal fluid (CSF) are provided in the tables on the following pages. Administration of AmBisome resulted in relatively higher serum concentrations of amphotericin B at each of the sampling time points compared to when Fungizone (conventional amphotericin B) was administered. However, CSF concentrations were detected in only 5 out of 180 patients for AmBisome and 1 patient who was administered Fungizone. The mean amphotericin B concentration in CSF after administration of AmBisome 3, 6 and Fungizone 0.7 mg/kg/day were reported to be 85.7 mg/L (n=1), 13.7 mg/L (n=4) and 0.1 mg/L (n=1), respectively. Amphotericin B does not appear to significantly enter CSF after administration of either AmBisome or Fungizone.

Reviewer's comments: From evaluation of individual data, the patient who was administered 3 mg/kg/day and had detectable concentrations of amphotericin B in the CSF may have been inaccurate. This patient had no detectable serum concentrations of amphotericin B in the serum. A couple of patients in the 6 mg/kg/day AmBisome group with detectable CSF amphotericin B concentration had no detectable serum concentrations of amphotericin B. The patient on Fungizone 0.7 mg/kg/day with detectable CSF amphotericin B concentrations had no detectable serum concentrations. The higher amphotericin B serum concentrations observed after administration of AmBisome did not appear to translate into a poorer safety profile (refer to medical review).

Amphotericin B concentrations are not detected in significant concentrations in the CSF at week 2 after administration of either AmBisome 3, 6 mg/kg/day or Fungizone 0.7 mg/kg/day.

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 SUMMARY TABLE FOR AMBISOME 94-0-013

CSP AMPHOTERICIN B CONCENTRATION (mg/L) AT WEEK 2 (1)

Parameter	Class	TREATMENT GROUP		
		AMBISOME 3.0 MG/KG/DAY (N=86)	AMBISOME 6.0 MG/KG/DAY (N=94)	AMBISOME BOTH (N=180)
AMPHOTERICIN B 0.7 MG/KG/DAY (N=87)				
ABOVE DETECTION LIMIT (>= 0.1 mg/L)				
	MISSING	40 (46.5%)	36 (38.3%)	76 (42.2%)
	NO	45 (52.3%)	54 (57.4%)	99 (55.0%)
	YES	1 (1.2%)	4 (4.3%)	5 (2.8%)
WEEK 2 DETECTABLE RESULTS				
	N	1	4	5
	MEAN	85.7	13.7	28.1
	STD		26.4	36.2
	P25	85.7	0.2	0.3
	MEDIAN	85.7	0.8	1.2
	P75	85.7	27.3	53.3

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(1) DUE TO THE LARGE NUMBER OF BELOW-DETECTION-LIMIT RESULTS (<0.1 mg/L), ONLY WEEK 2 DETECTABLE RESULTS ARE SUMMARIZED.

APPENDIX 14.3.10
 SERUM AMPHOTERICIN B CONCENTRATION (mg/L) (1)

PARAMETER	CLASS	TREATMENT GROUP			
		AMBISOME 3.0 (N= 86)	AMBISOME 6.0 (N= 94)	AMBISOME BOTH (N=180)	AMPHO B 0.7 (N= 87)
BASELINE	N	55	69	124	52
	MEAN	0.2	3.0	1.7	0.3
	STD	0.2	12.2	8.2	0.3
	P25	0.0	0.0	0.0	0.0
	MEDIAN	0.0	0.0	0.0	0.2
	P75	0.3	0.6	0.4	0.4
WEEK 1	N	54	69	123	52
	MEAN	12.9	31.6	23.4	0.6
	STD	34.8	34.8	23.3	0.4
	P25	4.2	3.4	3.4	0.4
	MEDIAN	8.5	17.0	10.8	0.6
	P75	16.0	50.9	39.0	0.8
WEEK 2	N	49	67	116	53
	MEAN	20.3	39.0	31.1	0.5
	STD	26.0	40.8	16.4	0.5
	P25	3.1	6.7	3.8	0.4
	MEDIAN	13.2	22.0	16.9	0.5
	P75	24.8	65.9	45.9	0.7
WEEKS 5 & 6	N	22	29	51	24
	MEAN	0.2	0.2	0.2	0.2
	STD	0.1	0.1	0.1	0.1
	P25	0.2	0.2	0.2	0.1
	MEDIAN	0.2	0.3	0.3	0.2
	P75	0.3	0.3	0.3	0.2
WEEKS 9 & 10	N	18	21	39	21
	MEAN	0.4	0.2	0.3	0.1
	STD	1.0	0.1	0.7	0.1
	P25	0.1	0.2	0.2	0.0
	MEDIAN	0.2	0.2	0.2	0.0
	P75	0.2	0.2	0.2	0.1

(1) RESULTS BELOW THE DETECTION LIMIT (0.1 mg/L) ARE REPRESENTED BY 0.

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Question: Is the pharmacokinetics of AmBisome dose proportional or linear in patients with proven or presumptive aspergillosis or infections due to other filamentous fungi

In an attempt to answer the above question, the applicant referenced in this application a final report for a maximum tolerated dose study (MTD) submitted to IND [redacted]. The following is a summary and the conclusions based on the review of the study.

Study Title (Protocol 96-0-017): A Pharmacokinetic Evaluation of AmBisome (Liposomal Amphotericin B) During A Maximum Tolerated Dose in Patients with Proven or Presumptive Aspergillosis or Infections Due to Other Filamentous Fungi: Pharmacokinetic Report (Submitted under IND [redacted])

Objective: To assess the pharmacokinetic profile of amphotericin B following the administration of escalating doses (7.5, 10, 12.5 and 15 mg/kg) of AmBisome in patients with proven or presumed fungal infections.

Study Design: This was a phase 4, open-label, sequential dose escalation, maximum tolerated dose (MTD) study in patients ages 16 to 80 years old with proven or presumed fungal infections. Thirty-four patients were evaluable for the pharmacokinetic analysis. Three patients (#57-303, 57-307, 57-308) who were originally enrolled in the 7.5 mg/kg group were re-enrolled in the 10 mg/kg group (57-312, 57-310 and 57-313). The study required a minimum of 6 patients at each of the 4 dose levels and additional 12 patients at the dose defined as the Maximum Tolerated Dose (MTD). The length of therapy (up to maximum of 100 days) was determined by the patient's response; to be included in the pharmacokinetic cohort the patient must have had at least 7 consecutive days of AmBisome therapy. Patients received a 2 hour infusion of AmBisome once daily. On the initial dose (Day 1), Day 7 and last day of therapy, blood samples for the determination of amphotericin B serum pharmacokinetics were drawn immediately pre-dose, at the end of infusion (2hr), and at 2.5, 3, 4, 6, 8, 12, 18, and 24 hours after the start of the infusion. On the last day of therapy additional samples were drawn at 48, 72 and 96 hours after initiation of the last infusion. On days 3-6 of therapy, a pre-dose trough sample was collected. AmBisome was supplied as a 50 mg lyophilized powder for reconstitution. Each 50 mg vial was reconstituted with 12.5 mL of sterile water for injection to a concentration of 4 mg/mL then further reconstituted in 5% Dextrose Injection. The lot numbers used in the study were: 424021R, 425021E, 425023E, 426002E and 142502GA.

Analytical Method: [redacted]

Data Analysis: The pharmacokinetic analyses were conducted using model independent methods.

Results: Serum concentrations of amphotericin B after administration of AmBisome varied considerably. Serum concentrations were generally higher for each patient/group on days 7 and last day of administration than day 1 suggesting accumulation of amphotericin B after

administration of AmBisome. The increases in serum concentrations were not proportional to dose and remained similar or decreased at doses of 10 mg/kg/day and above; the mean concentrations 12.5 and 15 mg/kg/day were lower than at 10 mg/kg/day. Pre-dose concentration was highly variable and mean trough concentrations suggest that steady state conditions may be reached by day 8 of daily dosing of AmBisome. A summary of the pharmacokinetic parameters is presented in the following table

Summary (Mean \pm SD) of Pharmacokinetic Parameters

Dose (mg/Kg)	Day	N	C _{max} (μ g/mL)	AUC (μ g*hr/mL)		T _{1/2} * (hr)	CL (mL/hr/kg)	V (L/kg)	V _{ss} (L/Kg)
				AUC ₂₄	AUC _{inf}				
7.5	1	8	75.9 \pm 58.4	692 \pm 834	815 \pm 1068	6.8 \pm 1.9	23 \pm 14	0.20 \pm 0.18	0.24 \pm 0.18
	7	6	115.1 \pm 104.9	1333 \pm 2153	1670 \pm 2868	6.0 \pm 0.8	15 \pm 11	0.14 \pm 0.10	0.14 \pm 0.11
	L	4	144.3 \pm 61.6	1286 \pm 973	1498 \pm 1040	6.5 \pm 3.4	11 \pm 13	0.08 \pm 0.08	0.18 \pm 0.12
10	1	7	119.6 \pm 47.8	1062 \pm 971	1188 \pm 1058	8.0 \pm 1.5	18 \pm 19	0.23 \pm 0.24	0.22 \pm 0.23
	7	6	164.7 \pm 119.7	1919 \pm 2056	2156 \pm 2221	8.4 \pm 2.6	12 \pm 12	0.16 \pm 0.17	0.14 \pm 0.14
	L	4	208.9 \pm 47.7	1944 \pm 592	2431 \pm 942	10.5 \pm 6.6	5 \pm 3	0.05 \pm 0.03	0.06 \pm 0.03
12.5	1	7	116.3 \pm 47.8	860 \pm 390	902 \pm 450	7.1 \pm 3.5	16 \pm 6	0.18 \pm 0.13	0.16 \pm 0.07
	7	5	147.4 \pm 69.2	1168 \pm 911	1292 \pm 1010	8.2 \pm 2.5	13 \pm 7	0.16 \pm 0.10	0.13 \pm 0.08
	L	1	754.8	13919	46558	48	0.3	0.07	19
15	1	11	105.1 \pm 30.9	554 \pm 174	685 \pm 252	9.0 \pm 3.1	25 \pm 8	0.33 \pm 0.12	0.23 \pm 0.09
	7	6	178.6 \pm 49.0	1152 \pm 617	1355 \pm 653	9.0 \pm 0.9	14 \pm 7	0.18 \pm 0.09	0.14 \pm 0.06
	L	2	231	2168	2300	8.5	9	0.14	0.12

*= Based on 24-hr sampling schedule.

C_{max} and AUC increased with dose escalation from 7.5 to 10 mg/kg but proportional increase were not observed. At the 12.5 and 15 mg/kg, there appeared to be no increase, rather, a slight decrease in C_{max} and AUC was observed as the doses were escalated from 12.5 to 15 mg/kg. In an exploratory population analysis, two fixed effects (outcome status and infection status) demonstrated a significant effect on the central compartment volume of distribution and on clearance. Fixed effects tested included: type of bone marrow transplant patient, infection status, outcome status and immediate prior exposure to amphotericin B.

Summary: Serum concentration of amphotericin B in patients following AmBisome doses of 7.5, 10, 12.5 and 15 mg/kg per day were higher following multiple dosing compared to single doses and were not dose proportional. Maximum amphotericin B serum concentrations were greatest following a 10 mg/kg AmBisome dose and remained the same or decreased with higher

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AmBisome doses. Amphotericin B AUC₂₄ similarly reached a maximum at 10 mg/kg and decreased with further increasing doses.

Reviewer's Comments: Serum concentrations were highly variable which resulted in very high variability in the pharmacokinetic parameters. 12.5 and 15 mg/kg dose level had very few patients with concentrations measured at these dose levels.

There was an appearance of increasing concentration when the doses were increased from 7.5 to 10 mg/kg; however, clearance at 12.5 and 15 mg/kg doses were similar. This may suggest saturation of clearance pathways for liposomal amphotericin.

Evaluation of the trough concentrations suggests steady state conditions may have been achieved by day 8 of daily administration. Because of the high variability in the data and the relatively few patients especially at the 12.5 and 15 mg/kg dose level, the interpretation of the results is difficult and should be treated with caution.

Generally, the pharmacokinetics of amphotericin B after administration of AmBisome to patients with aspergillosis or non-filamentous infection appears to be non-linear. The concentration of amphotericin B did not increase proportionally with an increase in the dose of AmBisome.

Question: What is the pharmacokinetics of amphotericin B after administration of AmBisome in immunocompromised children?

The applicant submitted in this supplemental application a dose escalation study conducted in pediatric patients ages 1 to 17 years. The following is an evaluation of the study. The individual data are provided in the appendix on file in Division of Pharmaceutical Evaluation III

Objective: To assess the pharmacokinetic profile of amphotericin B in immunocompromised children following the administration of escalating doses (2.5, 5, 7.5 and 10 mg/kg/day) of AmBisome

Study Design: This was an open-label, sequential dose escalation study in 47 immunocompromised pediatric patients, aged 1 – 17 years, with proven or presumed fungal infections. To be included in the pharmacokinetic analysis, a patient must have received AmBisome for at least three consecutive days. Re-enrollment at the same or higher dose levels was permitted. Serial blood samples for pharmacokinetic analysis were obtained on Day 1 and Day last at 0, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 hours; (additional samples on Day last at 48, 72 and 96 hours) of AmBisome therapy. Pre-dose trough blood samples were drawn twice weekly through the duration of AmBisome treatment. AmBisome was supplied as 50 mg lyophilized powder for reconstitution

Analytical Method:

Data Analysis: The pharmacokinetic profile of amphotericin B following AmBisome administrations was obtained by model-independent methods

Results: Serum amphotericin B concentrations following the 5 mg/kg dose were consistently higher than after the 7.5 mg/kg dose on both the first and last day of AmBisome therapy. However, there was large inter-patient variability in the data. There was a large degree of variability in the trough concentrations. A large degree of variability was also observed in the computed pharmacokinetic parameters. The following table contains the pharmacokinetic parameters for amphotericin B after administration of AmBisome on day 1 and day last.

Mean ± SD Serum Pharmacokinetic Parameters of Amphotericin B in Pediatric Immunocompromised Patients Following the Single Dose (Day 1) or Multiple Dose (Day Last) 1-Hour Infusions of AmBisome

Dose (mg/kg)	Day	N	C _{max} (µg/mL)	AUC		T _{1/2} (hr)	Cl (mL/hr/kg)	V (L/kg)
				AUC ₂₄ (µg*hr/mL)	AUC _{inf}			
2.5	1	10	15.1 ± 9.0	54.7 ±32.9	75.7 ±31.9 ¹	8.8 ±2.1 ²	38 ±13 ²	0.47 ±0.18 ²
	L	4	49.5 ±31.9	301± 180*	326 ±194	14.3 ±7.5	10 ±6	0.20 ±0.16
5.0	1	13	46.2± 46.7	351 ±445	442 ±551	12.6 ±8.4	45 ±38	0.86 ±0.86
	L	5	64.1 ±45.8	767 ±1115*	821 ±1118	17.9 ±4.8 ³	13 ±12 ³	0.31 ±0.20 ³
7.5	1	8	30.0± 20.5	134 ±181	168 ±95	13.5 ±8.6	60 ±38	1.22 ±1.37
	L	3	57.4 ±24.0	395 ±216*	482 ±166	21.3 ±8.8	17±7	0.53 ±0.35
10	1	8	67.9 ±74.2	430 ±566	548 ±604 ⁴	8.7 ±3.8 ⁵	46 ±39 ⁵	0.68 ±0.90 ⁵
	L	5	83.1 ±48.9	786 ±689*	857 ±696	27.4 ±23.5	17 ±11	0.63 ±0.51

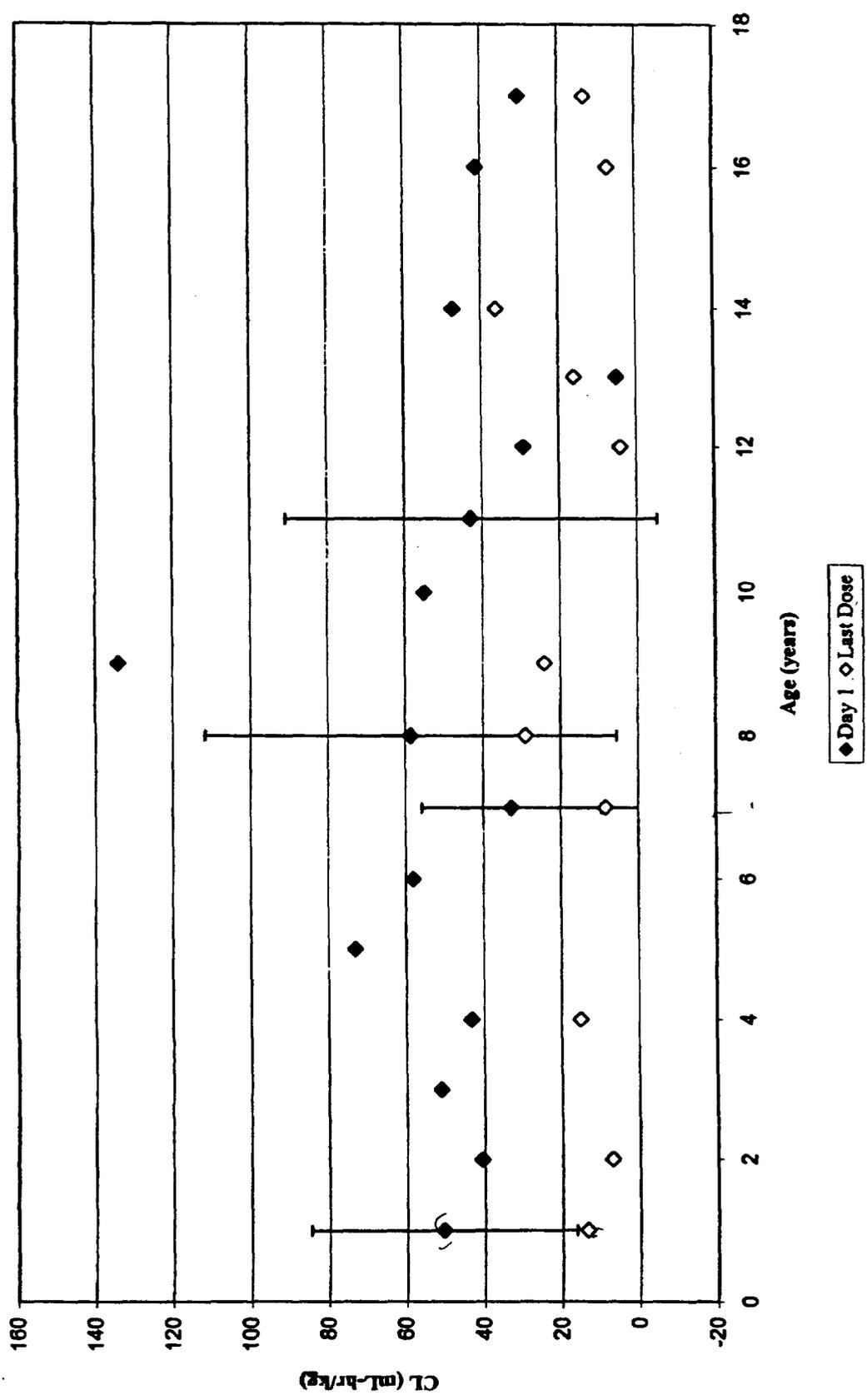
*= AUC(0-T); 1: n=8, 2: n=8; 3: n= 4, 4: n=7, 5:n= 6

C_{max} = Highest concentration quantitated

The increase in mean AUC_{inf} on day 1 was more than proportional increase in dose for the 5 and 10 mg/kg dose groups. On day last after multiple dose administration, the mean AUC_{inf} at 5 mg/kg was higher than expected but at the 7.5 mg/kg and 10 mg/kg, the mean AUC_{inf} was lower than would be expected for a linear increase in dose. However, there was one patient at the 5 mg/kg dose who had an exceptionally high amphotericin B concentrations both on day 1 and day last. Excluding this patients AUC_{inf}, the mean value for the 5 mg/kg is lower than expected (mean 329 ± 230). There was a suggestion of accumulation of amphotericin B after multiple dose administration of AmBisome. There was prolonged elimination of amphotericin B beyond 24 hours post the last dose. When plasma concentration data was available out to 96 hours post dose, the estimated elimination half-life of amphotericin B was generally greater than 20 hours. Thus

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Day 1 and Last Dose Mean (\pm SD) Serum Clearance Values as a Function of Age



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the estimated elimination $t_{1/2}$ of amphotericin B following AmBisome is dependent upon the length of the post dose sampling period.

Summary

The pharmacokinetics of amphotericin B at doses of 2.5 to 10 mg/kg/day in these pediatric patients were demonstrated not to be linear. Generally, lower than expected increase in concentration were observed with an increase in dose. AmBisome doses of 1 to 7.5 mg/kg/day administered to adult neutropenic patients with suspected or confirmed fungal infections were also reported (NDA 50,740) to result in amphotericin B pharmacokinetics that were not linear.

Reviewer's Comments

There was very large interpatient variability in the pharmacokinetic data for these patients. Hence, definite conclusions could not be inferred from the data. The sponsor attributes high variability to the patient's health status and possible concomitant medications. It is reasonable to assume that these factors may have contributed to the variability in the data

There were some patients whose amphotericin B concentrations were relatively too high compared to the rest in the dose group; however, there was no apparent explanation from the data for such high concentrations.

The sponsor does not have specific and sensitive assay to detect the amphotericin B bound to liposomes and that which is unbound. Hence, the amphotericin B concentration reported are total amphotericin B.

An evaluation of the AUC/dose, C_{max} /dose and clearance did not suggest that changes in any of these parameters with age indicating the pharmacokinetics of amphotericin B after administration of AmBisome was not dependent on age of the patient, but the number of patients were too few to make any definite conclusions. Amphotericin B concentrations increased upon multiple dosing for all age groups.

General Comments

1. Amphotericin B concentrations were not detected in the CSF at week 2 after administration of AmBisome to AIDS patients with cryptococcus meningitis. Higher serum concentrations were observed after administration of AmBisome than Fungizone. Serum concentrations were highly variable and declined rapidly after daily infusions were stopped.
2. The pharmacokinetics of amphotericin B after administration of AmBisome to patients with aspergillosis or non-filamentous infection was non-linear. The concentration of amphotericin B did not increase proportionally with an increase in the dose of AmBisome from 7.5 to 15 mg/kg
3. There was a suggestion from this study that the pharmacokinetics of amphotericin B after administration of AmBisome to immunocompromised pediatric patients ages 1 – 17 years old was not dependent on age of the patient. However, on the last day of dosing, there was a trend towards slightly higher mean clearance for the higher age group but the number of patients

was too small and the interpatient variability was large. Amphotericin B concentrations increased upon multiple dosing for all age groups. Dose adjustments may not be needed for the pediatric patients.

It must be noted that there were relatively too few patients (especially on the last day of dosing) and there was high variability in the pharmacokinetic data to make definite conclusions. Hence, the data should be interpreted with caution.

Label Comments

1) Since doses of 7.5 mg/kg/day or higher will not be recommended in the label and limited number of patients in the 12.5 and 15 mg/kg/day dose groups, it is recommended that the pharmacokinetic information from the adult maximum tolerated dose study should NOT be included in the label at this time.

2) There was relatively few number of patients for the last dose at the recommended doses, there was high variability in the data and the pediatric MTD information will not provide additional information on how AmBisome is used in children. Hence, it is recommended that the pharmacokinetic information from the pediatric MTD study should NOT be included in the label.

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Reviewer
HFD-590 Section
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6/15/00

Concurrence

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CC:

HFD 50,740 SE1-002
HFD-590

HFD-880

CDR

/MO/Z Akl
/PM/L Chan
/TLDPEIII/F Ajayi
/DPEIII/K Kumi
/Division Files
/B Murphy

CPB Briefing on 6/1/2000. Attendees: John Lazor, Pharm.D., Arzu Selen, Ph.D., Dennis Bashaw, Pharm.D., Sandra Suarez, Ph.D., Funmi Ajayi, Ph.D. and Kofi Kumi, Ph.D.