CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-740/SE8-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 50,740 (SE8-001) **Date of Submission:** 3/26/99

Drug: Amphotericin B Liposome for Injection, 50mg

Brand Name: AmBisome **Date Assigned:** 4/5/99

Applicant: Fujisawa Healthcare, Inc **Final Review:** 1/10/00

Submission Code: S **Reviewer:** Kofi A. Kumi, Ph.D.

Background

The applicant has submitted an efficacy supplement for use of AmBisome (amphotericin B liposome) in the empiric treatment of febrile neutropenia patients. The submission consisted of one randomized, double blind comparative trial in which AmBisome was compared to Abelcet (Amphotericin B Lipid Complex) for injection. The primary objective of the study was to compare the safety, primarily chills/rigors on Day 1 (primary endpoint) of 5 mg/kg/day Abelcet to an equivalent dose of AmBisome as well as to a lower yet efficacious dose of AmBisome (3 mg/kg/day). There were no pharmacokinetic evaluation conducted in this study; however, peak and trough total amphotericin B concentrations were measured in a subset of patients at specified time points. This review provides a descriptive analysis of the peak and trough concentrations obtained during the study.

Study Title (Protocol 97-0-034): A Randomized, Double-Blind Comparative Trial of AmBisome® versus Abelcet® in the Treatment of Febrile Neutropenia: Pharmacokinetic Report (Vol 2 page 1)

Background: The two most common invasive fungal infections in neutropenic patients are reported to be candidiasis and aspergillosis. Amphotericin B has demonstrated efficacy against these organisms. Amphotericin B is reported by the applicant to be the standard of care for febrile neutropenic patients unresponsive to broad spectrum antibiotic therapy. Conventional amphotericin B deoxycholate (Fungizone) is reported to have less than optimum safety profile and its therapeutic efficacy can be limited by toxicity-associated dosing constraints. AmBisome is a liposomal formulation of amphotericin B which is approved for empirical treatment of fungal infection. Abelcet, a lipid complex formulation of amphotericin B, is approved as a 2nd line therapy for patients with aspergillosis who are intolerant or refractory to amphotericin B deoxycholate. The incidence of infusion related adverse events with Abelcet (i.e. chills/rigors, headache, nausea/vomiting) is reported by the applicant to be comparable to that seen with conventional amphotericin B. The present study is to directly compare the incidence of adverse events (particularly chills/rigors and other infusion related reactions) and the incidence of nephrotoxicity in febrile neutropenic patients administered Abelcet or AmBisome for the empirical treatment of fungal infection

Objectives: 1) To compare the safety, primarily chills/rigors on Day 1 (primary endpoint), of 5 mg/kg/day Abelcet (amphotericin B lipid complex) to an equivalent dose of AmBisome (liposomal amphotericin B) as well as to a lower yet efficacious dose of AmBisome (3 mg/kg/day) 2) To compare the incidence of other safety variables such as nephrotoxicity (secondary endpoint), other infusion related reactions on day 1, all adverse events, hepatotoxicity, hypokalemia, anemia 3) To evaluate efficacy among the treatment groups.

Study Design: This was a randomized, double-blind study in 18 centers in the United States. Two hundred and forty four patients were administered at least one dose of study drug. The study drugs were Lyophilized liposomal amphoetericin B for infusion; 3 mg/kg/day (0.6 mg/mL solution) or 5 mg/kg/day (1 mg/mL solution) infused over a 120 minutes once daily and Abelcet intravenous infusion; 5 mg/kg/day (1 mg/mL solution) infused over a 120 minutes once daily. The treatment continued until the patient's absolute neutrophil count recovered to at least 500/mm^3 (or up to 3 days after recovery) or for a maximum of 42 days. Refer to medical officer's review for details of study design.

Blood samples were collected from a subset of patients (AmBisome 3 mg/kg/day = 26, AmBisome 5 mg/kg/day = 24, Abelcet 5 mg/kg/day = 18; total=68) for the determination of total amphotericin B concentrations as follows:

On day 3, prior to the day 3 infusion (i.e. 24 hours after the day 2 dose of study drug) and 15 minutes after the end of the day 3 study drug infusion

On day 4, prior to the day 4 infusion (i.e., 24 hours after the day 3 dose of study drug)

Analytical Method:

Data Analysis: Descriptive statistics of peak and trough total amphotericin B concentrations were conducted. No other pharmacokinetic analysis was conducted.

Results: Two hundred and fifty patients were enrolled in the study. Total amphotericin B concentrations (peak and/or trough) were available for 68 patients. The following table is a summary of the peak and trough concentrations for the subset of patients in which amphotericin B concentrations were determined.

Mean Peak and Trough Concentrations* of Amphotericin B

Day Concentration Taken	AmBisome		Abelcet
	3 mg/kg/day [n]	5 mg/kg/day [n]	5 mg/kg/day [n]
	Mean ± SD (µg/mL)		
Trough day 3	1.6 ± 0.9 [25]	4.1 ± 3.9 [23]	0.9 ± 0.4 [18]
Maximum day 3#	16.5 ± 9.0 [26]	32.1 ± 21.4 [24]	2.1 ± 0.7 [18]
Trough Day 4	2.3 ± 2.5 [23]	3.2 ± 1.9 [21]	0.9 ± 0.4 [16]

15 mins post infusion; * Total amphotericin B (encapsulated + unencapsulated amphotericin B)

The mean trough and maximum serum concentrations of amphotericin B were higher for both AmBisome 3 and 5 mg/kg/day than for Abelcet 5 mg/kg/day.

The following table provides a summary of the maximum infusion duration during days 1 to 5 for all the patients in the study. Summary study drug administration for all the patients is provided in the appendix.

Maximum Infusion Duration During Days 1 - 5

Number of patients	AmBisome		Abelcet
	3 mg/kg/day (n=85)[%]	5 mg/kg/day (n=81)[%]	5 mg/kg/day (n= 78)[%]
≤ 2 hours	9 [10.6]	11 [13.6]	10 [12.8]
> 2 - ≤ 3 hours	68 [80.0]	69 [85.2]	64 [82.1]
> 3 - ≤ 4 hours	5 [5.9]	1 [1.2]	4 [5.1]
> 4 hours	3 [3.5]	0	0

The majority of patients had the study drug administered for 2 to 3 hours and this was consistent across all treatment groups.

Adverse Events: The following is a very brief summary of infusion related reactions as summarized by the applicant. Refer to the medical officer's review for complete discussion of safety and efficacy.

The applicant reported that the overall incidence of infusion related events on day 1, as well as for individual infusion related events other than chills/rigors, was significantly lower for patients administered AmBisome compared with Abelcet. Fever, chills/rigors and hypoxia were significantly lower for each AmBisome group compared with the Abelcet group. After day 1, when premedication was permitted, again the applicant reports the overall incidence of infusion related reactions was still statistically different between AmBisome and Abelcet treatment groups. The incidence of chills and tachycardia remained lower for patients administered AmBisome compared with those administered Abelcet. The applicant reported that patients in the Abelcet treatment group required more medication for the treatment and prevention of infusion related reactions compared with patients receiving AmBisome. Compared with Abelcet, the applicant reported significantly lower incidence of nephrotoxicity. The applicant reported that the safety advantages observed with AmBisome were better than Abelcet even though the mean serum concentrations of total amphotericin B was significantly higher after administration of AmBisome compared to Abelcet.

Summary: Abelcet and AmBisome are lipid formulations of amphotericin B and have been approved for the treatment of amphotericin B resistant disease. Both lipid formulations have a lessened nephrotoxicity compared with amphotericin B deoxycholate, the traditional formulation of amphotericin B. The infusion related toxicity of amphotericin B is reported to be related to the release of TNF, IL-1 and IL-6 from monocytes and macrophages. The applicant reported that encapsulation of amphotericin B by the liposomal structure of AmBisome has been demonstrated to attenuate the release of TNF, IL-6 and IL-1 receptor antagonist. In contrast, the applicant reports the rapid removal of Abelcet from circulation by the reticuloendothelial tissues, particularly the liver, may result in the release of pro-inflammatory cytokines from the engulfing macrophages and account for the infusion related reactions associated with Abelcet administration.

Comments: The applicant reported peak concentrations on day 3 and trough concentrations on days 3 and 4. Mean peak serum concentrations of total amphotericin B were higher after about 2 hour infusion of AmBisome compared to Abelcet. However, since total amphotericin B concentrations were measured, it is not known if the unencapsulated amphotericin B serum concentrations is higher after AmBisome or Abelcet administration.

The applicant did not conduct exposure-response evaluation in this study possibly due to inadequate information. A visual inspection of the peak and trough concentrations and the infusion related adverse events reported in the subset of patients involved in the pharmacokinetic section indicated that adverse events were generally not recorded at the time the serum concentrations were taken. It was therefore not possible to directly correlate the adverse events to the serum concentrations of amphotericin B. Nevertheless, based on the physicochemical properties of Abelcet (large multilamellar lipid complex) and AmBisome (relatively small unilamellar liposomes), the applicant's hypothesis of why Abelcet may have higher infusion related toxicity than AmBisome is reasonable.

Labeling Comments: The applicant did not recommend any changes in the clinical pharmacology sections of the approved label for AmBisome. This is acceptable.

Recommendation

1) This phase 4 safety study was not adequately designed to evaluate exposure- clinical outcome relationships between serum amphotericin B concentrations after administration of AmBisome or Abelcet. Therefore, a direct correlation between serum concentration of ampotericin B and safety profile could not be assessed in this study.

2) It is recommended that in future planned studies the sponsor should make efforts to evaluate the relationship between serum concentrations of amphotericin B after administration of AmBisome and/or Abelcet and clinical outcome such as chills/rigors and nephrotoxicity

3) It is further recommended that in future planned studies, the applicant evaluate any potential effect of premedications and concomitant medications have an effect on serum concentrations of amphotericin B after administration of AmBisome

/S/ 1/10/00

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Concurrence 1/10/00

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NDA 50,740 (original)

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