DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 21-506

Astellas Pharma US, Inc.
Attention: Robert M. Reed
Director, Regulatory Affairs
3 Parkway North
Deerfield, IL 60015

Dear Mr. Reed:

Reference is made to your Proposed Pediatric Study Request submitted July 25, 2006, to NDA 21-506 for Mycamine® (micafungin sodium).

To obtain additional pediatric information on micafungin sodium which supplements your current pediatric program, the Food and Drug Administration (FDA) is hereby making a formal Written Request pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

A. Type of Studies:

***Study 1*:** A phase 1 study to evaluate the pharmacokinetics and safety of repeated dose intravenous micafungin sodium, 3.0 mg/kg/day for body weight ≥ 25 kg, and 4.5 mg/kg/day for body weight < 25 kg in pediatric patients from 2 to 16 years old.

***Study 2*:** A phase 1 study to evaluate the pharmacokinetics and safety of repeated dose intravenous micafungin sodium, 4.5 mg/kg/day in pediatric patients from ≥ 4 months to < 2 years old.

***Study 3*:** A phase 1 study to evaluate the pharmacokinetics and safety of repeated dose micafungin sodium, 1.0 mg/kg/day for body weight ≥ 25 kg, and 1.5 mg/kg/day for body weight < 25 kg in pediatric patients from ≥ 4 months to 16 years old.

***Study 4*:** A phase 1 study to evaluate the pharmacokinetics and safety of repeated dose intravenous micafungin, 7 mg/kg/day in neonates and infants weighing ≥ 1000 grams , and 10 mg/kg/day in neonates and infants weighing < 1000 grams, to establish the appropriate dose (s) of micafungin in this age group.

***Study 5*:** A phase 3, randomized, double-blind trial to evaluate the safety and efficacy of intravenous micafungin sodium vs. an appropriate comparator (e.g. amphotericin B deoxycholate) for treatment of serious *Candida* infections in neonates and infants.

B. Objectives/Rationale:

***Study 1*:** The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose micafungin, 3.0 mg/kg/day for body weight ≥ 25 kg and 4.5 mg/kg/day for body weight < 25 kg, in pediatric patients from 2 to 16 years old. These weight-based dosing regimens of micafungin are predicted to result in micafungin exposures in children similar to that observed in adults dosed at the approved micafungin dose of 150 mg/day.

***Study 2*:** The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose 4.5 mg/kg/day micafungin in pediatric patients from ≥ 4months to < 2 years old. This proposed weight-based dosing regimen of micafungin is predicted to result in micafungin exposures in younger children similar to that observed in adults dosed at the approved micafungin dose of 150 mg/day.

***Study 3*:** The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose micafungin, 1.0 mg/kg/day for body weight ≥ 25 kg and 1.5 mg/kg/day for body weight < 25 kg in pediatric patients ≥ 4 months to 16 years old. These proposed weight-based dosing regimens of micafungin for antifungal prophylaxis are predicted to result in micafungin exposures in children similar to that observed in adults dosed at the approved micafungin dose of 50 mg/day.

***Study 4*:** The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose intravenous micafungin, 7 mg/kg/day in neonates and infants weighing ≥ 1000 grams, and 10 mg/kg/day in neonates and infants weighing < 1000 grams, to establish the appropriate dose (s) of micafungin in this age group. This study must be performed and analyzed by the sponsor, and the results reviewed by the FDA prior to initiating Study 5 to ensure appropriate micafungin dose selection for that study.

***Study 5*:** The primary objective of this study will be to evaluate the efficacy and safety of intravenous micafungin in comparison to an appropriate comparator (e.g. amphotericin B deoxycholate) for treatment of serious *Candida* infections in neonates and infants. A sub study will be conducted to evaluate the pharmacokinetics of micafungin and the comparator in this patient population.

C. Indications to be studied:

***Studies 1 and 2*:** Treatment of serious *Candida* infections in pediatric patients

***Study 3*:** Prevention of serious *Candida* infections in pediatric patients

***Study 4*:** Treatment of serious *Candida* infection in neonates and infants

***Study 5*:** Treatment of serious *Candida* infection in neonates and infants

D. Age Group in which studies will be performed:

***Study 1*:** Ages 2 to 16 years old (age cohorts: 2-5 years, inclusive; 6-11 years, inclusive; and 12-16 years, inclusive)

***Study 2*:** Ages ≥ 4 months to < 2 years old

***Study 3*:** Ages ≥ 4 months to 16 years old (age cohorts: ≥4 months to < 2 years; 2-5 years, inclusive; 6-11 years, inclusive; and 12-16 years, inclusive)

***Studies 4 and 5*:** Neonates and infants from ≥48 hours of age up to day of life 120

E. Number of Patients to be studied:

***Study 1*:** A minimum of 20 evaluable patients in each of the 3 specified age cohorts, resulting in a total of 60 evaluable patients in the study:

***Pharmacokinetics*:** A minimum of 8 evaluable patients in each of the 3 specified age cohorts for pharmacokinetics and safety evaluation for a total of 24 patients.

***Safety*:** A minimum of 12 additional evaluable patients in each of the 3 specified age cohorts for safety evaluation for a total of 36 patients.

***Study 2*:** A minimum of 8 evaluable patients for pharmacokinetics and safety evaluation.

***Study 3*:** A minimum of 8 evaluable patients in each of the 4 specified age cohorts for pharmacokinetics and safety evaluation for a total of 32 patients.

***Study 4*:** A minimum of 6 evaluable patients in each weight group (< 1000 g and ≥ 1000 g), resulting in a total of 12 evaluable patients.

***Study 5*:** A minimum of 225 patients in the study, with a minimum of 150 patients randomized to receive micafungin, and a minimum of 75 patients to receive the comparator.

Among patients receiving micafungin, at least 10 evaluable patients must have culture-proven *Candida* meningitis. No more than 20% of enrolled patients should have isolated candiduria. In the pharmacokinetic sub-study, approximately 35 patients in each of the two weight groups designated in Study 4 for the micafungin group and approximately 30 patients for the comparator group will be studied. When clinically justified, cerebrospinal fluid (CSF) will be collected to determine CSF drug concentrations from at least 10 patients receiving micafungin and 5 patients receiving the comparator.

F. Study endpoints:

***Studies 1, 2, 3, and 4*:** Steady state pharmacokinetic parameters of micafungin will be determined using traditional pharmacokinetic sampling methods. The following PK parameters will be determined: steady state $AUC_{0\text{-}24}$, C_{max}, and T_{max}, clearance, steady state volume of distribution, elimination half-life, and pre-dose (trough) measurements, as appropriate.

Safety endpoints which will be evaluated include physical examinations, vital signs, electrocardiograms, clinical laboratory assessments, and adverse events.

***Study 5*:** The primary efficacy endpoint will be fungal-free survival measured 1 week after the last dose of study drug. Secondary efficacy endpoints will include clinical and mycological response, recurrence of *Candida* infection, and development of an emergent fungal infection.

Safety endpoints which will be evaluated include adverse events, clinical laboratory assessments, vital signs, and physical examinations.

In the pharmacokinetics sub-study, pharmacokinetic parameters will be determined using standard population pharmacokinetic approaches using sparse sampling techniques.

G. Drug Information:

- **Dosage Form:** Micafungin sodium for Injection
- **Route of Administration:** Intravenous
- **Dosage Regimens:**

***Study 1*:** Micafungin 3.0 mg/kg (for body weight ≥ 25 kg), and 4.5 mg/kg (for body weight < 25 kg) daily

***Study 2*:** Micafungin 4.5 mg/kg/day

***Study 3*:** Micafungin 1.0 mg/kg/day (for body weight ≥25 kg), and 1.5 mg/kg/day (for body weight < 25 kg)

***Study 4*:** Micafungin 7 mg/kg/day for neonates weighing ≥ 1000 grams, and 10 mg/kg/day, for those weighing <1000 grams

***Study 5*:** The doses of micafungin used in this study will be based on the results of Study 4. The appropriate dose of the comparator will be stated and justified in the study protocol.

H. Drug-specific safety concerns:

Clinical and laboratory assessments for adverse events, including potential hepatotoxicity, nephrotoxicity, hematological toxicity, and electrolyte abnormalities will be defined in the study protocols. The study protocols will also specify how patients will be monitored for serious hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, histamine-mediated reactions, such as rash, pruritus, facial swelling, and vasodilatation, and for serious skin reactions, hepatic, renal, hematological, and cardiovascular adverse events, phlebitis, thrombophlebitis, and infusion-related reactions such as hyper- or hypotension, and cyanosis. A Data and Safety Monitoring Board (DSMB) will be established for Study 5 in order to monitor safety periodically throughout the study conduct.

I: Statistical Information:

***Studies 1, 2, 3, and 4*:** The steady state pharmacokinetic profile of micafungin will be characterized. Plasma concentration data and pharmacokinetic parameters will be summarized by descriptive statistics. The incidence of all adverse events, treatment discontinuation due to adverse events, serious adverse events, and deaths will be summarized.

***Study 5*:** The observed primary outcome (fungal-free survival at one-week following the last dose of study drug) will be adjusted for birth weight (< 750 g, 750-1000 g, and > 1000 g), and by site of infections (e.g. *Candida* meningitis, candiduria, candidemia, or other invasive candidiasis). A two-sided 95% confidence interval will be constructed for the difference in success rates between micafungin and comparator, adjusting for birth weight and site of infection, as described above.

The incidence of all adverse events, treatment discontinuation due to adverse events, serious adverse events, and deaths will be summarized.

J. Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of these studies.

K. Format of Reports to be submitted:

Full study reports addressing the issues outlined in this request with full analysis, assessment and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

L. Time Frame for submitting Study Reports:

Reports for the above referenced studies must be submitted to the Agency on or before October 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

M. Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reason(s) for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As a reminder, you are responsible for compliance with section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002 by registering certain clinical trials in the Clinical Trials Data Bank (http://clinicaltrials.gov/). If your drug is for the treatment of a serious or life-threatening disease or condition and you are conducting trials to test its effectiveness, then you must register the trials. Although not required, we encourage you to register trials for non-serious diseases. For additional information on registering your clinical trials, including the required and optional data elements, refer to the Protocol Registration System (PRS) Information Site (http://prsinfo.clinicaltrials.gov) and FDA's Guidance for Industry entitled "*Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*" (March 2002; revised draft January 2004).

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox

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