DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21506

REVISED WRITTEN REQUEST
AMENDMENT 3

Astellas Pharma US, Inc.
Attention: Jeanne Jarzabek
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Jarzabek:

Please refer to your correspondence dated August 26, 2011, requesting changes to FDA's May 23, 2007, Written Request for pediatric studies for Mycamine (micafungin sodium).

We have reviewed your proposed changes and are amending the below-listed section of the Written Request. All other terms stated in our Written Request issued on May 23, 2007, and as amended on October 22, 2009, and April 8, 2011, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

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 of whom 8 are evaluable for pharmacokinetics in each of the 3 specified age cohorts 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.

The regulatory contacts for both the Agency and Astellas have also been changed.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated May 23, 2007, as amended by this letter and by previous amendments dated October 22, 2009, and April 8, 2011, must be submitted to the Agency on or before January 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

    1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the studies demonstrate that micafungin sodium is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies.

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

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

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

WRITTEN REQUEST – AMENDMENT 2

NDA 21-506

Astellas Pharma US, Inc.
Attention: Jeanne Jarzabek
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Jarzabek:

Reference is made to your Proposed Pediatric Study Request submitted July 25, 2006, to IND 55,322 for Mycamine® (micafungin sodium).

We also refer to the your correspondence to IND 55,322, dated October 3, 2008, requesting changes to FDA's May 23, 2007 Written Request for pediatric studies for mycafungin, to the amended written request issued by the Agency on October 22, 2009, and to your correspondence to NDA 21-506 dated March 11, 2011, requesting a correction on the dates for the submission of your Pediatric Studies

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 60 evaluable patients of whom 8 are evaluable for pharmacokinetics in each of the 3 specified age cohorts in the study.

***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 any stratification factors. A two-sided 95% confidence interval will be constructed for the difference in success rates between micafungin and comparator, adjusting for the stratification factors.

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.

Reports of the studies that meet the terms of the Written Request dated May 23, 2007, as amended on October 22, 2009, and by this revised Written Request must be submitted to the Agency on or before January 31, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

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  4) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  5) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  6) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that mycafungin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
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- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial

results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
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 M COX
12/05/2011