DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21506

WRITTEN REQUEST

Astellas Pharma Global Development, Inc.
Attention: Robert Reed
Senior Director for Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Mr. Reed:

We refer to the Written Request for pediatric studies for Mycamine (micafungin sodium) for Injection issued on May 23, 2007, and amended on October 22, 2009, April 8 and December 5, 2011, and January 23, 2013. Additionally, reference is made to the correspondence submitted to your IND 55,322, for micafungin sodium, dated April 10, 2017.

We have reviewed your submission and are issuing a new Written Request.

A copy of the Written Request is attached to this letter.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Copy of Written Request

WRITTEN REQUEST

NDA 21-506

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

Dear Mr. Reed:

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 your correspondence to IND 55,322, dated October 3, 2008, requesting changes to FDA's May 23, 2007, Written Request (WR) for pediatric studies for micafungin, to the amended written requests issued by the Agency on October 22, 2009, April 8 and December 5, 2011, and January 23, 2013, and to your correspondence to IND 55,322 dated April 10, 2017, in which you responded to our request for information dated October 21, 2014, and comments discussed during a teleconference on October 4, 2016.

We acknowledge that you have completed four of the five studies in the original written request (WR Studies 1-4) and submitted them to the Agency on September 27, 2012. The data from the submitted studies were reviewed by the Agency and the Mycamine product labeling was updated to extend approval of the following adult indications to pediatric patients 4 months of age and older:

- Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses
- Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation
- Treatment of Esophageal Candidiasis

These studies are no longer included in this written request.

Upon review of the information provided on January 4, 2016 and April 10, 2017, we have determined that the decreased incidence of invasive candidiasis in neonates and changes in the standards of medical care for neonates with suspected invasive candidiasis (e.g. institution of empiric treatment, choice of antifungal agent, and infrequent use of lumbar puncture for diagnosis and follow up) have made the enrollment of the number of patients in the controlled trial previously requested in serious neonatal *Candida* infections, including meningitis (original WR Study 5) highly impracticable. Therefore, two studies in neonatal candidiasis: a comparative study and a non-comparative study, aimed at describing micafungin safety, pharmacokinetics, treatment outcomes, and cerebrospinal fluid (CSF) penetration are being requested to better inform use of micafungin in neonates and young infants. The clinical studies and information requested are intended to obtain pediatric efficacy, safety, and pharmacokinetic information needed to label micafungin regarding use in pediatric populations from birth to 4 months of age.

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 3, randomized, double-blind trial to evaluate the safety and pharmacokinetics and to describe treatment outcomes with intravenous micafungin sodium compared to amphotericin B deoxycholate for treatment of serious *Candida* infections in neonates and infants.

Study 2: A non-comparative study to collect safety, pharmacokinetics, CSF penetration, and outcome data in neonates with candidiasis treated with micafungin.

B. Objectives/Rationale:

***Study 1*:** The primary objective of this study will be to evaluate safety and to describe treatment outcomes with intravenous micafungin in comparison to 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 in this patient population.

***Study 2*:** The primary objectives of this study will be to describe safety, pharmacokinetics, CSF penetration, and treatment outcomes in neonates with candidiasis treated with intravenous micafungin.

C. Indications to be studied:

***Studies 1 and 2*:** Treatment of serious *Candida* infection in neonates and infants

D. Age Group in which studies will be performed:

***Studies 1 and 2*:** Neonates and infants from ≥48 hours of age up to day of life 180

E. Number of Patients to be studied:

***Study 1*:** A minimum of 30 patients, with a minimum of 20 patients randomized to receive micafungin, and a minimum of 10 patients to receive the comparator.

In the pharmacokinetic sub-study, approximately 12 patients in the micafungin group will be studied.

Study 2: A minimum of 30 patients exposed to micafungin at a dose of 8 mg/kg/day. Micafungin concentration in plasma will be determined in at least 5 patients receiving micafungin and micafungin concentration in the CSF relative to concurrent plasma concentrations will be determined in at least 4 patients.

F. Study endpoints:

***Study 1*:** 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 evaluated will include adverse events, clinical laboratory assessments, vital signs, and physical examinations.

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

***Study 2*:** Clinical and mycological outcomes in neonates with candidiasis treated with micafungin will be described, including survival at the end of micafungin treatment, need for additional antifungal medications, clinical and mycological response, and recurrence of *Candida* infection where available.

Safety assessment will include adverse event monitoring.

CSF and concomitant plasma concentrations will be determined.

G. Drug Information:

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

  ***Study 1*:** Micafungin IV, daily Amphotericin B IV, daily

  ***Study 2*:** Micafungin IV, daily

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.

I: Statistical Information:

***Study 1*:** The observed primary outcome (fungal-free survival at one week following the last dose of study drug) will be summarized by treatment group.
The incidence of all adverse events, treatment discontinuation due to adverse events, serious adverse events, and deaths will be summarized.

***Study 2*:** The observed outcomes (survival, clinical and microbiologic response) following the last dose of study drug) will be summarized. The incidence of serious adverse events and deaths will be summarized. Plasma concentration data and pharmacokinetic parameters will be summarized by descriptive statistics. Micafungin penetration in CSF will be summarized.

J. Labeling that may result from the studies:

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

Reports of the studies 1- 2 that meet the terms of this Written Request must be submitted to the Agency on or before October 8, 2019, 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 II, 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 study(ies) demonstrate that micafungin 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);
- 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 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
12/15/2017