DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST-AMENDMENT # 4

NDA 21-227

Merck & Co., Inc.
Attention: Theresa M. Wizemann, PhD
Director, Regulatory Affairs
P. O. Box 1000, UG2D-68
North Wales, PA 19454-1099

Dear Dr. Wizemann:

Please, refer to your correspondence dated January 3, 2006, to NDA 21-227, requesting changes to FDA's January 26, 2001, Written Request for pediatric studies for Cancidas™ (caspofungin acetate), for Injection, 50 mg/vial and 70 mg/vial.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes our Written Requests to NDA 21-227 dated January 26, 2001, December 20, 2004, February 10, 2005, and July 16, 2007.

A. Type of Studies

Study 1: Sequential, dose-escalation pharmacokinetic study in pediatric patients ranging from ages 2 to 17 years with new onset of fever and neutropenia.

Study 2: Pharmacokinetic study in pediatric patients ranging from ages 3 to 24 months with new onset of fever and neutropenia.

Study 3: Pharmacokinetic study in pediatric patients ranging from ages 0 to 3 months with documented or suspected cases of invasive candidiasis.

Study 4: A prospective, randomized, double-blind, comparator controlled empiric therapy study examining the safety, tolerability, and efficacy of caspofungin acetate in pediatric patients with persistent fever and neutropenia.

Study 5: An open label, non-comparative study examining the safety, tolerability and efficacy of caspofungin acetate in pediatric patients with documented aspergillosis, esophageal candidiasis or invasive candidiasis. This study will include a prospective evaluation of cerebrospinal fluid (CSF) distribution of caspofungin at steady state for pediatric patients provided that a medically necessary procedure is performed to allow collection of a CSF sample between 4-10 days following the initial caspofungin acetate dose or at any time thereafter while on therapy.

B. Objectives/Rationale

Study 1: This study will evaluate the pharmacokinetics of 2 different doses of caspofungin acetate to establish the appropriate dosage regimen in pediatric patients between ages 2-17 years.

Study 2: This study will evaluate the pharmacokinetics of caspofungin acetate to establish the appropriate dosage regimen in pediatric patients between the ages of 3-24 months.

Study 3: This study will evaluate the pharmacokinetics of caspofungin acetate to establish the appropriate dosage regimen in pediatric patients between ages of 0-3 months.

Study 4: The primary objective will be to provide comparative safety data for caspofungin acetate and comparator in pediatric patients with persistent fever and neutropenia. The secondary objective will be to evaluate the efficacy of caspofungin acetate and comparator in pediatric patients with persistent fever and neutropenia.

Study 5: The primary objective will be to provide safety data for caspofungin acetate in pediatric patients with documented aspergillosis, esophageal candidiasis or invasive candidiasis. The secondary objective will to evaluate the efficacy of caspofungin acetate in pediatric patients with documented aspergillosis, esophageal candidiasis or invasive candidiasis. When possible, an evaluation of CSF distribution will be performed in pediatric patients with documented aspergillosis or invasive candidiasis.

C. Indications to be studied:

Study 1: New onset of fever and neutropenia

Study 2: New onset of fever and neutropenia

Study 3: Documented or highly suspected invasive candidiasis

Study 4: Persistent fever and neutropenia

Study 5: Treatment of documented *Candida* infections-esophageal candidiasis and invasive candidiasis (including candidemia and deep tissue infections); treatment of invasive aspergillosis in pediatric patients that are refractory to, or intolerant of, standard antifungal therapies.

D. Age group in which studies will be performed

Study 1: Will be performed in patients between 2-17 years of age.

Study 2: Will be performed in patients between 3-24 months of age.

Study 3: Will be performed in patients between 0-3 months of age.

Study 4: Will be performed in patients between 2-17 years of age.

Study 5: Will be performed in patients between 3 months to 17 years of age.

E. Number of patients to be studied

Studies 1, 2, and 3: A minimum of a total of 32 evaluable pediatric patients across the three studies. In *Study 3*, a minimum of 18 evaluable patients, with at least 6 patients receiving caspofungin acetate in a single-dose panel, and at least 12 patients receiving caspofungin acetate in a multiple-dose panel.

Study 4: A minimum of 50 pediatric patients on caspofungin acetate with additional data on a minimum of 25 patients on a comparator antifungal agent.

Study 5: A minimum of 30 pediatric patients; a minimum of 10 of these patients should have the diagnosis of invasive aspergillosis.

F. Study endpoints

Study 1: Pharmacokinetic data including area under the curve (AUC), C_{1hr}, and $C_{24\ hr}$.

Study 2: Pharmacokinetic data including area under the curve (AUC), C_{1hr}, and $C_{24\ hr}$.

Study 3: Pharmacokinetic data limited to C_{1hr}, and $C_{24\ hr}$.

Study 4 and 5: Endpoints will include efficacy, safety and plasma pharmacokinetic measurements. In Study 5, if a medically necessary procedure is performed to collect CSF between 4-10 days following the initial caspofungin acetate dose or at any time thereafter while on therapy, a CSF sample will be collected to allow for the evaluation of CSF distribution of caspofungin acetate in pediatric patients with CNS mycoses.

G. Drug Information:

Dosage Form:	Caspofungin acetate injection
Route of administration:	Intravenous
Regimen:	The daily dose of intravenous caspofungin acetate for Studies 4 and 5 will be determined based on the results of the pediatric pharmacokinetic studies (Studies 1-2). The daily dose of caspofungin acetate may vary with patient age.

H. Drug-specific concerns:

Conduct specific appropriate clinical and laboratory assessments for nephrotoxicity, hepatotoxicity, and electrolyte abnormalities in pediatric patients, as defined in the protocols.

I. Statistical analyses of the data to be performed:

Studies 1, 2, and 3: Appropriate statistical analyses for the characterization of the pharmacokinetics of caspofungin acetate in pediatric patients.

Study 4: The proportion of patients that experience one or more drug-related adverse events will be evaluated, including those adverse events that resulted in drug discontinuation. The main efficacy parameter will be the proportion of patients who have a successful treatment outcome as defined in the protocol.

Study 5: The proportion of patients that experience one or more drug-related adverse events will be evaluated, including those adverse events that resulted in drug discontinuation. Efficacy analysis will include and evaluation of the proportion of patients with a favorable response within each diagnosis, with the criteria for favorable response for each particular diagnosis to be included in the protocol. Provided CSF samples are available, appropriate statistical analyses to characterize CSF distribution of caspofungin acetate will be performed; These may require the pooling of pharmacokinetic data across patients to draw any meaningful conclusions about steady state distribution.

J. Labeling that may result from the studies:

Appropriate changes to the label may be made based on the findings derived from the studies.

K. Format of reports to be submitted:

Full study reports not previously submitted to the Agency 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. All pediatric patients enrolled in the study should be categorized using one of the following designations of 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

Reports of the above studies that meet the terms of this Written Request must be submitted to the Agency on or before September 30, 2009, in order to possibly qualify for pediatric exclusivity extension under Section 505 A of the Federal Food, Drug, and Cosmetic Act (the Act).

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.

Submit protocols for the above studies to your IND 48,484 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.

Submit reports of the studies as a supplement to your approved NDA 21-227 with the proposed labeling changes you believe are 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. 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.

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, please submit proposed changes and the reasons 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 required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits for the pediatric population.

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

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 Cox
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