DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-227/S-021

Merck Research Laboratories
Attention: Chitrananda Abeygunawardana, Ph.D.
Associate Director, Regulatory Affairs
PO Box 1000
UG2D-068
North Wales PA 19454

Dear Dr. Abeygunawardana:

Please refer to your supplemental new drug application (sNDA) dated and received January 31, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CANCIDAS® (caspofungin acetate) for Injection, 50mg/vial and 70 mg/vial.

We acknowledge receipt of your submissions dated:

February 20, 2008	March 6, 2008	March 19, 2008
March 20, 2008	March 27, 2008	April 7, 2008
April 25, 2008	April 29, 2008	May 5, 2008
May 9, 2008	May 19, 2008	May 30, 2008
June 25, 2008	July 7, 2008	July 11, 2008
July 22, 2008	July 28, 2008	July 29, 2008 (2)

This supplemental new drug application provides for the use of CANCIDAS® (caspofungin acetate) for Injection, 50mg/vial and 70 mg/vial for pediatric use (3 months to 16 years of age) for the following indications:

1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients.

2. Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*.

3. Treatment of Esophageal Candidiasis.

4. Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). CANCIDAS has not been studied as initial therapy for invasive aspergillosis.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (package insert, and carton and container labels) submitted July 29, 2008, with the following minor editorial correction:

In the HIGLIGHTS of PRESCRIBING INFORMATION, RECENT MAJOR CHANGES, Indications and Usage (1), Dosage and Administration subsection, the parenthetical phrase that reads "(> 3 month of age)" is added as follows (<u>underline</u> indicates added text)

Recommended Dosing in Pediatric Patients <u>(> 3 month of age)</u> (2.3)

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, and carton and container labels. Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

A. We note that you have fulfilled the pediatric study requirement for ages 3-months to 16 years for the following indications:

1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
2. Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections.
3. Treatment of Esophageal Candidiasis.
4. Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

B. We waive the requirements to study the following indications for pediatric patients 0 to 3 months in age, as these conditions are extremely rare in this age group and such studies would be highly impractical or impossible to conduct:

1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
3. Treatment of Esophageal Candidiasis.
4. Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

C. We are deferring submission of your pediatric studies for ages 0 to 3 months, for the indication of Candidemia and *Candida* infections because the application is ready for approval in older pediatric populations and pediatric studies in neonates and young infants have not yet been initiated.

The Division was unable to conclude that neonatal candidiasis is sufficiently similar to the adult indication of candidemia and *Candida* infections (intra-abdominal abscesses, peritonitis and pleural space infections), because there are higher rates of multiorgan dissemination and up to 40% CNS involvement in neonatal candidiasis compared to adults. Also, there is no data on caspofungin efficacy in adults with *Candida* meningitis. Additionally, candidemia in neonates is a high burden disease, significantly affecting neonatal morbidity and mortality. Therefore, extrapolation of efficacy based on PK information from the adult population to the neonatal population was not possible in this case.

Efficacy and safety information is lacking for the currently marketed antifungal drugs in the neonatal population, including caspofungin, and such information is needed so that neonatal patients with systemic *Candida* infections can be treated with a safe and effective product.

Therefore, the Agency determined that an unmet medical need currently exists for the indication of neonatal candidiasis and requests you to conduct a study in pediatric patients 0 to 3 months of age to provide data and information regarding a safe and effective dosing regimen of CANCIDAS for this indication. To provide the needed data, you may conduct an adequate and well controlled study as defined by 21CFR 314.126. Other alternate approaches may also be considered following a discussion with the Agency. Within your study protocol, you are encouraged to provide the rationale for how you will achieve the targeted therapeutic dose of caspofungin in neonates.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Deferred pediatric study under PREA for the treatment of candidemia and *Candida* infections in pediatric patients ages 0 to 3 months.

Protocol Submission:	July 31, 2012
Final Report Submission:	July 31, 2020

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert
Carton and Container Labels

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

/s/

Renata Albrecht

7/29/2008 07:55:06 PM