CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-227

Merck Research Laboratories
Attn: Tamra Goodrow, Ph.D.
P.O. Box 4
West Point, PA 19486

Dear Dr. Goodrow:

Please refer to your new drug application (NDA) dated July 28, 2000, received July 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cancidas® (caspofungin acetate) for injection.

We acknowledge receipt of your submissions dated below:

December 8, 1999	September 20, 2000	November 13, 2000	January 15, 2001
January 21, 2000	September 25, 2000	November 15, 2000	January 17, 2001
March 15, 2000	October 16, 2000	November 16, 2000	January 18, 2001 (2)
April 3, 2000	October 19, 2000	November 21, 2000 (2)	January 19, 2001
May 24, 2000	October 20, 2000	November 28, 2000	January 22, 2001
June 28, 2000	October 26, 2000	December 13, 2000 (2)	January 23, 2001
July 17, 2000	October 27, 2000	December 15, 2000 (2)	January 24, 2001
July 31, 2000	October 31, 2000	December 21, 2000	January 25, 2001
August 14, 2000	November 8, 2000	December 22, 2000	January 26, 2001 (2)
August 29, 2000			

This new drug application provides for the use of Cancidas® (caspofungin acetate) for injection for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate carton and container label submitted January 26, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-227." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated January 25, 2001. These commitments are listed below.

1. You will evaluate the safety and pharmacokinetics of higher doses of caspofungin in healthy subjects and patients with invasive aspergillosis who are refractory to or intolerant of standard therapies. Information on efficacy at higher doses of caspofungin will also be collected in patients.

   The following timelines are required:

   A. Phase I study to evaluate PK and safety of higher doses:

Protocol submission to FDA:	2Q01
Proposed completion of patient portion of study:	4Q01

   B. Amendment to ongoing study in invasive aspergillosis to evaluate increase in caspofungin dose to 70 mg daily

Protocol amendment submission to FDA:	2Q01
Completion Date:	2005

   C. Non-comparative study to evaluate doses above 70 mg daily in patients with invasive aspergillosis (assuming favorable tolerability and pharmacokinetics in the phase I study)

Protocol submission to FDA:	1Q02
Proposed completion of patient portion of study: with annual interim summaries of data as it is accrued	2005

2. You will obtain additional clinical safety information on patients receiving concomitant caspofungin and cyclosporine, including trough concentrations from patients receiving concomitant caspofungin and cyclosporine.

   The following timelines are required:

   A. Amendment to ongoing study in invasive aspergillosis to encourage enrollment of patients receiving cyclosporine: 2Q01

   B. Interim review of clinical experience: 1Q02

   C. Assuming a favorable safety profile in additional patients receiving caspofungin and cyclosporine, submit a protocol for additional study of caspofungin in patients receiving cyclosporine who are at high risk for fungal infections: 3Q02

3. You will evaluate the use of combination therapy of caspofungin and other antifungal agents in the treatment of invasive aspergillosis using animal models and clinical studies in patients refractory to or intolerant of standard therapies.

The following timelines are required:

A Initiation of studies evaluating the use of caspofungin in combination with other antifungal agents in animals	2Q01
B. Submission of results of animal studies to the FDA	4Q02
C. Submission to FDA of a protocol evaluating use of caspofungin in combination with other antifungals in the treatment of invasive aspergillosis	1Q02
D. Completion of patient portion of study: with annual interim summaries of data as it is accrued	1Q05

4. You will continue to evaluate population pharmacokinetics for all ongoing caspofungin Phase III studies. Continue to obtain trough concentrations in the ongoing Phase III studies for establishing attainment of steady state. The submission of population pharmacokinetics reports will be included with supplemental NDAs that contain the clinical study reports for ongoing Phase III studies.

5. You will continue to monitor for resistance of caspofungin in clinical trials until 2005 and will characterize the resistance, where possible.

6. You will submit final clinical study reports for protocols 030, 032, and 035. The final clinical study report for protocol 030 is targeted for submission to the FDA by April 30, 2001. The final clinical study reports for protocols 032 and 035 are targeted for submission to the FDA by October 31, 2001.

7. You agree to provide updates, in the annual NDA update report for Cancidas®, on the status of the progress of your discussions with recognized experts in the fungal community regarding the definition and prioritization of research issues surrounding the clinical use of caspofungin. You agree to provide these annual updates for a period of 5 years.

8. You commit to working with FDA to obtain descriptive information on the patient population treated with Cancidas® post-approval (market use) including patient demographics, indication for use, underlying disease, concomitant medications and duration of therapy. This will be accomplished by the following:

   A. You will provide on a semi-annual basis for the next 5 years, patient use information for caspofungin obtained from the US Hospital Antifungal Market Guide or an equivalent source.

   B. You commit to providing in 2Q01 an assessment of the feasibility of obtaining, from targeted medical centers, more detailed patient information on caspofungin usage.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each

commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until January 28, 2006.

In addition, please submit three copies of the introductory promotional materials that you propose to use for Cancidas®. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the reviewing Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

We also note that you have agreed to submit post-marketing reports of the following adverse experiences as "15-day reports" for the period of one year after approval of Cancidas® :

1. any clinically significant hepatotoxicity (transaminase elevations >3 times ULN with elevated bilirubin or transaminase elevations >5 times ULN)
2. any anaphylactic events
3. any drug related renal insufficiency

If you have any questions, call Leo Chan, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research