DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-227/S-015

Merck & Co., Inc
Attention: Tamra L. Goodrow, Ph.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Goodrow:

Please refer to your supplemental new drug application (NDA) dated April 15, 2004, received April 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CANCIDAS™ (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial.

We acknowledge receipt of your submissions dated:

April 21, 2004	July 1, 2004	August 18, 2004	September 17, 2004
May 17, 2004	July 15, 2004	August 19, 2004	February 11, 2005
May 19, 2004	July 16, 2004	August 20, 2004	February 15, 2005 (5)
June 30, 2004	July 23, 2004	September 2, 2004	

This supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. DESCRIPTION

- The second paragraph in the DESCRIPTION section was revised to read:

  CANCIDAS (caspofungin acetate) is 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-N^2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine] pneumocandin B_0 diacetate (salt). ~~In addition to the inactive ingredient caspofungin acetate,~~ CANCIDAS 50 mg also contains ~~the following inactive ingredients~~: 39 mg sucrose, 26 mg mannitol, glacial acetic acid, and sodium hydroxide. CANCIDAS 70 mg also contains 54 mg sucrose, 36 mg mannitol, glacial acetic acid, and sodium hydroxide. Caspofungin acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol.

2. WARNINGS

- The WARNINGS section regarding the concomitant use of CANCIDAS™ and cyclosporine was revised to read:

  Concomitant use of CANCIDAS with cyclosporine ~~is not recommended unless~~ should be limited to patients for whom the potential benefit outweighs the potential risk ~~to the patient~~. In

one clinical study, 3 of 4 healthy subjects who received CANCIDAS 70 mg on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporine 12 hours apart on Day 10, developed transient elevations of alanine transaminase (ALT) on Day 11 that were 2 to 3 times the upper limit of normal (ULN). In a separate panel of subjects in the same study, 2 of 8 who received CANCIDAS 35 mg daily for 3 days and cyclosporine (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude (see ADVERSE REACTIONS). ~~Hence, concomitant use of CANCIDAS with cyclosporine is not recommended until multiple-dose use in patients is studied.~~

In a retrospective study, 40 immunocompromised patients, including 37 transplant recipients, were treated during marketed use with CANCIDAS and cyclosporine for 1 to 290 days (median 17.5 days). Fourteen patients (35%) developed transaminase elevations >5X upper limit of normal or >3X baseline during concomitant therapy or the 14-day follow-up period; five were considered possibly related to concomitant therapy. One patient had elevated bilirubin considered possibly related to concomitant therapy. No patient developed clinical evidence of hepatotoxicity or serious hepatic events. Discontinuations due to laboratory abnormalities in hepatic enzymes from any cause occurred in four patients. Of these, 2 were considered possibly related to therapy with CANCIDAS and/or cyclosporine as well as to other possible causes.

In the prospective invasive aspergillosis and compassionate use studies, there were 4 patients treated with CANCIDAS (50 mg/day) and cyclosporine for 2 to 56 days. None of these patients experienced increases in hepatic enzymes.

Given the limitations of these data, CANCIDAS and cyclosporine should only be used concomitantly in those patients for whom the potential benefit outweighs the potential risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated.

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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted February 15, 2005). 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 an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved supplement NDA 21-227/S-015."** Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use based on this revised labeling. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this 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, MD 20857

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, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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) 827-2127.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Package Insert

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

2/16/05 05:54:38 PM